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PR-02/Pacific

A Randomized Phase II Study Evaluating OGX-427 in Patients with Metastatic Castrate-Resistant Prostate Cancer Who Have PSA Progression While Receiving Abiraterone

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CONFIDENTIAL

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Investigator's Signature

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SYNOPSIS

Protocol Number: PR-02/Pacific
Title of Study: A Randomized Phase II Study Evaluating OGX-427 in Patients with Metastatic Castrate-Resistant Prostate Cancer Who Have PSA Progression While Receiving Abiraterone
Study Population: Men with metastatic castrate resistant prostate cancer (CRPC) who are currently receiving abiraterone therapy and have documented PSA progression
Rationale: Prostate cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in men in North America.[1] Patients with metastatic disease have a poor prognosis, and although hormonal therapy in the form of medical or surgical castration can induce significant long-term remission, development of androgen-independent disease is inevitable. The current standard of care for CRPC is mainly palliative in its intent, with proven treatment options currently including analgesia, radiation, bisphosphonates, chemotherapy such as mitoxantrone or docetaxel, and abiraterone acetate. Abiraterone acetate inhibits cytochrome P450 17α-hydroxylase/C17,20-lyase (CYP17a), a key enzyme involved in *de novo* androgen biosynthesis, thereby broadly decreasing the levels of androgens in both non-castrate and castrate patients. Abiraterone acetate with prednisone has been demonstrated in a phase III study to improve overall survival in patients with metastatic CRPC who have previously been treated with docetaxel chemotherapy, and it is now considered a standard of care. Median duration of treatment on the study was 8 months, although median progression-free survival was 5.6 months. PSA response rates were only 29%, and median PSA progression-free survival was 10.2 months, but the PSA analyses are difficult to interpret as PSA testing was only performed every 3 months on study. In the phase III study, patients were continued on study protocol unless they met all three criteria for progression (PSA, objective disease, symptoms); this study currently forms the basis for the duration of therapy as standard of care treatment with abiraterone acetate. Phase II studies of abiraterone acetate in the post-docetaxel patient population have demonstrated PSA declines of >50% occurring in approximately 50% of patients and median PSA progression-free survival in the range of 5-6 months. Given that patients on abiraterone acetate can first progress with PSA without symptoms or objective disease progression, this provides an opportunity to evaluate novel agents that target potential mechanisms of CRPC resistance in combination with abiraterone acetate. Heat shock protein (Hsp) family members, including Hsp27, have attracted attention as new therapeutic targets for cancer. Hsp27 is a small, ATP-independent Hsp which is highly conserved across species. Hsp27 is expressed in prostate cancer and other malignancies. Expression of Hsp27 is induced by cell stress, including cytotoxic chemotherapy, radiation therapy, and hormone therapy. Overexpression of Hsp27 confers a resistant phenotype and is implicated in castration resistant progression of prostate cancer through multiple mechanisms including apoptosis, growth factor signaling, and ligand-dependent and -independent activation of the androgen receptor. OGX-427 is a second generation antisense oligonucleotide (ASO) that inhibits expression of Hsp27. A number of *in vitro* and *in vivo* pharmacological studies have demonstrated that OGX-427 (or an Hsp27 ASO) has single-agent activity in reducing Hsp27 mRNA and protein, inhibiting cell proliferation, and inducing apoptosis in several human cancer cell lines. In a completed Phase I trial, OGX-427 has been administered as a single agent in doses from 200 to 1000 mg with weekly infusions occurring after a loading dose period of three infusions within the first 10 days of initiating treatment. OGX-427 treatment has been well tolerated, with the majority of the adverse events and laboratory toxicities reported being Grade 1 or Grade 2, although a symptom complex of rigors, pruritus, and erythema during or shortly after infusion of drug have required steroid prophylaxis and/or treatment in some patients at higher doses. No maximum tolerated dose has been identified based on toxicity. OGX-427 was also administered in combination with docetaxel in the above-

mentioned phase I study.

OGX-427 is also in testing in an ongoing randomized phase II study in patients with metastatic CRPC who are chemotherapy naïve with minimal symptoms. In this study, patients are being randomized to receive either OGX-427 with prednisone or prednisone alone. Preliminary results in the first 32 patients suggest interesting activity, with 59% of OGX-427-treated patients achieving a PSA decline of >30% and 50% having a circulating tumour cell (CTC) count conversion (≥5 to <5 CTC/7.5 mL), while 33% of prednisone-only treated patients had a PSA decline of >30% and 31% had a CTC conversion. Treatment has been well tolerated with infusion reactions (e.g., chills, flushing, diarrhea, nausea, vomiting) occurring in 47% of patients receiving OGX-427. One patient developed hemolytic uremic syndrome after week 7, probably related to OGX-427.

This Phase II study has been designed to evaluate the anti-tumor effects of adding OGX-427 to continuing abiraterone acetate and prednisone treatment in men with metastatic CRPC who have PSA progression.

Objectives:

Patients will be randomized with equal probability to one of two arms, designated as the Experimental Arm (A) and the Control Arm (B). The intended intervention in Arm A is continued use of abiraterone/prednisone plus the addition of OGX-427. The intended intervention in Arm B is continued use of abiraterone/prednisone.

Primary:

Progression-Free Survival at the milestone Day 60 assessment: To ascertain whether Arm A has a greater proportion of patients observed to be alive without progression at Day 60 (±7 days) as compared to Arm B.

Secondary: The secondary objectives are based on comparing the arms with respect to the following outcomes:

1. The proportion of patients who have a PSA response (≥ 30% decline) and any PSA decline post-randomization
2. Objective response
3. Progression-free survival (PFS)
4. Time to disease progression (see Section 6.4.1)
5. Circulating tumor cell (CTC) counts at baseline and on study
6. Levels of Hsp27, clusterin, and other relevant proteins at baseline and during study
7. PTEN deletion status in original pathology specimens correlated with clinical outcomes

Study Design: This is an open-label, randomized, Phase II clinical trial designed to evaluate the anti-tumor effects of OGX-427 and continuing abiraterone acetate and prednisone versus continuing abiraterone acetate and prednisone alone in men with metastatic CRPC who have evidence of PSA progression but no evidence of symptomatic or radiographic progression that would require alternative therapy (e.g., needing radiation therapy for pain or significant progression of visceral metastases).

Patients on the control arm will be allowed to cross-over to receive OGX-427 following documented disease progression. This study will be conducted at approximately 12-15 sites in Canada and the United States. Patients will be randomized with equal probability to one of the following arms:

<table>
<tr>
<td>Screening Period
Day – 28 to Randomization</td>
<td>Randomization</td>
<td>Experimental Arm (Arm A):
OGX-427 Starting within 7 days of randomization, three loading doses of 600 mg IV within Week 1 if possible (up to 10 days of initiating treatment), followed by weekly doses of 800 mg IV
Continuation of standard therapy with abiraterone acetate 1000 mg PO daily and prednisone 10-20 mg PO daily

Control Arm (Arm B):
Continuation of standard therapy with abiraterone acetate 1000 mg PO daily and prednisone 10-20 mg PO daily

After documented disease progression, patients on Arm B may opt to receive OGX-427 treatment (according to the Arm A schedule) following a screening evaluation (i.e. all inclusion and exclusion criteria have been met).</td>
<td>Both Arms:
Evaluations at 4 week-intervals. Disease assessments required at the milestone Day 60 assessment (expected to occur after 8 weeks of treatment and prior to Day 1, Week 9) and at 16, 24, 32, 40, and 48 weeks (if applicable) or until documented disease progression. Patients who are withdrawn from the study for a reason other than documented disease progression (Section 6.4.1) or patient withdrawal of consent will be followed every 4 weeks in the Off-Treatment Follow-up Period until documented disease progression.</td>
<td>End of Study Treatment</td>
<td>Off-Treatment Follow Up Period for disease progression (if applicable)</td>
</tr>
</table>

Eligible patients will be stratified by prior chemotherapy (yes versus no) and prior PSA response >30% to abiraterone acetate (yes versus no) prior to randomization. Abiraterone acetate and prednisone therapy will continue, with or without OGX-427, until disease progression is documented (Section 6.4.1) or another End of Study Treatment criterion is met (Section 5.5). Arm A patients with PSA progression in the absence of other indicators for progression (by bone scan, CT scan, or need for palliative radiation therapy) may continue therapy until disease progression by bone scan, CT, or need for palliative radiation therapy, or until disease related deterioration in ECOG performance status to Grade 3 or higher or initiation of other treatments (see Section 6.4.1.2), whichever comes first. All patients will be followed for the date of documented disease progression.

Number of Patients: A total of 74 patients will be randomized to the study.

Study Agent, Dose and Mode of Administration:

Study Agent: OGX-427

Dose and Mode of Administration: 600 mg intravenous (IV) infusion over 2 hours for three loading doses within Week 1 if possible (up to the first 10 days of initiating treatment), followed by weekly 800 mg IV infusions given over 2 hours

Premedications Required:

Patients on the Experimental Arm should be premedicated with an H2 antagonist, e.g. Ranitidine (150 mg PO or 50 mg IV) and an antihistamine, e.g., diphenhydramine (25-50 mg). It is recommended that these premedications be administered 30-90 minutes prior to infusion unless there is a medical reason they cannot receive one or more of the drugs (see Section 6.7.3).
Standard Treatment Agents, Doses and Mode of Administration: *Abiraterone acetate:* *Dose and Mode of Administration:* 1000 mg orally once daily, to be given along with prednisone *Prednisone:* *Dose and Mode of Administration:* 10-20 mg/day orally
Duration of Treatment: Study treatment for both arms will continue until disease progression or another End of Study Treatment criterion is met (see Section 5.5). Patients who are withdrawn from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in the study will be followed every 4 weeks in the Off-Treatment Follow-up Period until documented disease progression.
Definition for Primary Endpoint: **Progression-Free Survival at the milestone Day 60 assessment:** the proportion of patients alive without disease progression at the milestone Day 60 assessment Disease progression is defined on the basis of PSA progression, measurable or non-measurable disease progression, ≥2 new lesions on bone scan, disease-related deterioration in ECOG performance status to Grade 3 or higher, requiring palliative radiation therapy, systemic anti-cancer therapy, surgery for disease-related complication, or cancer pain requiring either initiation of chronic opiate analgesia (oral or parenteral) or a consistent increase >33% in daily opioid use from baseline (see Section 6.4.1.2).
Statistical Considerations: The study is designed to assess the primary endpoint as defined in the objectives. Overall study success is defined as meeting statistical criterion on the primary endpoint. The primary endpoint will be tested at a one-sided 10% significance level in an intention-to-treat analysis using Fisher's exact test. Seventy-four patients are required for a hypothesized Arm A probability of success that is 25%-points superior than that for Arm B. Given the Arm B probability of success at 5%, there will be 90% power. A conservative statement of the overall study type I error probability is 20%.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION/TERM	DEFINITION
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event(s)
AI	Androgen Independent
AKT	Serine/threonine Kinase (Protein Kinase B)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Androgen Receptor
ARAS	All Randomized Analysis Set
ASCO	American Society of Clinical Oncology
ASO	Antisense Oligonucleotide(s)
AST	Aspartate Aminotransferase
ATP	Adenosine 5'-triphosphate
AUC	Area Under the Curve
BAD	Bcl-2/Bcl-XL-associated death promoter
Bb	Blood marker-complement split products
Bcl-2/Bcl-XL	Prototypes for a family of mammalian genes and the proteins that govern mitochondrial outer membrane permeabilisation (MOMP) apoptosis
BID	Twice Daily
BP	Blood Pressure (Vital sign)
BSA	Body Surface Area
°C	Centigrade, Celsius
C3a	Blood marker-complement split products
CBC	Complete Blood Count
CD45-	Absence of this Protein Tyrosine Phosphatase (CD45)
CGE	Capillary Gel Electrophoresis
cGy	Centi Gray (unit of radiation)
CK+	Cytokeratin positive cells
Cl	Chloride
CO_2	Carbon Dioxide
CR	Complete Response
CRPC	Castrate Resistant Prostate Cancer
CRF	Case Report Form
CT	Computerized Tomography
CTC	Circulating Tumor Cell(s)
CTCAE	Common Toxicity Criteria for Adverse Events
C_{max}	Maximum Concentration
D5W	5% Dextrose in Water
Daxx	Death associated protein 6
DAPI+	4',6-diamidino-2-phenylindole positive (fluorescent stain that binds to DNA)
dL	Deciliter
DNA	Deoxyribonucleic Acid
DSM	Data Safety Monitor
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetate
EOT	End of Treatment
Fas	Apoptosis antigen ligand 1
FDA	Food and Drug Administration (USA)
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
H2	Histamine-2 Receptor

ABBREVIATION/TERM	DEFINITION
hERG	Human ERG gene (ether à go go related)
HR	Heart Rate (Vital sign)
Hsp	Heat Shock Protein
HUS	Hemolytic Uremic Syndrome
I-κBα	Main apoptosis inhibitor
ICH	International Conference on Harmonization
I.D.	Identification (number)
IGF	Insulin-like growth factor
INR	International Normalized Ratio (anticoagulant monitoring)
IP	Intraperitoneal(ly)
IRB	Institutional Review Board
IV	Intravenous(ly)
K	Potassium
Kb	Kilobases
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LHRH	Luteinizing Hormone-releasing Hormone
LNCaP	Androgen-sensitive Prostate Cancer Cells
MAP	Mitogen-Activating-Protein
MAPKAP	Mitogen-Activating-Protein Kinases
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter
MOE	Methoxyethyl
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
N or n	Number of
Na	Sodium
NCI	National Cancer Institute
NE	Not Evaluable
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
ng	Nanogram
nM (nmol)	Nanomole or Nanomolar
NOAEL	No Observed Adverse Effect Level
OGX-427	2'-Methoxy-Ethyl-Phosphorothioate Antisense to Heat Shock Protein-27
p90Rsk	Ribosomal s6 kinase
PC-3	Human Caucasian Prostate Adenocarcinoma Cell Line
PD	Progressive Disease
PFS	Progression-free Survival
pH	Hydrogen-ion Concentration (acid / alkaline)
PI	Principal Investigator
PO or po	By Mouth
PR	Partial Response and PR Interval
PSA	Prostate Specific Antigen
PTEN	Phosphatase and tensin homolog (Tumor Suppressor Gene)
PTT	Partial Thromboplastin Time
QT/QTc	Interval of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA and RNase H	Ribonucleic Acid (RNA) and enzyme that cleaves RNA (RNase H)
RPM	Revolutions per Minute
SAE	Serious Adverse Event(s)
SD	Stable Disease
SGOT	Serum glutamic-oxalacetic transaminase (see AST)

ABBREVIATION/TERM	DEFINITION
SGPT	Serum glutamic-pyruvate transaminase (see ALT)
SI	Standard international
SPM	Study Procedures Manual
ssDNA	Single strand DNA
TNM	T=size and extent of primary tumor; N=degree of regional lymph node involvement; M=presence or absence of distant metastases
TDF	Task Delegation Form (for delegation of study responsibilities)
TPD	Therapeutic Products Directorate (Canada)
TPR	Tetratricopeptide repeat
ULN	Upper Limit of Normal
USP	United States Pharmacopeia
µm	Micrometer
vs	Versus
WBC	White Blood Cell
WT	Wild Type

1. INTRODUCTION AND BACKGROUND

1.1. Treatment of Castrate Resistant Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in men in North America.[1] Patients with metastatic disease have a poor prognosis, and although hormonal therapy in the form of medical or surgical castration can induce significant long-term remissions, development of androgen-independent disease is inevitable. The current standard of care for castrate resistant prostate cancer (CRPC) is mainly palliative in its intent, with proven treatment options currently including analgesia, radiation, bisphosphonates, chemotherapy, and abiraterone acetate. Abiraterone acetate inhibits cytochrome P450 17α-hydroxylase/C17,20-lyase (CYP17a), a key enzyme involved in *de novo* androgen biosynthesis, thereby broadly decreasing the levels of androgens in both non-castrate and castrate patients. Abiraterone acetate with prednisone has been demonstrated in a phase III study to improve overall survival in patients with metastatic CRPC who have previously been treated with docetaxel chemotherapy,[2] and is now considered a standard of care. Median duration of treatment on the study was 8 months, although median progression-free survival was 5.6 months. Prostate-specific antigen (PSA) response rates were only 29%, and median PSA progression-free survival was 10.2 months; however, the PSA analyses are difficult to interpret as PSA testing was only performed every 3 months on the study. In the phase III study, patients were continued on study protocol unless they met all three criteria for progression (PSA, objective disease, symptoms); this study currently forms the basis for duration of therapy as standard of care treatment with abiraterone acetate. Phase II studies of abiraterone acetate in the post-docetaxel patient population have demonstrated PSA declines of >50% occurring in approximately 50% of patients, and median PSA progression-free survival in the range of 5-6 months. Given that patients on abiraterone acetate can first progress with PSA (indicating androgen receptor [AR] signaling activation) without symptoms or objective disease progression, this provides an opportunity to evaluate novel agents that target potential mechanisms of CRPC resistance in combination with abiraterone acetate, particularly those that target AR signaling.

1.2. Antisense Technology Platform

Antisense therapeutics are based on the premise that sequences of single-stranded nucleic acids (antisense oligonucleotides, or ASOs) will bind to complementary strands of nucleic acids through hybridization. A cancer cell with overexpression of a specific protein produces an abundance of messenger RNA that is translated into excess protein.[3] The introduction of a specific complementary or "antisense" strand of single-stranded DNA can bind to the abundant mRNA strands, leading to degradation before translation can occur and reduction in protein levels of the target gene.[4]

Various antisense chemistries have been evaluated to generate potential drug candidates for cancer therapy. Over the last ten years, considerable effort has been made by numerous groups to improve the in vivo potency of ASOs by modifications of the phosphodiester-linkage and heterocyclic structure of the sugar. Advances in modified nucleic acid chemistry[5-7] have yielded "second-generation" ASO modifications which improve both

RNA binding affinity and resistance to nuclease degradation, thereby increasing its half-life and resulting in increased potency.

Second-generation chemistry, used by OGX-427, applies 2′-O-(2-methoxyethyl) (2′-MOE modification) at the 2′ position of the carbohydrate moiety on both ends of the oligonucleotide, resulting in increased target binding affinity, resistance to degradation, and substantially better tissue pharmacokinetics. The improved affinity of a second-generation drug is primarily attributable to its design and composition. In particular, second-generation drugs are composed of both RNA-like and DNA-like nucleotides, while first-generation drugs are entirely DNA-like. Because RNA hybridizes more tightly to RNA than to DNA, the second-generation drugs have a greater affinity for RNA targets and therefore greater potency, as demonstrated by the improved antisense potency observed in cell culture systems and in animals. In addition, the 2′-MOE modification results in decreased binding affinity to RNase H, the principal nuclease that cleaves ASO-bound RNA, which results in significantly improved tissue half-life *in vivo*.[8] This produces a longer duration of action, allowing less frequent dosing.[6] Finally, 2′-MOE ASOs have been reported to have a more attractive safety profile than unmodified phosphorothioate ASOs.[5]

Recent technology developments have opened new avenues to identify and validate target genes involved in oncogenesis and disease progression, especially in the area of treatment resistance. A number of genes have been identified as possible targets for the antisense approach. Antisense strategies have demonstrated an ability to specifically inhibit the expression of these genes in animal models, resulting in clear antitumor activity.[4,9-14] Antisense therapeutics are particularly well suited for inhibiting targets that are considered not amenable to small molecule or monoclonal antibody inhibition.

1.3. Apoptosis Inhibitors

As mentioned above, one of the main obstacles in the treatment of advanced prostate cancer by androgen ablation is androgen-independent (AI) progression and development of treatment-resistant disease. AI progression is a complex process involving: adaptive upregulation of anti-apoptotic survival genes; variable combinations of clonal selection; androgen receptor transactivation in the absence of androgen from mutations or increased levels of co-activators; and alternative growth factor pathways. Research during the past decade has identified several proteins that may promote progression and resistance by inhibiting apoptosis. Laboratory studies at the Prostate Centre at Vancouver General Hospital have identified and functionally characterized several survival proteins that increase after castration and appear to function to accelerate time to AI recurrence and resistance by inhibiting apoptosis. These include clusterin,[15] Bcl-2 family members,[16] insulin-like growth factor (IGF) binding proteins[17] and heat shock protein 27 (Hsp27).[18,19] Agents targeting Bcl-2,[20,21] clusterin[20,21] and Hsp27 (abstract) have been successfully translated from the lab into the clinic. Human clinical trials are underway for several phosphorothioate ASOs.[4,22]

1.4. Hsp27 as a Therapeutic Target for Cancer

Heat shock proteins (Hsps) are a family of highly conserved proteins whose expression is induced by cell stressors such as hyperthermia, oxidative stress, activation of the Fas death

receptor, and cytotoxic drugs.[23-25] Hsps have attracted attention as new therapeutic targets for cancer, especially since the discovery and characterization of geldanamycin as an inhibitor of Hsp90[26,27] and the targeting of the clusterin gene,[28] whose product has small heat shock protein-like function. Molecules inhibiting both these targets have entered into clinical trials. Hsp27 is classified among the small heat shock proteins (15-30 kDa) and functions as an ATP-independent molecular chaperone. Depending on the phosphorylation status and cell stresses, Hsp27 can form oligomers which allow it to have affinity for client proteins, preventing their precipitation and aggregation.[23-25] Phosphorylation is catalyzed by MAPKAP kinase-2, which is downstream of the p38 MAP kinase.[29] Increased expression of Hsp27 increases tumorigenic and metastatic potential and inhibits apoptotic cell death from a variety of causes.[30-34]

Hsp27 can inhibit apoptotic cell death by a variety of mechanisms. It prevents formation of the apoptosome, apparently doing so by either preventing release of mitochondrial cytochrome-c or directly sequestering cytochrome-c in the cytosol after mitochondrial release.[34] Also, as interference to the intrinsic pathway, Hsp27 may directly interact with caspase-3, although this is still of some debate.[35,36] It may also interfere with the extrinsic pathway and has been shown to inhibit Daxx, a mediator of Fas-induced caspase-independent apoptosis.[37] Furthermore, Hsp27 has been shown to inhibit apoptosis by decreasing reactive oxygen species within cells by increasing glutathione and reducing the toxic effect of oxidized proteins.[38-41] In addition, it can act early during cell stress to stabilize and accelerate recovery of actin filaments, thus preventing disruption of the cytoskeleton.[42-44] Hsp27 is also involved in regulation of the serine/threonine kinase AKT (Protein Kinase B), an important signaling molecule for cell survival and proliferation downstream of growth factor stimulation.[45,46] Furthermore, AKT is constitutively activated by loss of the PTEN tumour suppressor gene, one of the most frequently mutated genes in cancer including prostate cancer. Hsp27 can also exert its anti-apoptotic effects through enhancement of NF-κB activity, by increasing degradation of its main inhibitor I-κBα. Recently, Hsp27 has been shown to promote IGF-I survival signaling via p90Rsk (Ribosomal s6 kinase) dependent phosphorylation and inactivation of BAD (Bcl-2/Bcl-XL-associated death promoter).[47]

Many malignancies have been shown to express Hsp27, including breast, ovarian, prostate, lung, endometrial, gastric, hepatic, and bladder cancers plus leukemia and osteosarcoma.[48] Increased expression of Hsp27 increases tumorigenicity and metastatic potential and inhibits apoptotic cell death from a variety of causes.[30-34] In prostate cancer, increased expression has been associated with increasing Gleason score, poor outcome, and development of AI progression.[49-51] Over-expression of Hsp27 in the androgen-dependent LNCaP prostate cancer cell line suppressed castration-induced apoptosis and conferred castration resistance.[19] Hsp27 knockdown using ASO potently decreased Hsp27 levels, increased caspase-3 cleavage and apoptosis, enhanced paclitaxel chemosensitivity, and delayed tumor progression in vivo.[18,19] It has also been recently identified that a feed-forward loop whereby androgen bound AR induced rapid Hsp27 phosphorylation that in turn cooperatively facilitated genomic activity of the AR, thereby enhancing prostate cancer cell survival.[52] OGX-427-induced knockdown of Hsp27, destabilized the AR, enhanced ubiquitination and degradation, and, thus, implicated Hsp27 in castration resistant progression.

Therefore, targeting Hsp27 as a therapy is very attractive as it would affect multiple pathways implicated in cancer progression and resistance, as well as CRPC specifically through the AR, as opposed to the targeting of a single pathway, which might be expected to have limited benefits in the face of the heterogeneity and redundancy that exists in cancer cells.

1.5. OGX-427 as a Therapeutic Agent

OGX-427 is a 4-12-4 2´-MOE gapmer oligonucleotide with phosphorothiolated internucleotide linkages designed to bind to Hsp27 mRNA, resulting in the inhibition of the production of Hsp27 protein. OGX-427 is similar to endogenous DNA, but contains second-generation ASO chemical modifications intended to optimize its pharmacological potency, pharmacokinetics, and safety profile. A number of *in vitro* and *in vivo* pharmacological studies have demonstrated that OGX-427 (or an Hsp27ASO) has single-agent activity in reducing Hsp27 mRNA, inhibiting cell growth, and inducing apoptosis in several human cancer cell lines. OGX-427 has also demonstrated chemosensitizing activity both *in vitro* and *in vivo* in combination with several cytotoxic drugs, including docetaxel.

1.5.1. Preclinical Studies

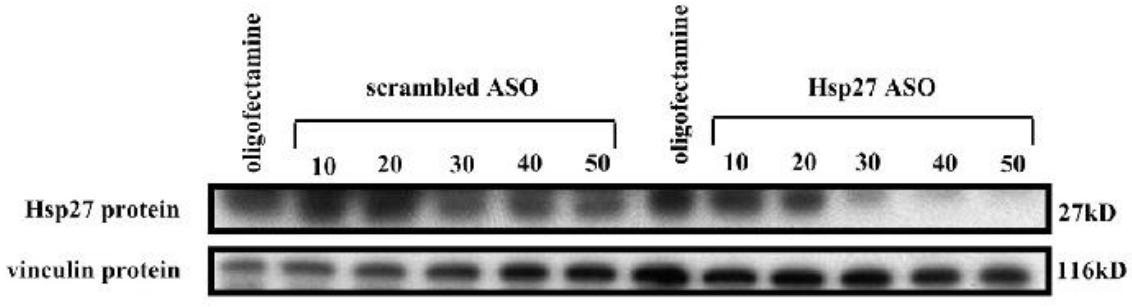
In preclinical studies, OGX-427 (or a sequence equivalent Hsp27 ASO) was tested alone or in combination with other drugs in various animal tumor models. Experimental evidence *in vitro* suggests that Hsp27 plays a role in mediating cell growth and acts as a prosurvival protein in Hsp27-expressing human malignancies, including prostate, breast, ovarian, and lung. OGX-427, or an Hsp27 ASO, can ameliorate these effects by down-regulation of Hsp27. In addition, Hsp27 ASOs have been shown to enhance the effect of chemotherapy.

All studies were conducted with a control group administered a mismatched-sequence control ASO to the target mRNA.

1.5.1.1. In vitro Studies in Prostate Cancer

Figure 1 represents an example of Hsp27 down-regulation in the human PC-3 prostate cell line by an Hsp27 ASO. Vinculin demonstrated equal protein loading for each sample.

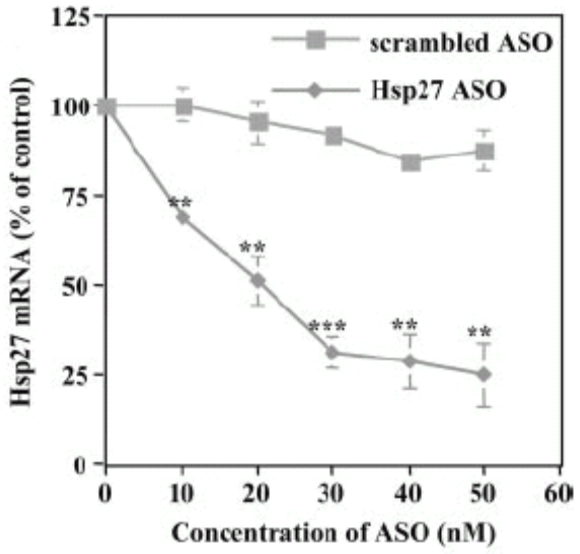
Figure 1: Hsp27 Concentrations in PC-3 Human Prostate Cancer Cells Following Treatment With Control ASO or Hsp27 ASO



PC-3 cells were incubated with Hsp27 ASO or scrambled ASO control at 10, 20, 30, 40, or 50 nM concentrations.

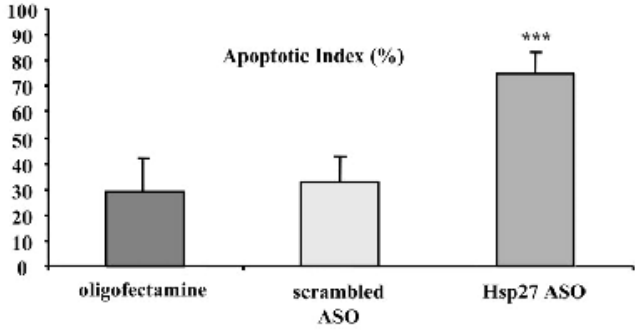
Figure 2 and Figure 3 demonstrate that an Hsp27 ASO can both inhibit cell growth and induce apoptosis in the human prostate cancer PC-3 cell line. In Figure 2, PC-3 cells were treated for 2 days with 30 nmol/L Hsp27 ASO or scrambled ASO control. Growth rates of PC-3 cells were examined daily for 4 days using a non-radioactive cell proliferation assay. Compared to a scrambled ASO control, an 87% reduction in PC-3 cell growth 4 days after treatment with Hsp27 ASO 30 nM was observed.[18]

Figure 2: Hsp27 ASO Inhibits Human Prostate Cancer Cell Growth



In addition, treatment of the PC-3 cells with the Hsp27 ASO for 2 days induced morphological changes characteristic of apoptosis. Haematoxylin and eosin staining showed nuclear shrinkage with chromatin condensation and fragmentation, indicative of apoptotic cell death. Apoptosis detected by ssDNA nuclear staining increased 2.5-fold in PC-3 cells treated with Hsp27 ASO compared to those treated with scrambled ASO control.

Figure 3: Hsp27 ASO Induces Apoptosis in Prostate Cancer Cells

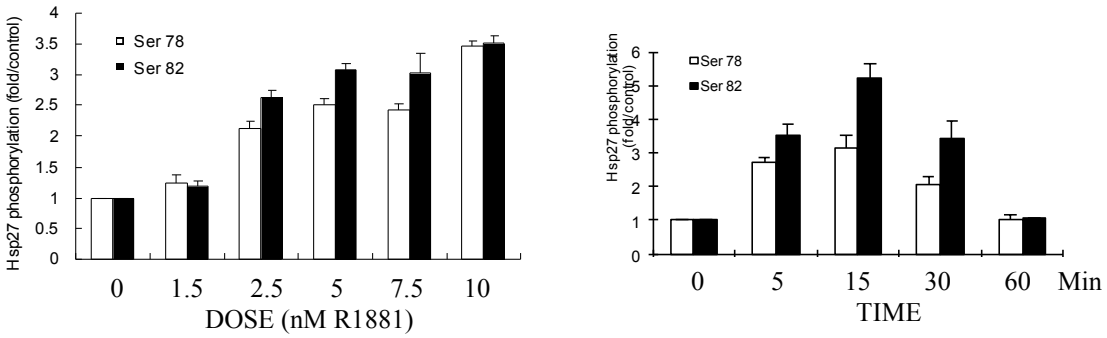


Induction of apoptosis by Hsp27 ASO was also demonstrated by flow cytometry, with the fraction of cells undergoing apoptosis (sub G1-G0 fraction) being significantly higher after

treatment with 30 nM Hsp27 ASO compared with control (33.8 vs. 9.04 %; respectively; $p \leq 0.01$).

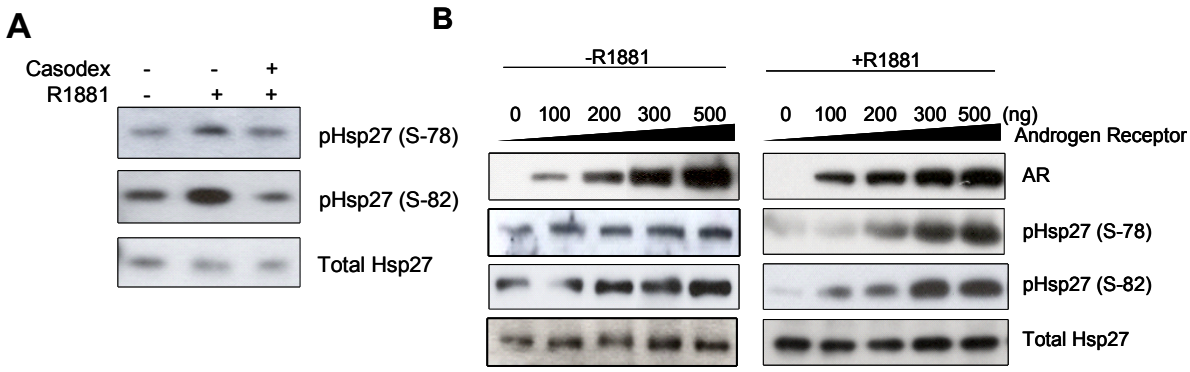
Molecular chaperones are involved in processes of folding, activation, trafficking, and transcriptional activity of most steroid receptors, including AR. In the absence of ligand, steroid receptors are predominately cytoplasmic, maintained in an inactive but highly responsive state by a large dynamic heterocomplex composed of Hsp, co-chaperones and tetratricopeptide repeat (TPR)-containing proteins.[53-55] Gleave and colleagues have identified a novel feed-forward loop involving cooperative interactions between ligand-activated AR and Hsp27 phospho-activation that facilitate AR stability, shuttling, and transcriptional activity.[56] Recently identified non-genomic effects of ARs include activation of Src, PI3 Kinase, and AKT. Androgen induced rapid phosphorylation of Hsp27 on both Ser 78 and Ser 82 residues in a dose- and time-dependent manner as shown in Figure 4. Ser 78 and Ser 82 phosphorylation levels increased 3.2- and 5.3-fold, respectively, after 15 minutes of incubation with the synthetic androgen R1881.

Figure 4: Androgen Induced Rapid Phosphorylation of Hsp27 on Both Ser 78 and Ser 82 Residues in a Dose- and Time-Dependent Manner



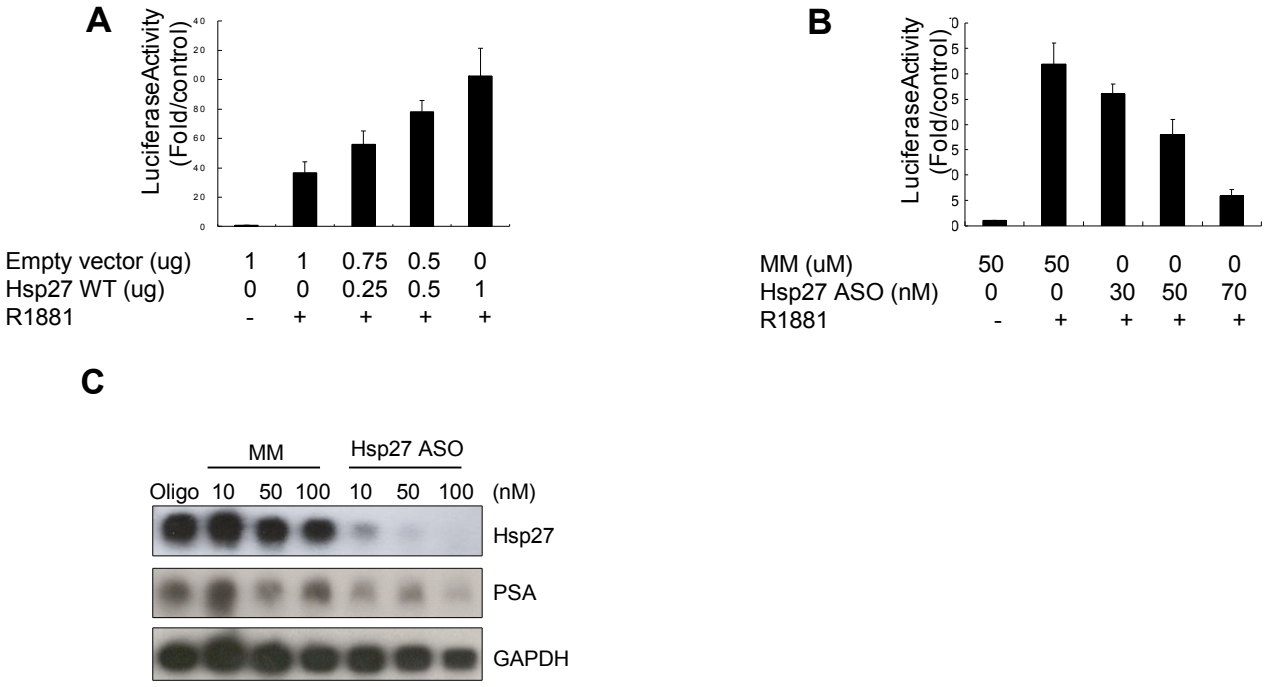
AR is required for androgen-induced phosphorylation of Hsp27, since the anti-androgen bicalutamide inhibited R1881-induced Hsp27 phosphorylation (see Figure 5A). To further support the data, PC3 cells, which do not express endogenous ARs, were transfected with increasing amounts of AR or empty vector with or without R1881. As shown in Figure 5B, Hsp27 phosphorylation levels at both Ser 78 and Ser 82 sites increased with increasing androgen receptor levels after R1881 treatment.

Figure 5: Androgen-induced Hsp27 Phosphorylation is Androgen-Receptor Dependent



Hsp27 co-localizes with and shuttles ligand-activated AR during nuclear translocation and enhances AR transcriptional activity. PSA transactivation assays were performed using LNCaP cells transiently transfected with the PSA (6.1 Kb)-luciferase reported plasmid in the presence or absence of increasing amount of wild type (WT) Hsp27. As shown in Figure 6A, R1881 treatment induced a 34-fold increase in AR reporter gene expression. WT Hsp27 overexpression increases androgen-stimulated transcriptional activity of PSA a further 3-fold. Conversely, Hsp27 knockdown using OGX-427 decreased PSA transactivation in a dose-dependent manner (Figure 6B). Moreover, Hsp27 knockdown by OGX-427 inhibited androgen-induced PSA expression in a dose dependent manner (Figure 6C). These results indicate that Hsp27 expression enhances androgen-stimulated transactivation of ARs.

Figure 6: Effect of Hsp27 on Transcriptional Activity of Androgen Receptors

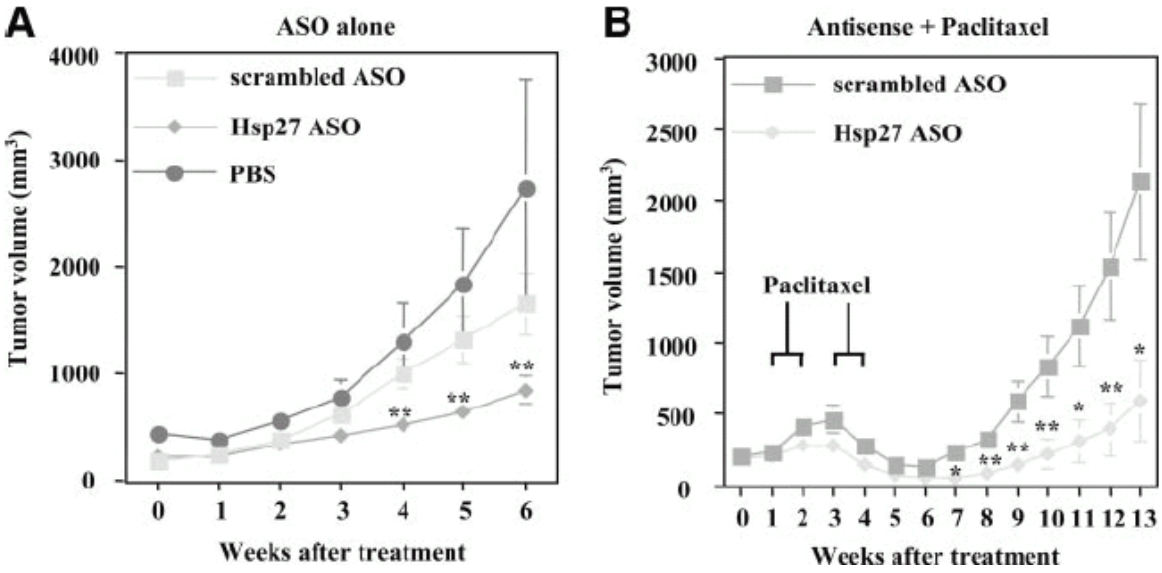


1.5.1.2. In vivo Studies in Prostate Cancer

The effects of Hsp27 ASO on the growth of human tumors have been examined. Male nude mice bearing PC-3 tumors (200 mm^3) were randomly selected for Hsp27 ASO versus scrambled ASO control. Ten mg/kg of ASO were administrated once daily by intraperitoneal (IP) injection for 91 days. No adverse events were observed in the animals. As shown in Figure 7A, Hsp27 ASO administration as a monotherapy significantly reduced PC-3 tumor volume by at least 50% from weeks 4 through 6.

Synergy between Hsp27 ASO and chemotherapy has also been demonstrated. Male nude mice bearing PC-3 tumors (200 mm^3) were randomly selected for Hsp27 ASO versus scrambled ASO control. Similarly, 10 mg/kg of Hsp27 ASO were administrated once daily by IP injection for 91 days. From days 7 to 14 and 21 to 28, 0.5 mg of micellar paclitaxel was administrated intravenously (IV) once daily. Mean tumor volume was similar in all groups before therapy. As shown in Figure 7B, treatment with Hsp27 ASO significantly enhanced the apoptotic effects of paclitaxel *in vivo*, reducing mean PC-3 tumor volume by >70% by 13 weeks after initiation of treatment, compared with scrambled ASO control. Under the experimental conditions described above, no adverse effects were observed.

Figure 7: Effect of Hsp27 ASO Treatment on PC-3 Tumor Growth and Chemosensitivity *In Vivo*



(** = P 0.01)

1.5.2. Nonclinical Drug Disposition and Toxicity Evaluation of OGX-427

1.5.2.1. Drug Disposition

Characterization of plasma kinetics, tissue distribution, excretion and metabolism of OGX-427 was accomplished by applying "cold" bioanalytical methods to numerous plasma, tissue and urine samples collected during 4-week toxicity studies in monkeys and mice, as well as plasma samples obtained from a safety pharmacology study conducted in monkeys. In both mice and monkeys, the total dosing period was four weeks, beginning with a loading dose period followed by once-weekly maintenance doses thereafter to 28 days (i.e., dosing on Days 1, 3, 5, 7, 14, 21, and 28).

The results demonstrated that the disposition of OGX-427 following single or repeated intravenous infusion is generally similar to that reported for numerous other phosphorothioate oligonucleotides.[57-59] Specifically, plasma levels of OGX-427 were maximal at the end of infusion (monkeys) or shortly following injection (mice), and the C_{max} and AUC values were generally dose-proportional and not influenced by gender. The mean values for clearance and volume of distribution were not highly variable across dose levels or over time for both species. In monkeys, the initial half-life, reflecting distribution into tissues, was on the order of 0.5 to 1 hours. The terminal half-life in monkeys was estimated to range from approximately 50 to 190 hours, and this component most likely reflects the rate of clearance of the intact OGX-427 oligonucleotide from tissues.

The pattern of tissue distribution of OGX-427 was similar between mice and monkeys. At all dose levels, the highest tissue concentrations of OGX-427 were observed in the kidney, liver and spleen, with substantially lower levels in all other tissues. The levels of OGX-427 in the brain and testes were exceptionally low (near or below the limits of detection), consistent with the inability of oligonucleotides to cross the blood-brain or blood-testes

barriers. For both species, tissue concentrations were maximal at the earliest collection time-point following a single dose (Day 2), and tissue concentrations decreased slowly thereafter such that OGX-427 was detectable in most tissues (excluding brain) two months after a single dose. As expected from this long tissue retention, OGX-427 levels accumulated substantially (several fold, relative to Day 2 data) during the every-other-day dosing phase (doses on Days 1, 3, 5 and 7). However, tissue accumulation was generally observed only up to Day 8, with a maintenance of tissue levels during the weekly dosing period in the 4-week studies (i.e., between Days 8 and 29).

Up to approximately 35% of the total dose of OGX-427 was eliminated as intact drug over a 24-hour period, although this excretion occurred relatively slowly. Therefore, the initial rapid multi-log decline in plasma concentrations (over the first few hours after dosing) was considered a reflection of mainly rapid distribution to tissues and not elimination in urine.

Greater than 90% of the circulating oligonucleotide detectable by capillary gel electrophoresis (CGE) was in the form of intact OGX-427, consistent with the dramatic nuclease resistance imparted by the dual chemical modifications in OGX-427, as a second-generation ASO. The data indicate that clearance from tissues largely occurs via egress of intact oligonucleotide, rather than by metabolism. These observations suggest that the terminal elimination half-life in plasma likely reflects the rate of clearance from tissues. Published information on this relationship for closely related oligonucleotides was the basis for selecting the dosing schedules employed in the 4-week toxicity studies.[58,59]

1.5.2.2. Nonclinical Toxicity Studies

A comprehensive series of nonclinical toxicity studies were conducted with OGX-427. The primary toxicity studies were the 4-week studies in mice and monkeys. These studies were supplemented with a series of investigations to assess the cardiovascular safety of OGX-427. The first of these studies to be conducted was the standard hERG assay. A positive response was obtained in this assay, which prompted a follow-up study in a rabbit Purkinje fiber system, as well as a cardiovascular safety study in cynomolgus monkeys. The results of these studies indicated no risk of adverse effects on cardiac conductance or other forms of myocardial injury.

The no-adverse effect levels (NOAEL) established in monkeys and mice were, respectively 10 mg/kg and >50 mg/kg. The proximal tubule degeneration in the kidneys of monkeys observed at the 40 mg/kg dose level appears to be the dose-limiting toxicity. The most salient effect observed at the 10 mg/kg and 40 mg/kg dose-level in monkeys was the increase in complement split products (i.e., Bb and C3a), which was indicative of mild activation of the alternative complement pathway. This increase in complement split products in monkeys was observed at the end of infusion (absent by 6 hours post-infusion) and was not associated with deleterious sequelae at doses up to 40 mg/kg.

1.6. Phase I Clinical Study OGX-427-01

OGX-427-01 was the first open-label, dose-escalation, Phase I clinical study designed to evaluate the safety profile, determine the maximum tolerated dose (up to a maximum dose of 1000 mg), characterize the pharmacokinetic profile, and document objective responses or disease stabilization for OGX-427 when administered weekly as a single agent and

when administered in combination with chemotherapy (docetaxel). The study also assessed the potential for OGX-427 to delay cardiac repolarization (QT/QTc interval) and levels of specific complement split products following OGX-427 infusion. All patients enrolled had cancers that have been shown to overexpress Hsp27 (breast, ovarian, prostate, non-small cell lung, and bladder). Patients had to have metastatic disease and have failed all therapies felt to be curative or for which no curative therapy existed. Refer to the Investigator's Brochure for more detailed information.

OGX-427 was administered to patients in 7 cohorts. In Cohorts 1 to 5, OGX-427 was administered weekly as a single agent per dose-level in 3-week cycles starting at a dose of 200 mg OGX-427 in Cohort 1. Dose escalations of 200 mg each occurred within cohorts up to 1000 mg of OGX-427 in Cohort 5. Weekly OGX-427 plus docetaxel was administered to two subsequent cohorts, Cohorts 6 and 7, at 800 mg and 1000 mg, respectively. Intra-patient dose escalation was not allowed.

The study was initiated in June of 2007 and 65 patients were enrolled. One patient was consented but not treated. Data are available from 64 patients who received at least one dose of OGX-427: 42 treated in the first five cohorts with OGX-427 as a single agent and 22 treated with OGX-427 plus docetaxel.

1.6.1. Patient Demographics, Number of Cycles Received, and Reasons for Discontinuation of Therapy

The median age of the 64 patients was 64 years; 43 patients (67%) were male. The majority of patients (58%) had prostate cancer, followed by breast (19%), ovarian (11%), lung (9%), and bladder (3%) cancers. Ten patients (16%) were unable to complete a minimum of one cycle of therapy due mainly to adverse events/safety concerns (4 patients) or early disease progression/global deterioration (3 patients). The remaining patients completed a range of treatment from one to 10 cycles, with a median of 2 cycles.

As of the data cut-off (January 2012), 56 of 64 (86%) patients had expired, 1 patient was lost to follow-up, 1 patient withdrew consent, and 6 patients remained in follow-up. Four patients completed ten cycles of therapy, and 60 patients discontinued therapy prior to completion of 10 cycles. Forty-six of 60 (77%) patients discontinued for disease progression/global deterioration. Fifteen patients discontinued for other reasons, including 4 patients who discontinued due to toxicity or adverse event, 3 patients for investigator decision, 2 patients for treatment delay, 3 patients for withdrawal of consent, and 2 for other reasons.

1.6.2. Adverse Events

A maximum tolerated dose (MTD) was not observed at the highest dose evaluated (1000 mg) with or without docetaxel treatment; however, there was one dose-limiting toxicity. A breast cancer patient in Cohort 3 (600 mg OGX-427 monotherapy) with undiagnosed brain metastases experienced cerebral hemorrhage. The protocol was subsequently amended to exclude patients with brain metastases.

All subjects experienced at least one treatment-emergent adverse event. The majority of the adverse events (AEs) reported were Grade 1 or Grade 2 (88% of all AEs). Among patients receiving OGX-427 monotherapy, the most common non-laboratory adverse

events (i.e., occurring in 20% or more of the patients) included: infusion-related reaction (64% of patients), chills (55%), fatigue (38%), pruritus (36%), diarrhea (31%), dyspnoea (31%), anemia (29%), nausea (26%), flushing (26%), blood creatinine increased (26%), back pain (24%), arthralgia (24%), vomiting (24%), hypokalemia (24%), peripheral edema (21%), pyrexia (21%), and decreased appetite (21%). There were no clear trends observed across the OGX-427 dosing cohorts for the most common non-laboratory adverse events. Non-laboratory adverse events observed in patients receiving OGX-427 plus docetaxel are detailed in the Investigator's Brochure.

During the Loading Dose Period and Cycle 1, the most common adverse events observed in patients receiving OGX-427 monotherapy were similar to those for the treatment period as a whole. Events that occurred during the Loading Dose Period and Cycle 1 in 20% or more of patients receiving OGX-427 monotherapy were: infusion-related reactions (60% of patients), chills (52%), pruritus (33%), fatigue (26%), flushing (24%), anemia (24%), diarrhea (21%), nausea (21%), and blood creatinine increased (21%). Prophylaxis with ibuprofen or acetaminophen was required per protocol for a 24-hour period on infusion days during the Loading Dose Period only in an attempt to decrease the rigors and fevers often associated with administration of ASOs. All infusion related reactions (infusion reactions plus cytokine release syndrome) during the loading doses and Cycle 1 were Grade 1 or 2, except for Grade 3 events experienced by three patients (two treated with 600 mg OGX-427 monotherapy and one treated with 800 mg OGX-427 monotherapy).

The incidence of Grade 3 or higher non-laboratory adverse events observed is summarized by cohort below (sorted by overall decreased frequency). Among patients receiving OGX-427 monotherapy, there were 11 non-laboratory Grade 4 events: 3 reports of dyspnea and one report each of: dehydration, hyponatremia, hypoglycemia, anemia, neutropenia, lymphopenia, cardio-respiratory arrest; one Grade 4 event was reported as not coded.

Table 1: Incidence of Non-laboratory Grade 3 or 4 AEs Observed in More than One Patient Receiving OGX-427 Monotherapy

	OGX-427 Monotherapy				
Event	**200 mg (N=6)**	**400 mg (N=7)**	**600 mg (N=7)**	**800 mg (N=8)**	**1000 mg (N=14)**
Any Grade 3 or Higher	2 (33%)	6 (86%)	5 (71%)	5 (63%)	8 (57%)
Dyspnoea	1 (17%)	2 (29%)	3 (43%)	0 (0%)	3 (21%)
Anemia	0 (0%)	0 (0%)	0 (0%)	2 (25%)	4 (29%)
Fatigue	0 (0%)	0 (0%)	2 (29%)	1 (13%)	2 (14%)
Hypoxia	1 (17%)	1 (14%)	2 (29%)	0 (0%)	1 (7%)
Chills	0 (0%)	0 (0%)	1 (14%)	1 (13%)	1 (7%)
Back pain	0 (0%)	1 (14%)	0 (0%)	1 (13%)	0 (0%)
Infusion related reaction	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (7%)
Cytokine release syndrome	0 (0%)	0 (0%)	1 (14%)	1 (13%)	0 (0%)
Platelet count decreased	0 (0%)	0 (0%)	1 (14%)	1 (13%)	0 (0%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (14%)
Hypokalemia	0 (0%)	0 (0%)	1 (14%)	0 (0%)	2 (14%)
Blood creatinine increased	0 (0%)	0 (0%)	0 (0%)	1 (13%)	1 (7%)
Hyponatremia	1 (17%)	1 (14%)	0 (0%)	0 (0%)	1 (7%)

Among patients receiving OGX-427 monotherapy, 13 events of laboratory toxicities (31%) were Grade 1 or Grade 2; 26 events (62%) were Grade 3. Three laboratory toxicities (7%) were Grade 4. The most common laboratory events (i.e., occurring in 25% or more of all monotherapy patients) included: transient prolongation of PTT (100% of patients), lymphopenia (93%), anemia (88%), elevated AST (50%), hypokalemia (50%), hyponatremia (48%), elevated alkaline phosphatase (45%), elevated serum creatinine (43%), thrombocytopenia (38%), elevated ALT (36%), elevated INR (33%), and leukopenia (33%).

Transient prolongation of PTT is a known class effect of ASOs. The prolongation of PTT stems from interaction of phosphorothioate oligonucleotides with thrombin.[60] This effect is highly blood-level related; hence, it is typically maximal at the end of a short infusion (e.g., 2-hour infusion) and during the Loading Dose Period (three infusions in 5-9 days), when high levels of ASOs can be attained. The PTT prolongation diminished in parallel with the decline in plasma levels, such that it was largely recovered by 24 hours after the infusion. There was no evidence of an increase in bleeding events.

Lymphopenia, also a known class effect of ASOs, was seen in 93% of patients receiving OGX-427 as monotherapy and was Grade 3 or 4 in 36% of the patients. There were no clinical sequelae.

The incidence of all Grade 3 or higher laboratory AEs by cohort is shown in Table 2. Three patients in the monotherapy cohorts had Grade 4 AEs, including hyponatremia and lymphopenia (Cohort 1: two patients), and thrombocytopenia and neutropenia (Cohort 3: one patient).

Table 2: Number (%) of Patients with at Least One Grade 3 or 4 Laboratory Value on Study: Safety Population of Patients Receiving OGX-427 Monotherapy

	OGX-427 Monotherapy				
Event	**200 mg (N=6)**	**400 mg (N=7)**	**600 mg (N=7)**	**800 mg (N=8)**	**1000 mg (N=14)**
Overall	2 (33%)	4 (57%)	5 (71%)	8 (100%)	10 (71%)
Hematology	2 (33%)	2 (29%)	4 (57%)	6 (75%)	7 (50%)
Lymphopenia	2 (33%)	2 (29%)	2 (29%)	5 (63%)	4 (29%)
Leukopenia	0 (0%)	0 (0%)	2 (29%)	0 (0%)	0 (0%)
Neutropenia	0 (0%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)
Anemia	0 (0%)	0 (0%)	0 (0%)	2 (25%)	4 (29%)
Thrombocytopenia	0 (0%)	0 (0%)	1 (14%)	1 (13%)	1 (7%)
Coagulation	1 (17%)	2 (29%)	2 (29%)	5 (63%)	6 (43%)
Prolonged PTT	0 (0%)	1 (14%)	2 (29%)	5 (63%)	6 (43%)
Elevated INR	1 (17%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Serum Chemistry	1 (17%)	1 (14%)	3 (43%)	3 (38%)	6 (43%)
Hyponatremia	1 (17%)	1 (14%)	1 (14%)	2 (25%)	1 (7%)
Hypokalemia	0 (0%)	0 (0%)	1 (14%)	0 (0%)	3 (21%)
Elevated Serum Creatinine	0 (0%)	0 (0%)	1 (14%)	1 (13%)	1 (7%)
Elevated Bilirubin	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (7%)

	OGX-427 Monotherapy				
Event	200 mg (N=6)	400 mg (N=7)	600 mg (N=7)	800 mg (N=8)	1000 mg (N=14)
Elevated Alkaline Phosphatase	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (14%)
Elevated AST	0 (0%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)
Elevated ALT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)

Twenty-six serious adverse events (SAEs) were reported among 20 patients treated with OGX-427 monotherapy. SAEs were reported for 48% of patients receiving OGX-427 monotherapy and 45% of patients receiving OGX-427 plus docetaxel. Among patients treated with OGX-427 monotherapy, SAEs reported for more than one patient included: dyspnea (4 patients), disease progression (4 patients) and blood creatinine increased (2 patients). All remaining SAEs were reported for 1 subject each. Refer to the Investigator's Brochure for more information about SAEs classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and for SAEs among patients receiving OGX-427 plus docetaxel.

Within the total study population, 56 patients (88%) have died. The cause of death was progressive disease for 52 of the 56 subjects (93%). Four subjects died due to other causes, including bilateral upper extremity venous thrombosis, pancreatic cancer, tumor bleeding following right hip gamma nail placement for pathological fracture, and cardiopulmonary arrest. The Investigators considered these deaths to be unrelated to treatment with OGX-427.

1.6.3. Cardiac Repolarization

There was no evidence for prolongation of the QTcF interval or change in electrocardiogram (ECG) morphology.

1.6.4. Complement

Levels of complement split products (Bb, C3a, and C5a) were evaluated following three loading doses and on Day 1 of each cycle immediately following the infusion of OGX-427. There was a significant correlation between the pre- and post-time-weighted ratios of all three complement fragments and the dose of OGX-427. Activation of the alternative pathway/amplification loop of complement (C3a and Bb) was apparent at low doses of OGX-427, whereas activation of the terminal pathway (C5a) did not become apparent until the highest doses. Cohorts where docetaxel was combined with OGX-427 appeared to generate lower levels of complement, presumably due to the concomitant use of steroid prophylaxis for docetaxel. There was no apparent relationship between the time-weighted ratios of complement and the incidence of infusion reactions. There was no evidence for an increase in significant bleeding events.

1.6.5. Efficacy Outcome Measures

Biological activity of OGX-427 when used as monotherapy was observed at doses ≥400 mg by measurable disease response, decrease in tumor markers (prostate and ovarian) and decline in circulating tumor cells (CTCs).

1.6.5.1. Measurable Disease

Efficacy data are available for 53 of the 59 patients. Forty-eight of the 53 patients had measurable disease at baseline. Thirty patients had baseline and at least one post-baseline assessment of measurable disease.

Eight of the 30 patients (27%) had a decrease in measurable disease from baseline of at least 15%. For patients treated with OGX-427 monotherapy, three patients had tumor reductions: one patient with prostate cancer (Cohort 4) had a reduction of 25%; one with breast cancer (Cohort 2) had a reduction of 23%; and one with lung cancer (Cohort 5) had a reduction of 21%. For patients treated with OGX-427 plus docetaxel, five patients had tumor reductions: one patient with prostate cancer (Cohort 7) met the definition for a partial response (35%) and two had reductions of 19% and 23%; two patients with lung cancer (Cohort 7) had reductions of 19% and 87%.

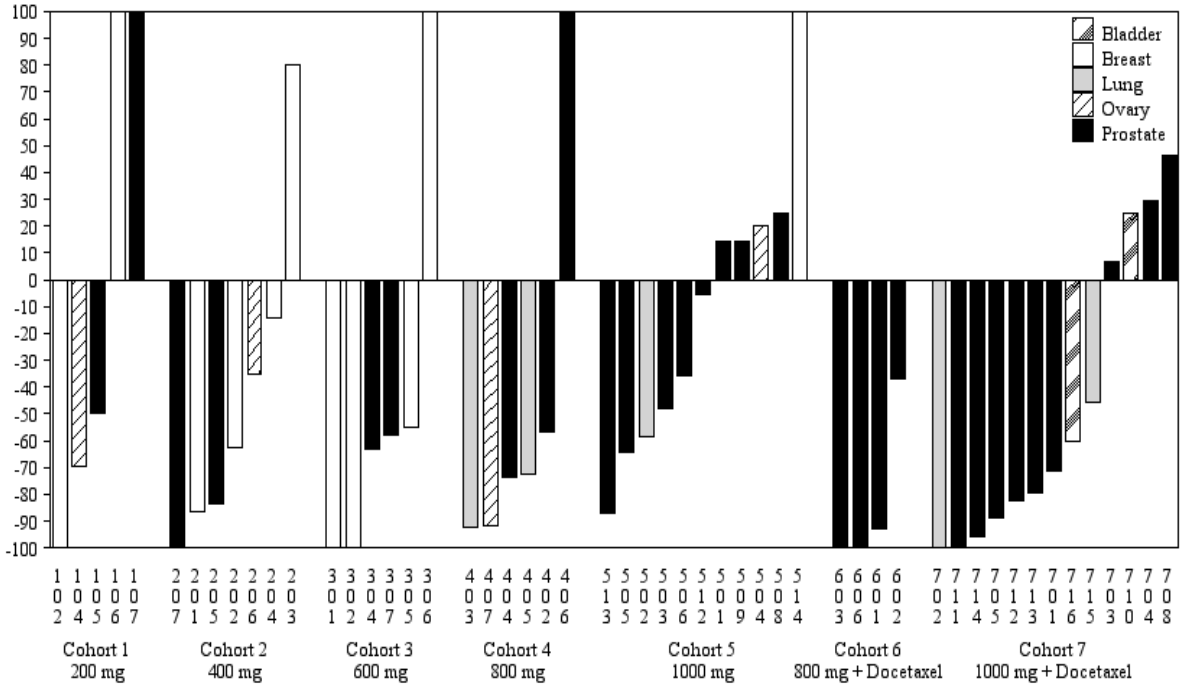
Thirty-three of 36 patients with prostate cancer had at least one post-baseline PSA assessment. Three of 21 patients in the monotherapy cohorts had reductions in PSA ≥30% as did six of twelve patients in the combination therapy cohorts.

1.6.5.2. Circulating Tumor Cells

Blood for total CTCs and Hsp27+ CTCs was collected at screening, prior to the first loading dose, and prior to drug administration on Cycles 1, 2, 3, and 5. On average, 75% of the baseline total CTCs were Hsp27+ CTCs. Total CTC data at baseline and at least once post-study drug administration were available for 55 of 59 patients and for 54 of 59 patients for Hsp27+ CTCs. Fourteen patients had Hsp27+ CTCs ≤5 /7.5 mL at baseline. Responses by CTC and Hsp27+ CTC assessment were documented in all diseases evaluated and at all dose levels. A best reduction in both total CTCs and Hsp27+ CTCs of ≥50% was seen in >50% of patients in all cohorts. Eighteen patients had a reduction of Hsp27+ CTCs to ≤5 /7.5 mL. There did not appear to be a dose response.

Figure 8 represents the number of patients in each cohort who demonstrated a decrease in Hsp27+ CTCs for each of the five disease categories.

Figure 8: Best Change in Hsp27+CTCs* by Disease Category & Cohort (in %)



1.6.6. Pharmacokinetics

Over the dose range of 200 mg to 1000 mg, there was a moderate non-proportional increase in both C_{max} and $AUC_{0\text{-inf}}$, a moderate decrease in plasma clearance, and a minor increase in plasma half-life value for OGX-427 with increasing dose. When OGX-427 was administered at the 800 mg or 1000 mg doses in combination with docetaxel (75 mg/m^2), there was no effect on the plasma pharmacokinetic parameters ($AUC_{0\text{-last}}$, volume of distribution, C_{max}) of OGX-427.

1.7. Phase II Clinical Study PR-01

Study PR-01 is a Phase 2, open-label, two-stage, randomized cross-over study designed to evaluate the anti-tumor effects of OGX-427 plus low-dose prednisone versus low-dose prednisone alone in men with CRPC who have not previously received chemotherapy for metastatic disease. This study is currently on-going. The primary endpoint is the proportion of patients without disease progression at 12 weeks after start of study treatment. The study also assesses the proportion of patients with a PSA decline and/or stable disease at the 12-week evaluation; measurable disease response; progression-free survival; time to disease progression; circulating tumor cells counts pre- and post-study drug; levels of Hsp27, clusterin, and other relevant proteins; and PTEN deletion status.

Patients are randomized to either a Treatment Arm or a Control Arm. Patients randomized to the Treatment Arm begin with three loading doses of 600 mg OGX-427 IV within 10 days, followed by weekly doses of 1000 mg OGX-427 IV along with 5 mg prednisone BID; patients randomized to the Control Arm receive 5 mg prednisone BID. Evaluations are conducted at 4-week intervals and disease assessments at weeks 12, 24, and 36 or until

disease progression. Patients who are withdrawn from study treatment for a reason other than disease progression are followed every 4 weeks until disease progression.

The first stage of the study will accrue 18 subjects per arm. If one patient or more on the Treatment Arm has a response or stable disease at 12 weeks, the second stage will enroll an additional 14 evaluable patients on each arm (total of 32 subjects per arm), for a total of 64 evaluable patients in both arms. Patients on the Treatment Arm with PSA progression in the absence of progression by imaging or need for radiotherapy may continue therapy up to a maximum of 24 weeks or until disease progression. Patients on the Treatment Arm who have a documented response (not stable disease) at the 24-week evaluation can continue to receive an additional 24 weeks of therapy (or until disease progression). Patients on the Control Arm with a response or stable disease at the 24-week evaluation may continue on treatment until disease progression. After documentation of disease progression, patients on the Control Arm have the option to cross-over to receive OGX-427 plus prednisone per the Treatment Arm.

1.7.1. Patient Disposition and Demographics

As of the cutoff date of January 17, 2012, 37 patients have been enrolled on the study. Safety and efficacy data are available for the first consecutive 32 patients (17 in the Treatment Arm and 15 in the Control Arm). Eight patients in each arm have been withdrawn from study treatment. In the Treatment Arm, patients have been withdrawn for adverse events (4 patients; events include grade 3 thrombocytopenia and grade 1 renal insufficiency; grade 3 elevated creatinine due to hemolytic uremic syndrome; grade 2 dyspnea and grade 3 fatigue; and grade 1 elevated creatinine); withdrawal of consent (2 patients); disease progression (1 patient); and other (1 patient). In the Control Arm, patients have been withdrawn for disease progression (7 patients) and death (1 patient). Five patients on the Control Arm had disease progression and crossed over to the Treatment Arm.

The median age of patients is 67 years on the Treatment Arm and 72 years on the Control Arm. All patients had an ECOG status of 0 or 1. Baseline patient characteristics are shown in the table below.

Table 3: Baseline Patient Characteristics

Parameter	OGX-427 + Prednisone (N=17)	Prednisone (N=15)
Age: median (range)	67 (53-86)	72 (62-89)
PSA: median (range)	66 (6-260)	58 (6-606)
Hemoglobin: median (range)	135 (118-157)	130 (104-152)
ECOG		
0	13 (76%)	8 (53%)
1	4 (24%)	7 (47%)
Disease sites:		
Bone	13 (76%)	11 (73%)
Liver	0 (0%)	1 (7%)
Lung	2 (12%)	0 (0%)
Lymph Node	8 (47%)	10 (67%)
Gleason Score:		
≤7	9 (53%)	6 (40%)

>7	7 (41%)	8 (53%)
Not available	1 (6%)	1 (7%)
Lactate Dehydrogenase >ULN	6 (35%)	2 (13%)
Alkaline Phosphatase >ULN	5 (29%)	2 (13%)
Prior Prednisone Therapy: Yes	6 (35%)	4 (27%)
Circulating Tumour Cells:		
Median, /7.5 mL (Range)	15 (2-72)	25 (3-273)
≥5 /7.5 mL	14 (82%)	13 (87%)

1.7.2. Adverse Events

Overall, 94% of patients on Treatment Arm and 80% on the Control Arm experienced at least one treatment-emergent AE. The majority of AEs were grade 1 or grade 2, occurring in 69% of patients on the Treatment Arm and 75% patients on the Control Arm who experienced AEs. Refer to the Investigator's Brochure for a complete list of all adverse events.

The most frequently reported non-laboratory AEs in the Treatment Arm were chills, diarrhea, nausea, and fatigue; in the Control Arm the most frequent non-laboratory AEs were back pain, muscle spasm, and decreased appetite. There were 10 grade 3 or 4 non-laboratory AEs in 5 patients. Three patients in the Treatment Arm experienced 6 grade 3 non-laboratory AEs [fatigue (2), agitation (1), anxiety (1), hematuria (1), and presyncope (1)] and 2 grade 4 AEs (dizziness and pulmonary embolism). Two patients in the Control Arm experienced grade 3 or 4 AEs (1 grade 3 AE of cystitis and 1 grade 4 AE of spinal cord compression).

The most common laboratory AEs consisted of lymphopenia, anemia, and hyperglycemia. The majority of laboratory toxicities were grade 1 or 2 (76% of laboratory AEs in the Treatment Arm and 80% in the Control Arm). Seven Grade 3 or 4 laboratory AEs were experienced by patients on the Treatment Arm (lymphopenia [3], and hyperglycemia, elevated creatinine, thrombocytopenia, and hyponatremia [1 each]). One patient on the Treatment Arm developed grade 4 hemolytic uremic syndrome at week 7. Three Grade 3 or 4 laboratory AEs were experienced by patients on the Control Arm, including lymphopenia (2) and hyperglycemia (1).

Infusion Reactions

In the Phase 1 OGX-427-01 study, a high frequency of infusion reactions (>90%) was observed when some patients were given loading doses of 800 mg or 1000 mg and the only premedication administered was either ibuprofen or acetaminophen (compared to approximately 50% among subjects given loading doses ≤600 mg). In this protocol, the loading dose was fixed at 600 mg for all patients on the Treatment Arm, and all patients are receiving prophylactic premedication with a minimum of an antihistamine and an H2 blocker. As of January 17, 2012, infusion reactions to OGX-427 have been observed in 8 of 17 subjects (47%) on the Treatment Arm. The most common reactions were chills, flushing, diarrhea, nausea, and vomiting. There have been no treatment delays, and no doses of OGX-427 have been withheld. Four subjects (24%) had at least one infusion interrupted, and 2 administrations (12%) were discontinued due to infusion reactions.

Serious Adverse Events

As of January 17, 2012, a total of 8 SAEs have been reported in 6 patients treated with OGX-427: 7 events in the Treatment Arm and 1 event in a Control Arm patient who had crossed over to receive OGX-427 treatment on the Crossover Arm.

The SAEs in the Treatment Arm consisted of:

- Hemolytic uremic syndrome (HUS): A patient presented with grade 3 elevated creatinine, grade 3 anemia, and grade 1 thrombocytopenia after receiving 3 loading doses and 7 weekly doses of 1000 mg OGX-427. The diagnosis of grade 4 hemolytic uremic syndrome was confirmed by renal biopsy and described by the investigator as probably related to OGX-427. The patient required hemodialysis which is ongoing. The patient presented with a second SAE of gross hematuria on day 144 which was described by the investigator as not related to OGX-427. No other cases of HUS have been observed with OGX-427.
- Gross hematuria and recurrent hematuria: A patient with a history of prostate cancer and pelvic irradiation prior to study entry presented with grade 3 gross hematuria on study day 193 and with recurrent grade 3 hematuria on study day 288, both described by the investigator as not related to OGX-427. The patient remained on study treatment until day 302. The cause of bleeding was later confirmed at cystoscopy as diffuse ulcerative and hemorrhagic cystitis consistent with radiation cystitis.
- Atrial fibrillation: A patient presented with grade 2 atrial fibrillation on study day 22 with resolution within 24 hours. The patient continued on study treatment through day 57.
- Renal insufficiency due to dehydration and thrombocytopenia: A patient with a history of idiopathic vasculitis purpura managed with corticosteroids one year prior to study entry received 2 loading doses of OGX-427 and developed skin lesions consistent with recurrent vasculitic purpura concurrent with thrombocytopenia, peripheral edema, and poor oral intake resulting in dehydration. He was started on prednisone with resolution of the skin lesions and thrombocytopenia. The events were described by the investigator as probably related to OGX-427.
- Dizziness and shortness of breath: A patient developed grade 4 dizziness and grade 2 shortness of breath 10 days after discontinuation of study drug on day 66 for unacceptable toxicity (grade 1 confusion). The dizziness was described by the investigator as possibly related to OGX-427 and prednisone, and the shortness of breath was described as unrelated.

The SAE in the Crossover Arm consisted of:

- Bladder infection: A patient developed a grade 3 bladder infection on day 14 which resolved within 72 hours.

Deaths

One subject in the Control Arm has died from disease progression.

1.7.3. Efficacy Evaluations

The primary endpoint for the study is the proportion of subjects without disease progression at 12 weeks after start of study treatment. Disease progression is defined by any of the following: an increase in PSA per the Prostate Cancer Working Group 2 criteria;[61] measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[62] on CT scans; ≥2 new bone lesions on bone scan; disease-related global or severe deterioration of health status; or need for palliative radiation therapy. As of January 17, 2012, 14 patients in the Treatment Arm and 12 patients in the Control Arm were evaluable for disease progression on or prior to week 12. Ten of 14 (71%, 95% CI: 42-92%) patients in the Treatment Arm and 4 of 12 (33%, 95% CI: 10-65%) patients in the Control Arm had no documented disease progression at 12 weeks.

PSA Response

Of the first 32 evaluable patients, all had a baseline and at least one post-baseline PSA value. Ten of 17 (59%) patients on the Treatment Arm had at least a 30% decrease in PSA, compared to 5 of 15 (33%) patients on the Control Arm.

Measurable Disease

Eight patients on the Treatment Arm and 9 patients on the Control Arm had measurable disease at baseline. As of January 17, 2012, 3 (38%) patients on the Treatment Arm achieved a partial response, 1 (13%) had stable disease, and it was too early to evaluate disease progression in 4 (50%) patients. No patient in the Treatment Arm had disease progression. Among patients on the Control Arm, 4 (44%) had achieved stable disease and 2 (22%) had disease progression; it was too early to evaluate the remaining 3 (33%) patients.

Circulating Tumor Cells (CTCs)

Blood for both total and Hsp27+ CTCs was collected at screening and weeks 1, 5, 9, and 13. CTCs at baseline and at least once post-study treatment were available for 14 of 17 patients in the Treatment Arm and 13 of 15 in the Control Arm. Approximately 70% of the total CTCs were Hsp27+ at baseline. Among evaluable patients, 7 of 14 (50%) patients on the Treatment Arm and 4 of 13 (31%) patients on the Control Arm had a best total CTC change from baseline of ≥5 to <5 CTCs/7.5 mL. No patient had a change from <5 to ≥5 CTC/7.5 mL.

2. RATIONALE

2.1. Rationale for the Study

Many cancers, including prostate cancer, result in the increased expression of Hsp27, one of the heat shock proteins that are highly conserved and whose expression is induced by cell stress, including cytotoxic chemotherapy, radiation therapy and hormone therapy. Hsp27 has been shown to interact with key apoptosis-associated proteins and functions to inhibit apoptotic cell death through multiple pathways by a variety of mechanisms. In particular for prostate cancer, Hsp27 has been implicated in both ligand-dependent and -independent androgen receptor signaling. Given the redundancy that exists in cancers and their heterogeneity, targeting Hsp27 is attractive as a cancer therapy as it should result in down-regulation of multiple pathways implicated in cancer progression and development of resistance.

OGX-427 is a second-generation ASO that inhibits expression of Hsp27. A number of in vitro and in vivo pharmacological studies have demonstrated that OGX-427 (or a sequence equivalent Hsp27 ASO) has single agent activity in reducing Hsp27 mRNA, inhibiting cell growth and inducing apoptosis in several human cancer cell lines. OGX-427 has also demonstrated chemosensitizing activity both in vitro and in vivo in combination with several cytotoxic drugs, including docetaxel. In preclinical studies, OGX-427 or the first-generation Hsp27 ASO was tested alone or in combination with other drugs in various animal tumor models. Nonclinical toxicology results indicated that OGX-427 has a reasonable safety profile.

The Phase 1 clinical study was developed to evaluate the safety profile, determine the maximum tolerated dose, characterize the pharmacokinetic profile, and evaluate the efficacy of OGX-427 when administered as a single agent and when administered in combination with taxane chemotherapy (i.e., docetaxel). Enrollment into cohorts evaluating the combination of OGX-427 and docetaxel was also performed. Findings from this study support that OGX-427 has a reasonable safety profile in humans. A maximum tolerated dose was not reached. The highest dose of 1000 mg OGX-427 was well tolerated; however, prophylactic medications for potential infusion reactions appear to be indicated, at least for some patients, due to infusion reactions requiring treatment and subsequent prophylaxis with high-dose steroids at OGX-427 doses ≥800 mg.

As patients on abiraterone acetate without clinical progression continue treatment even in the event of PSA progression, this presents an opportunity to assess novel combinations with abiraterone acetate. This clinical study was designed as an open label, randomized Phase II clinical study to evaluate the effect of adding OGX-427 to ongoing standard therapy with abiraterone acetate and prednisone in men with metastatic CRPC who have evidence of PSA progression but no clinical evidence of symptomatic or radiographic progression. Given the variability of outcomes in different populations and the lack of consistent historical data on progression-free survival rates in this clinical situation, randomization to a control arm where patients continue standard therapy with abiraterone acetate and prednisone alone is required in order to put the results of the experimental arm into context. Patients in the control arm will be allowed to cross over to receive OGX-427

at disease progression, if eligible after a re-screening evaluation (i.e., all inclusion and exclusion criteria have been met).

2.2. Rationale Supporting Drug Dose Selection and Duration

A maximum tolerated dose for administering OGX-427 as a single agent was not reached in the Phase I trial (OGX-427-01) that evaluated doses up to a maximum of 1000 mg. OGX-427 appears to have an acceptable safety profile as a single agent up to a 1000 mg dose, which is the dose selected to be utilized in this Phase II study. The major non-laboratory toxicities among patients receiving OGX-427 monotherapy in the Phase I trial were infusion reactions (hypertension, influenza-like illness, rigors, pruritus, flushing, pyrexia, and erythema), observed in 76% of patients, with increased frequency and severity at the highest doses (800 mg and 1000 mg). Almost all infusion reactions (>95%) were Grade 1 or 2 and mainly occurred during the loading doses and Cycle 1. Only 6.3% of infusions were interrupted and 2.8% of infusions were delayed or discontinued due to reactions. Prophylaxis with ibuprofen or acetaminophen was required per protocol for a 24-hour period on infusion days during the loading dose period only, in an attempt to decrease the rigors and fevers often associated with administration of ASOs. However, despite this, many reactions required treatment with antihistamines, H2 antagonist and steroids, and some patients required steroid prophylaxis for repeated infusion reactions.

In the Phase II study (Study PR-01), the three loading doses of OGX-427 were decreased to 600 mg in an attempt to decrease the incidence and severity of infusion reactions. Thereafter, weekly dosing of OGX-427 was at the 1000 mg dose. In addition, prophylactic premedications (an antihistamine and H2 antagonist) were administered prior to each dose of OGX-427.

Results available from Study PR-01, based on 37 randomized patients, suggest that the 600 mg loading dose is better tolerated than higher doses when accompanied by premedication with a minimum of an antihistamine and an H2 blocker. As of January 17, 2012, infusion reactions to OGX-427 have been observed in 8 of 17 subjects (47%) on the Treatment Arm. The most common reactions were chills, flushing, diarrhea, nausea, and vomiting. There have been no treatment delays, and no doses of OGX-427 have been withheld. Four subjects (24%) had at least one infusion interrupted, and 2 administrations (12%) were discontinued due to infusion reactions.

The “mechanism of action” for OGX-427 is in part through effects on androgen receptor (AR) signaling, and measures of PSA, as an AR-regulated gene, would reflect OGX-427 efficacy. However, since PSA is an imperfect marker of disease progression, patients with PSA progression as best response will be allowed up to 24 weeks of this experimental therapy in the absence of other indicators of clinical progression to evaluate for a late response or for slowed progression. Due to limited drug supply at this time, responders will be limited to 48 weeks (12 cycles) of therapy.

2.3. Rationale Supporting Evaluation of Other Relevant Proteins

The purpose of the serum and plasma samples is to assess changes in Hsp27 and clusterin levels and to explore other proteins (e.g., other Hsp family members and their client proteins) and cancer-associated microRNA (e.g., miR-141, miR-126) to explore as

biomarkers that may emerge as prognostic or predictive factors in prostate cancer. Germline DNA will not be evaluated.

3. STUDY OBJECTIVES

Patients will be randomized with equal probability to one of two arms, designated as the Experimental Arm (A) and the Control Arm (B). The intended intervention in Arm A is continued use of abiraterone and prednisone plus the addition of OGX-427.The intended intervention in Arm B is continued use of abiraterone and prednisone.

3.1. Primary Objective

The primary objective for this study is progression-free survival at the milestone Day 60 assessment: to ascertain whether Arm A has a greater proportion of patients observed to be alive without progression as compared to Arm B.

3.2. Secondary Objectives

The secondary objectives are based on comparing the arms with respect to the following outcomes:

1. The proportion of patients who have a PSA response (≥30% decline) and any PSA decline post-randomization
2. Objective response
3. Progression-free survival (PFS)
4. Time to disease progression (see Section 6.4.1)
5. Circulating tumor cell (CTC) counts at baseline and on study
6. Levels of Hsp27, clusterin, and other relevant proteins at baseline and during study
7. PTEN deletion status in original pathology specimens correlated with clinical outcomes

4. STUDY DESIGN OVERVIEW

4.1. Study Design

This is an open-label, randomized, Phase II clinical trial designed to evaluate the anti-tumor effects of OGX-427 and continuing abiraterone acetate and prednisone versus continuing abiraterone acetate and prednisone alone in men with metastatic CRPC who have evidence of PSA progression but no evidence of symptomatic or radiographic progression that would require alternative therapy (e.g., needing radiation therapy for pain or significant progression of visceral metastases).

Stratified randomization will be used in order to minimize between-arm imbalance using the following stratification factors: prior chemotherapy (yes versus no), and prior PSA response >30% to abiraterone acetate (yes versus no). Individuals in the Control Arm will have the option to cross-over to receive OGX-427 as per the Experimental Arm schedule after documented disease progression if they continue to meet eligibility criteria.

Figure 9: Study Design

<table>
<tr>
<td>Screening Period
Day – 28 to Randomization</td>
<td>Randomization</td>
<td>Experimental Arm (Arm A):
OGX-427 Starting within 7 days of randomization, three loading doses at 600 mg IV within Week 1 if possible (up to the first 10 days of initiating treatment), followed by weekly doses of 800 mg IV
Continuation of standard therapy with abiraterone acetate 1000 mg PO daily and prednisone 10-20 mg PO daily

Control Arm (Arm B):
Continuation of standard therapy with abiraterone acetate 1000 mg PO daily and prednisone 10-20 mg PO daily

After documented disease progression, patients on the Arm B may opt to receive OGX-427 treatment (according to the Arm A schedule) following a screening evaluation (i.e., all inclusion and exclusion criteria have been met).</td>
<td>Both Arms:
Evaluations at 4 week-intervals. Disease assessments required at the milestone Day 60 assessment (expected to occur after 8 weeks of treatment and prior to Day 1, Week 9) and at 16, 24, 32, 40, and 48 weeks (if applicable) or until documented disease progression. Patients who are withdrawn from the study for a reason other than documented disease progression (Section 6.4.1) or patient withdrawal of consent will be followed every 4 weeks in the Off-Treatment Follow-up Period until documented disease progression.</td>
<td>End of Study Treatment</td>
<td>Off-Treatment Follow Up Period for disease progression (if applicable)</td>
</tr>
</table>

4.2. Study Treatment

The term, "Study Treatment," as used throughout the protocol, refers to general study-related procedures including the administration of abiraterone and prednisone (for patients on both study arms) and OGX-427 (for patients on the Experimental Arm only). Control Arm patients who "cross-over" to Experimental Arm intervention will follow the Experimental Arm schedule as outlined in this protocol. Regardless of study arm, all patients must begin study-related procedures within 7 days following randomization.

4.2.1. Experimental Arm: OGX-427 plus Abiraterone Acetate and Prednisone Continuation

4.2.1.1. Abiraterone acetate

Per inclusion criteria, patients should already be receiving abiraterone acetate at 1000 mg orally on a daily schedule. Abiraterone should be continued throughout the study unless discontinuation is required for toxicity or documented disease progression. Abiraterone usage must be adequately documented.

4.2.1.2. Prednisone

Per inclusion criteria, patients should already be receiving prednisone (10-20 mg PO/day). Prednisone should be administered at the same dose throughout the study unless dose modification or discontinuation is required for toxicity. Prednisone usage must be adequately documented.

4.2.1.3. OGX-427

OGX-427 Loading Dose Period

Patients randomized to the Experimental Arm will receive OGX-427 in addition to abiraterone and prednisone. The schedule of administration of OGX-427 begins with three loading doses. The first loading dose of OGX-427 should be administered within 7 days following randomization. The day on which the first loading dose is given will be considered Day 1, Week 1.

The three loading doses of 600 mg of OGX-427 will be administered IV over 2 hours during Week 1, if possible (up to 10 days of initiating treatment). There must be at least one "non-infusion" day between each administration of OGX-427 (i.e., every other day) during the Loading Dose week and between the third loading dose of OGX-427 and the Day 1, Week 2 dose of OGX-427 that initiates weekly OGX-427 administration. Note: If the third loading dose or the Day 1, Week 2 dose is delayed, subsequent weekly administration will continue based on the actual Day 1, Week 2 administration date.

Weekly Administration of OGX-427

Following completion of the Loading Dose Period, 800 mg OGX-427 will be administered weekly (IV over 2 hours, every 7 days +/- 2 days) during the OGX-427 Treatment Period. The day on which the first weekly dose of OGX-427 is given will be considered Day 1, Week 2. Patients will be evaluated in the clinic every 4 weeks. Disease assessments will

occur every 8 weeks or as indicated. Treatment with OGX-427 and abiraterone/prednisone will continue until disease progression is documented or another End of Study Treatment Criterion is met (Section 5.5). Patients who fulfill the criteria for either PSA response (per Section 6.4.2.2, ≥30% decline) or objective disease response (not stable disease) at Week 24 will receive 600 mg OGX-427 (rather than 800 mg) from Week 25 through Week 48 or until meeting an End of Study Treatment Criterion.

Patients who are removed from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in the study will be followed every 4 weeks in the Off Treatment Follow-Up Period until the date of documented disease progression.

4.2.1.4. Premedications for OGX-427

Patients on the Experimental Arm should be premedicated with an H2 antagonist, e.g., Ranitidine (150 mg PO or 50 mg IV) and an antihistamine, e.g., diphenhydramine (25-50 mg) It is recommended that these premedications be administered 30-90 minutes prior to infusion unless there is a medical reason they cannot receive one or more of the drugs (see Section 6.7.3).

If a patient manifests a Grade 2 or greater adverse event(s) during or subsequent to an infusion of OGX-427, despite the above premedications, treatment should follow Institutional Guidelines; recommendations, including the use of steroids, are available in Section 6.6.6/Table 11.

Following treatment with steroids (i.e., 8 mg of dexamethasone) on more than one occasion for a Grade 2 or greater adverse event associated with an infusion, the patient should receive 8 mg dexamethasone as prophylaxis in addition to continued premedication with an H2 antagonist and an antihistamine for a minimum of 12 weeks, or longer if necessary.

4.2.2. Control Arm: Abiraterone Acetate and Prednisone Continuation

4.2.2.1. Abiraterone acetate

Patients will continue on abiraterone acetate as per package insert and standard of care. Approved dosing of abiraterone acetate is 1000 mg orally daily on an empty stomach (1 hour before or 2 hours after a meal). Abiraterone should be continued throughout the study unless discontinuation is required for toxicity or documented disease progression. Abiraterone usage must be adequately documented.

4.2.2.2. Prednisone

Prednisone must be given with abiraterone acetate. The standard dosing of prednisone with abiraterone acetate is a total daily dose of 10-20 mg/day orally. Prednisone should be administered at the same dose throughout the study unless dose modification or discontinuation is required for toxicity. Prednisone usage must be adequately documented.

Patients who are withdrawn from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in the study will be

followed every 4 weeks until documented disease progression during the Off-Treatment Follow-up Period.

4.2.2.3 Missed or Delayed Evaluations (Control Arm)

If an every 4 week evaluation is missed or delayed, the next evaluation should continue on the original schedule. For example, patient misses their week 9 evaluation and comes in on week 10 for week 9 assessment, the next evaluation will occur in 3 weeks in order to keep on the original scheduled timeline.

4.3. Number of Patients

Approximately 80 patients will be screened in order to randomize 74 patients to the study (37 patients per arm).

4.4. Number of Clinical Sites

Approximately 12-15 sites will participate in Canada and the United States.

4.5. Estimated Duration/Completion of Study

Completion of accrual is projected for ≤18 months after all sites are activated, based on an accrual rate of approximately 4 patients per year per site.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Enrollment of Patients

Each potential patient will be provided with an informed consent form that has been reviewed and approved by the site's governing Institutional Review Board (IRB) or Research Ethics Board (REB). In accordance with the International Conference on Harmonization (ICH) guidelines on informed consent, the Principal Investigator (or designee) will provide potential patients with a verbal description of the study including, but not limited to, study purpose, study procedures, risks, and benefits. Potential patients will be asked to read the consent form and to sign and date it once all of their questions have been answered and they voluntarily agree to participate in the study. A copy of the signed informed consent form will be provided to the patient.

Upon obtaining signed informed consent, each patient will undergo the screening procedures outlined in Section 6.2.1. A screening log will be maintained by the site and will include documentation of screening failures. Patients meeting all inclusion/exclusion criteria will then be randomized to have OGX-427 added to their abiraterone/prednisone therapy or to continue abiraterone/prednisone therapy alone (see Section 6.2.2). All patients are considered enrolled once randomized.

5.2. Registration Procedures

All patients must be registered through Hoosier Cancer Research Network's Electronic Data Capture (EDC) system.

Detailed guidelines for patient registration and electronic case report form (eCRF) completion can be found in the Study Procedures Manual (SPM) associated with this protocol.

Patients must be registered prior to starting protocol therapy and begin protocol therapy within 7 calendar days after randomization.

Randomization will occur immediately after registering a patient.

5.3. Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for inclusion into the study.

1. ECOG performance status of 0 or 1
2. Histological or cytological diagnosis of adenocarcinoma of the prostate
3. Metastatic disease on chest, abdominal, or pelvic CT scan and/or bone scan
4. Currently receiving abiraterone acetate and prednisone and meeting the following criteria:
    a. Any PSA decline within 12 weeks from initiation of abiraterone
    b. Currently tolerating abiraterone acetate (1000 mg oral daily) and prednisone (10-20 mg oral daily)
    c. PSA progression, defined as an increase in PSA which is ≥25% above the nadir and an absolute value of ≥2 ng/mL, which is confirmed by a second value ≥2 weeks later.
    d. No evidence of symptomatic or radiographic progression that would require alternative therapy (e.g., needing radiation therapy for pain or significant progression of visceral metastases or >33% increase in daily opioid use within 2 weeks prior to randomization)
5. All patients who have not had a surgical orchiectomy must continue treatment with LHRH agonist or antagonist to maintain a castrate level of testosterone.
6. Patient must fulfill “Prior Therapy” criteria as follows:
    a. Chemotherapy: no more than 1 prior chemotherapy regimen for CRPC is permitted; a minimum of at least 28 days must have passed since the last dose of chemotherapy.
    b. Hormone therapy: hormonal androgen ablation therapy prior to abiraterone is required.
    c. Experimental therapy: prior non-cytotoxic experimental therapy is permitted provided a minimum of at least 14 days has passed since completing therapy. Prior treatment with MDV3100 is allowed.
    d. Radiation: prior external beam radiation is permitted provided a minimum of at least 14 days have passed since completing radiotherapy (exception for radiotherapy: at least 7 days since completing a single fraction of ≤800 cGy to a restricted field or limited-field radiotherapy to non-marrow bearing area such as an extremity or orbit) at the time of randomization

7. Baseline laboratory values as stated below:
    a. ANC ≥ 1.5 x 10^9 cells /L, platelet count ≥ 100 x 10^9 /L, and hemoglobin ≥ 9 g/dL without transfusion
    b. Creatinine ≤ 1.3 x upper limit of normal (ULN)
    c. Total bilirubin ≤ 1.1 x ULN (unless elevated secondary to conditions such as Gilbert's disease, in which case a direct bilirubin ≤ ULN is required)
    d. SGPT (ALT) and SGOT (AST) ≤ 3.0 x ULN
    e. Castrate serum testosterone level (< 50 ng/dL **or** < 1.7 nmol/L)
    f. Potassium within normal limits
8. Must be willing to use effective contraception throughout study treatment and for 3 months after completion of study treatment if able to father a child.
9. Must be willing not to change (add or subtract) bone protecting therapy (bisphosphonates and/or denosumab) during the study unless changed for toxicity.
10. Written informed consent must be obtained prior to any protocol-specific procedures being performed.
11. At least 14 days has passed since any major surgery and 5 days for minor surgery (i.e. port placement),

5.4. Exclusion Criteria

Subjects meeting ANY of the following exclusion criteria will NOT be eligible for inclusion into the study:

1. Currently receiving abiraterone acetate in combination with any other anti-cancer agent (except prednisone)
2. Documented brain metastases, or carcinomatous meningitis, treated or untreated (Brain imaging for asymptomatic patients is not required.)
3. Cord compression requiring surgery or radiation therapy while on abiraterone treatment
4. Active second malignancy (including lymphoid malignancies such as chronic lymphocytic leukemia or low grade lymphoma) defined, in general, as requiring anticancer therapy or at high risk of recurrence during the study; not including adequately treated non-melanomatous skin cancer or other solid tumors curatively treated with no evidence of disease in > 3 years
5. History of allergic reactions to therapeutic antisense oligonucleotides
6. Active autoimmune disease requiring treatment
7. Participated in a prior Phase 3 clinical study evaluating custirsen regardless of study arm assignment (i.e., either control or investigational arm), or prior exposure to OGX-427
8. Known LVEF <50% or NYHA Class III or IV heart failure

9. Uncontrolled medical conditions such as myocardial infarction, uncontrolled hypertension, stroke or treatment of a major active infection within 3 months of randomization, as well as any significant concurrent medical illness that in the opinion of the Investigator would preclude protocol therapy
10. Planned concomitant participation in another clinical trial of an experimental agent, vaccine, or device. Concomitant participation in observational studies is acceptable.

5.5. End of Study Treatment/Criteria for Withdrawal

Patients on the study should receive study treatment until disease progression or another End of Study Treatment criterion is documented. Patients should be withdrawn from study treatment **only for the following reasons**:

1. Documented progression of disease (Section 6.4.1)
   Note: Patients on the OGX-427 Experimental Arm with only PSA progression in the absence of other indicators for progression (by bone scan, CT, deterioration in ECOG performance status to Grade 3 or higher, or initiation of other treatments) may continue therapy up to a maximum of 24 weeks or until disease progression as defined in Section 6.4.1.2.
   Note: Patients on the Control Arm will be withdrawn from study if they are unable or unwilling to cross-over to receive OGX-427 after documented disease progression.
2. Unacceptable toxicity (toxicity that requires stopping study treatment)
3. Study treatment administration missed for more than 3 weeks (i.e., more than 4 weeks without study treatment)
4. Patient withdrawal of consent to continue participating in the study. Patients may withdraw from the study at any time, for any reason, without jeopardy to their current and future care.
5. Non-cancer related illness that in the view of the Investigator prevents continuation of study treatment
6. Completion of study treatment:
   a. Patients who have completed 24 weeks on the Experimental Arm and have stable disease or PSA only progression
   b. Patients who fulfill the criteria for disease response (not stable disease) and have completed 48 weeks on the Experimental Arm
   c. Patients on the Control Arm who have completed 48 weeks of treatment
7. Termination of study or of study drug supply by OncoGenex

Any patient withdrawn from study treatment for any reason must have the procedures outlined in the End of Treatment Visit (Section 6.2.7). The reason(s) for withdrawal from study treatment must be recorded on the End of Treatment electronic case report form (eCRF). Patients from the Control Arm who are crossing-over to the Experimental Arm will have a repeat Screening Visit at the time of cross-over instead of an End of Treatment Visit.

Note: Only patients on the Control Arm who remain on study treatment until disease progression will be allowed to cross-over to receive OGX-427 treatment. If disease progression is by PSA or bone scan only, confirmation of progression must be documented.

All patients will be followed for disease progression.

6. STUDY EVALUATIONS AND PROCEDURES

6.1. Schedule for Evaluations and Procedures

Table 4 provides a summary of required evaluations and procedures. The 28-day interval for screening can be extended by 1-3 working days. Patients on the Experimental Arm should receive the first loading dose of OGX-427 within 7 calendar days following randomization. All patients in the Treatment and Control Arms should continue abiraterone acetate and prednisone therapies uninterrupted. Patients crossing over from the Control Arm to the Experimental Arm must begin treatment with OGX-427 within 8 weeks of documented disease progression.

Table 4: Evaluations and Procedures Schedule

Procedure		Screening period (up to 28 days + 1-3 days)	Randomization Period[a]	Week 1 Study Evaluations			Subsequent Weekly Study Evaluations				Milestone Disease Assessment	Disease Assessments	End of Treatment Visit (EOT)[b]	Off Treatment Follow up Period (until disease progression)
		Screening Visit(s)[a]		All three OGX-427 loading doses should occur during Week 1			Study evaluations will occur on Day 1 (-/+ 2 days) and will be repeated every 4 weeks for both arms unless otherwise indicated				Obtain CT and bone scans and PSA at Day 60 (±7 days)	Obtain CT and bone scans at 16, 24, 32, 40, and 48 wks (if applicable) or as indicated	Within 21 (±7) days of meeting EOT criteria	Every 4 weeks (±5 days)
				Day 1 Week 1 Both Arms	Treat-ment Arm Dose 2	Treat-ment Arm Dose 3	Week 2	Week 3	Week 4	Week 5				
Signed/dated informed consent		•												
Demographics, disease/medical history, concurrent illnesses		•		•[c]										
Physical exam including weight[d]		•								•			•	•
Vital signs: temp, HR, BP[e]		•		•	•	•				•			•	
ECOG performance score		•		•						•			•	•
Chest/abdomen/pelvic CT scans and bone scan[f]		•[g]									•	•	•[h]	•[h]
Concomitant medications[e]		•		•						•	•		•[i]	•[i]
Safety evaluation/ AE recording[e]				•	•	•				•			•[i]	•[i]
CBC and serum chemistry[j]		•		•[k]				•[j]		•			•	
LDH and Testosterone		•												
PSA[l]		•		•[k]						•	•		•	•
Original pathology report and specimen or slides[m]		•												
Blood for Hsp27/clusterin/other relevant proteins[n]		•		•						•			•	•
Blood for CTC assessment[o]		•		•						•				
OGX-427 Experimental Arm	Pre-dose: anti-histamine, H2 antagonist[p]			•	•	•	•	•	•	•				
	OGX-427 infusion (every 7 ± 2 days starting Week 2)			•	•	•	•	•	•	•				
Both Arms	Abiraterone (1000 mg) and Prednisone (10-20 mg PO daily)[q]		→											

Note:

Control Arm: Patients will begin study evaluations within 7 days after randomization (considered Day 1 of Week 1). Evaluations on Day 1 of Week 1 and every 4 weeks thereafter include: vital signs (temp, HR, BP), ECOG performance score, recording of concomitant medications and adverse events, safety evaluation, and blood for PSA, Hsp27, clusterin, other relevant proteins, CBC, and chemistry. Disease assessments are completed every 8 weeks (at the milestone Day 60 assessment and at weeks 16, 24, 32, 40, and 48) until disease progression or another End of Study Treatment criterion is met (Section 6.4.1). Blood for CTCs will be collected during screening and at Weeks 1, 5, 9, and 13 only. Patients who have disease-related deterioration in ECOG performance status to Grade 2 or higher are not eligible to cross-over. Control Arm patients will be allowed to cross over to receive OGX-427 treatment identical to the schedule in the Experimental Arm only after documented disease progression and if within 48 weeks from study randomization; these patients must continue to meet inclusion/exclusion criteria and obtain sponsor (or delegate) approval. For patients eligible to cross over, the first Loading Dose of OGX-427 must be administered within 8 weeks of the date of progression. Patients who are crossed over can continue to receive OGX-427 treatment until an End of Study Treatment criterion is met (Section 5.5). Patients who are withdrawn from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in the study will be followed every 4 weeks and have disease assessments every 8 weeks in the Off-Treatment Follow-up Period until documented disease progression. (Cross-over to the Experimental Arm is not allowed for Control Arm patients who progress in the Follow Up Period.) If a Control Arm patient does not cross-over to receive OGX-427 treatment, an EOT visit is needed.

Experimental Arm: The first loading dose of OGX-427 (600 mg) will begin within 7 days following randomization and is considered Week 1, Day 1. Loading doses must be completed within Week 1 if possible (up to the first 10 days of initiating treatment). Following the three loading doses, OGX-427 (800 mg) is administered once weekly. Weekly treatment (every 7 days ±2 days) will continue until disease progression is documented or another End of Study Treatment criterion is met (Section 5.5). Patients who are withdrawn from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in study will be followed every 4 weeks and have disease assessments every 8 weeks in the Off-Treatment Follow-up Period until documented disease progression. Experimental Arm patients (including cross-over patients) with PSA progression in the absence of other indicators for progression may continue therapy up to a maximum of 24 weeks, or until disease progression by imaging, need for alternative or additional therapy, or deterioration in ECOG performance status to Grade 3 or higher, whichever comes first (see Section 6.4.1.2). **Note:** Patients treated with OGX-427 who fulfill the criteria for PSA response (per Section 6.4.2.2., ≥ 30% decline) or objective disease response (not stable disease) at the 24-week will receive 600 mg of OGX-427 (rather than 800mg) from Week 25 through Week 48 for an additional 24 weeks or until meeting an End of Study Treatment Criterion.. All patients will be followed every 4 weeks for date of documented disease progression.

[a] All patients will have an initial screening visit. Control Arm patients who are being screened for cross-over to receive OGX-427 will need to repeat the physical exam, vital signs, weight, ECOG performance status, disease assessment, CBC, chemistries, PSA, blood sampling for Hsp27, clusterin, and other relevant proteins, and CTCs after documented disease progression. Eligibility worksheets must be submitted to the study sponsor (or delegate), forms can be found in the Study Procedures Manual.

[b] EOT visit indicated for patients who received OGX-427 per the Experimental Arm schedule and patients who were randomized to the Control Arm and will not cross-over to the Experimental Arm.

[c] Current health status and concurrent illnesses only

[d] Conduct a **complete** physical exam at screening (including weight). Physical exams done at 4 week evaluations and at the End of Treatment and Off Treatment Follow Up visits are limited to weight, signs and symptoms of disease or toxicity.

[e] Vital signs are required at the 4-week evaluation visits and at the EOT Visit. For Arm A patients, vital signs will also be required pre and post loading doses during the Loading Dose Period. Additional vitals, recording of AEs, and recording of any concomitant medications administered will be required if any signs and symptoms of an infusion reaction arise (e.g., chills, flushing, itching) during or immediately after OGX-427 infusion.

[f] If new clinical signs and symptoms of disease progression: repeat chest/abdominal/pelvic CT scans and bone scan. Disease progression is defined as one or more of the following: 1) PSA: **If a decline from baseline**: an increase of ≥ 25% and ≥ 2 ng/ml above the nadir confirmed by a second value 3 or more weeks later. **If no decline from baseline**: an increase of ≥ 25% and ≥ 2 ng/ml from baseline confirmed by a second value 3 or more weeks later (Disease progression based on an increase in PSA cannot be documented prior to Day 60 (8 weeks). Patients may continue therapy, at the discretion of the Investigator, if there is only progression by PSA and there are no other indicators of progression); 2) Measurable disease progression per RECIST 1.1; 3) Bone scan: ≥ 2 new lesions (if the first on study bone scan (at Day 60) shows ≥ 2 new lesions, this requires confirmation on a second scan ≥ 4 weeks later); 4) Non-measurable disease: unequivocal progression of existing non-target lesions on CT scan; 5) Disease related deterioration in ECOG performance status to Grade 3 or higher; 6) Need for palliative radiation therapy; 7) initiation of any cytotoxic, systemic anti-cancer therapy; 8) surgery for any complication due to disease progression; 9) Cancer pain requiring chronic administration of opiate analgesia (oral or parenteral) or a consistent increase >33% in daily opioid use from baseline.

[g] Chest/abdominal/pelvic CT scans and bone scans performed at the facility where subsequent scans will be performed are acceptable within 28 days prior to randomization and do not need to be repeated for inclusion/exclusion unless patient has developed new signs and symptoms of disease.

[h] For Experimental Arm patients: obtain chest/abdomen/pelvic CT scans and a bone scan at Day 60, weeks 16, 24, 32, 40, and 48, if applicable and within two weeks of the EOT Visit (if not performed within the last 8 weeks). If disease progression is not documented at EOT, perform chest/abdomen/pelvic CT scans and a bone scan every 8 weeks during the Off-Treatment Follow-Up Period until disease progression is documented.

[i] Concomitant medications and adverse events (graded using the CTCAE v.4.0) should continue to be collected for 30 days after last dose of OGX-427 or until event resolves to ≤Grade 2 or is assessed as chronic, or until the EOT visit for patients who did not receive OGX-427. Subsequent anti-cancer therapy administered during Off Treatment Follow-Up Period should also be recorded.

[j] CBC includes: WBC, ANC, lymphocytes, platelets, and hemoglobin. Serum Chemistry includes: electrolytes (Na, K, Cl, and CO_2), serum creatinine, AST, ALT, alkaline phosphatase, total bilirubin, and glucose. CBC and serum chemistries are to be performed at screening, prior to the first loading dose (see note k below), on Week 1, Day 1 of the Treatment Period (7 days after randomization for patients on both Arms), at Week 3, Day 1 (of the first Treatment Period only), at every 4-week interval evaluation during the treatment period, and at the EOT visit (**not required in Off Treatment Follow Up). Patients on Experimental Arm:** CBC and serum chemistry samples can be collected 24 hours prior to Day 1 to assure that no new safety concerns have arisen since the last assessment.

[k] PSA, CBC, and serum chemistries are not required at Week 1 if previously performed at screening ≤14 days prior to visit.

[l] PSA will be obtained at screening (one time within 14 days prior to randomization or cross-over), at Week 1, Day 1 (not required if performed within 14 days prior to visit), at the milestone Day 60 (±7 days) assessment, at every 4-week interval evaluation visit, at EOT, and at 4-week intervals in the Off-Treatment Follow-up Period (if indicated). Note that PSA assessments should be conducted at the same time points as CT and bone scans. For patients on Experimental Arm (including patients who cross-over): blood for PSA is to be drawn prior to receiving OGX-427.

[m] Obtain and redact a copy of the original prostate cancer pathology report to be placed in the patient's medical record. **Once the patient has been randomized**, arrange for a paraffin block (block preferred but unstained slides are acceptable) of their primary tumor diagnostic specimen to be sent to the address specified in Section 14.3. This is **required** for participation in the study, if available. Tissue will be returned if requested. Slides will not be returned.

[n] Blood for assays for Hsp27, clusterin, and other relevant proteins is to be drawn during screening for both arms, at Week 1, Day 1 and at every 4-week interval evaluation visit, at the EOT visit, and in the Off-Treatment Follow Up Period (if indicated) (See Section 14.3 for details). For patients on Experimental Arm (including patients who cross-over): blood for evaluating Hsp27, clusterin and other relevant proteins is to be drawn prior to receiving OGX-427.

[o] Blood for CTCs is to be drawn during screening for both arms and at Weeks 1, 5, 9, and 13 only. CTC samples must be collected and shipped on the same day. For patients on Experimental Arm (including patients who cross-over): blood for CTCs is to be drawn prior to receiving OGX-427.

[p] Premedications include: an H2 antagonist, e.g., Ranitidine (150 mg PO or 50 mg IV); and an antihistamine, e.g., diphenhydramine (25-50 mg). It is recommended that these premedications be administered 30-90 minutes prior to infusion unless there is a medical reason they cannot receive one or more of the drugs. Following the need for treatment with steroids (8 g of dexamethasone) on more than one occasion for a Grade 2 or greater adverse event associated with an infusion, the patient should receive dexamethasone (8 mg) in addition to premedication with an H2 antagonist and an antihistamine for a minimum of 12 weeks, or longer if necessary.

[q] Both Arms: abiraterone acetate (1000 mg daily) and oral prednisone (10-20 mg/day total dose) must be continued until the End of Treatment Visit unless discontinued for toxicity. Missed doses are not made up.

6.2. Detailed Description of Study Visits

6.2.1. Screening Visit for *Both* Arms

Screening evaluations must be completed in up to a 28-day period (i.e. from the first screening evaluation to randomization) unless otherwise specified. The 28 day interval for screening can be extended by 1-3 working days. The purpose of the screening period is to ensure that patients meet all enrollment criteria and adequately comprehend the protocol and its requirements. A screening log at each site will document all patients who provide informed consent and are evaluated for the study. More than one clinic visit may be required in order to complete all screening evaluations.

Prior to the conduct of any study-related procedures, the Investigator (or designee) will explain the study, answer all questions to the patient's satisfaction, and obtain a signed, IRB/REB approved, informed consent form. A copy of the signed informed consent form will be given to the patient.

Note: Patients on the Control Arm of the study who have documented disease progression and are undergoing screening to receive OGX-427 will need to repeat screening procedures as detailed in Section 6.3.3 to ensure they meet eligibility criteria. Only patients on the Control Arm who remain in the study until disease progression will be allowed to cross-over to receive OGX-427 treatment.

The screening will include the following:

1. Collect a signed and dated informed consent form.
2. Collect demographics.
3. Document histological (or cytological) diagnosis.
4. Document TNM stage at diagnosis.
5. Document Gleason score.
6. Document prior administration of all cancer therapies, including adjuvant therapy, surgery, radiation therapy, hormonal therapy, and chemotherapy.
7. Document date of metastatic disease.
8. Document medical history to include: significant historical events or findings, including pre-existing conditions and concurrent illnesses.
9. Obtain and redact a copy of the original prostate cancer pathology report to be placed in the patient's medical record. (If the patient is randomized, a paraffin block or unstained slides from the primary diagnostic tumor specimen is required, if available, for PTEN analysis.)
10. Perform a complete physical examination.
11. Assess vital signs (temperature, heart rate, blood pressure).
12. Document weight.
13. Record ECOG performance status.

14. Obtain chest/abdomen/pelvic CT scans and a bone scan for disease assessment if not obtained within 28 days. Patients with scans performed as standard of care prior to consent for this study within 28 days of study enrollment that are available at the same facility where subsequent scans will be performed will NOT be required to have repeat scans unless they have developed new signs or symptoms of disease. CT scans should be performed per RECIST 1.1 criteria (see Section 6.4).
15. Record concomitant medications, including any pain analgesics.
16. At least 14 days has passed since any major surgery and 5 days for minor surgery (i.e. port placement),
17. Collect approximately **34.5 mL** blood as follows: (all CBCs, serum chemistries, and PSA assays will be performed in the local laboratory; the remaining assays will be performed at the Central Laboratory).

    5 mL of anticoagulated blood for a CBC to include:

    - white blood cell (WBC) count
    - absolute neutrophil and lymphocyte count
    - platelet count
    - hemoglobin

    5 mL of blood for serum chemistry testing**:**

    - electrolytes (Na, K, Cl, and CO_2)
    - serum creatinine
    - SGOT (AST)
    - SGPT (ALT)
    - alkaline phosphatase
    - bilirubin (total)
    - glucose
    - LDH

- serum testosterone **3 mL** of blood for PSA within 14 days prior to randomization

A separate blood draw of approximately **21.5 mL** for Hsp27, clusterin, other relevant proteins, and CTCs is to be obtained during screening to better assess the baseline levels.

7 mL of blood (red topped tube) and **7 mL** of blood (EDTA tube) for assays evaluating Hsp27, clusterin, and other relevant proteins (see Section 14.3). Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.

7.5 mL of blood for CTCs must be collected in a CellSave Preservative Tube™ supplied by the Sponsor (see Section 14.3) and shipped to the Central Laboratory on the same day.

6.2.2. Assignment of Patient Number, Stratification, and Randomization

Following completion of the screening evaluations, patients meeting all inclusion/exclusion criteria will be assigned a unique patient number during the registration through the Hoosier Cancer Research Network's Electronic Data Capture (EDC) system.

Randomization will take place immediately following registration. The stratification factors of prior chemotherapy (yes versus no) and prior PSA response >30% to abiraterone acetate (yes versus no) will be employed in randomization in order to minimize between-arm assignment imbalance. Within the strata, patients will be randomly assigned with equal probability to either the Experimental Arm: OGX-427 plus abiraterone/prednisone or the Control Arm: abiraterone/prednisone.

Patients on the Control Arm who cross over to receive OGX-427 therapy will NOT require further randomization. However, Sponsor (or delegate) approval of eligibility is required. (See section 6.3).

Once the patient has been randomized, arrange for a paraffin block (block preferred but slides are acceptable) of their primary tumor diagnostic specimen to be sent to the address specified in Section 14.3. This is **required** for participation in the study, if tissue is available. A redacted copy of the pathology report should accompany the tissue sample or slides.

All patients should continue their ongoing abiraterone and prednisone daily dosing uninterrupted during the study.

Patients on the Experimental Arm should initiate infusion of the first loading dose of OGX-427 within 7 days following randomization. All three loading doses should be completed within Week 1 if possible (within up to 10 days of initiating treatment) (Section 6.2.3). Patients crossing over from the Control Arm to receive OGX-427 must initiate the first loading dose within 8 weeks of documented disease progression.

6.2.3. Study Procedures During Week 1

For the Control Arm: Study procedures for Day 1, Week 1 should begin within 7 days following randomization. Study visits, evaluations, and procedures for the Control Arm will occur on Day 1 of Week 1 and then every 4 weeks, +/-2 days (28 days) unless otherwise indicated.

For the Experimental Arm: Study procedures for Day 1, Week 1 should begin within 7 days following randomization. OGX-427 loading dose infusions will be administered on three days beginning on Day 1, Week 1. Loading dose infusions must be a minimum of 36 hours apart (i.e., every other day). **All three loading doses should occur during Week 1, if possible. Note:** If the third loading dose or the Day 1, Week 2 dose is delayed, subsequent weekly administration will continue based on the Day 1, Week 2 administration date. Study visits, evaluations, and procedures for the Experimental Arm

will occur starting on Day 1 of Week 1 and then every 4 weeks, +/-2 days (28 days) unless otherwise indicated.

For both study arms, the following study procedures should be performed on Day 1, Week 1. **Note:** Procedures in the Experimental Arm should be performed prior to the first OGX-427 loading dose infusion unless otherwise specified.

- Assess vital signs (temperature, heart rate, blood pressure)
- Record ECOG score (see Section 14.5)
- Record concomitant medications
- Evaluate current health status and document concurrent illnesses
- Collect approximately **13 mL** blood as follows: (**Note**: not required prior to Day 1 Week 1 if previously performed within 14 days prior to study visit)

  5 mL of anticoagulated blood for a CBC to include:

  – WBC count

  – absolute neutrophil and lymphocyte count

  – platelet count

  – hemoglobin

  5 mL of blood for serum chemistry testing:

  – electrolytes (Na, K, Cl, and CO_2)

  – serum creatinine

  – SGOT (AST)

  – SGPT (ALT)

  – alkaline phosphatase

  – bilirubin (total)

  – glucose

  3 mL of blood for PSA (sent to Local Laboratory)

- Collect approximately **21.5** mL blood as follows:

  7 mL of blood (red topped tube) for serum and **7 mL** of blood (EDTA) for plasma for assays evaluating Hsp27, clusterin, and other relevant proteins (see Section 14.3). Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.

  7.5 mL of blood for CTCs must be collected in a CellSave Preservative Tube™ supplied by Sponsor and shipped to the Central Laboratory on the same day (see Section 14.3).

6.2.3.1. Administration of Loading Dose Infusions of OGX-427

1. Administer premedication with an H2 antagonist, e.g., Ranitidine (150 mg PO or 50 mg IV) and an antihistamine, e.g., diphenhydramine (25-50 mg). It is recommended that these premedications be administered 30-90 minutes prior to each loading dose infusion unless there is a medical reason the patient cannot receive one or more of the drugs. See Section 6.7.3 treatment recommendations for repeated infusion reactions.
2. Administer 600 mg OGX-427 over 2 hours using an infusion pump on each of the three non-sequential days starting on Day 1 of Week 1. Assess vital signs (temperature, heart rate, blood pressure) pre and post each infusion. There must be a minimum of one non-treatment day between each of the three loading dose infusion days (i.e. every other day). There must also be at least one but no more than 3 non-treatment day(s) between the last (third) loading dose infusion and the first weekly dose of OGX-427 (considered to be Week 2, Day 1) An example of a dosing schedule would be to give the three loading dose administrations of OGX-427 on Monday, Wednesday and Friday with the first weekly dose of OGX-427 (Week 2, Day 1) on the following Monday. The day prior to Day 1 of weekly OGX-427 administration must be a non-treatment day (i.e., Sunday in the above example).
3. If any signs or symptoms of an infusion reaction (i.e. chills, flushing, itching) occur during or immediately after any infusion, the following should be performed:
   - Record additional vital signs
   - Record AEs
   - Record any concomitant medications administered

6.2.4. Experimental Arm Only: Administration of Weekly OGX-427

1. Administer premedication with an H2 antagonist, e.g., Ranitidine (150 mg PO or 50 mg IV) and an antihistamine, e.g. diphenhydramine (25-50 mg). It is recommended that these premedications be administered 30-90 minutes prior to each infusion of OGX-427 unless there is a medical reason the patient cannot receive one or more of the drugs.
2. Administer 800 mg OGX-427 by infusion over 2 hours. Patients who fulfill the criteria for disease response (not stable disease) at Week 24 will receive 600 mg OGX-427 (rather than 800 mg) from Week 25 through Week 48 or until meeting an End of Study Treatment Criterion. After the Loading Dose Period, vital signs are only required at the 4-week evaluation visits and at the EOT visit.
3. If any signs or symptoms of an infusion reaction (i.e. chills, flushing, itching) occur during or immediately after any infusion, the following should be performed:
   - Record additional vital signs
   - Record any AEs
   - Record any concomitant medications administered

6.2.5. Study Procedures During Week 3

For both study arms, the following study procedures should be performed on Day 1 of Week 3**:**

- Collect approximately **10 mL** blood as follows:

  5 mL of anticoagulated blood for a CBC to include:

  – WBC count

  – absolute neutrophil and lymphocyte count

  – platelet count

  – hemoglobin

  5 mL of blood for serum chemistry testing:

  – electrolytes (Na, K, Cl, and CO_2)

  – serum creatinine

  – SGOT (AST)

  – SGPT (ALT)

  – alkaline phosphatase

  – bilirubin (total)

  – glucose

6.2.6. Both Study Arms: General Study Procedures at Day 1, Week 5 and Every 4 Weeks Thereafter During Study Treatment

For patients on the Experimental Arm: All study procedures must be completed prior to the OGX-427 infusion. The CBC and serum chemistry samples may be collected 24 hours prior the OGX-427 infusion.

For both study arms, the following study procedures should be performed:

- Conduct brief physical examination limited to signs and symptoms of disease or toxicity.
- Assess vital signs.
- Record weight.
- Record ECOG score (see Section 14.5).
- Update and record adverse events that occurred since the last visit.
- Update and record concomitant medications taken since the last visit.
- Collect approximately **27 mL** blood as follows:

  5 mL of anticoagulated blood for a CBC to include:

  – WBC count

– absolute neutrophil and lymphocyte count
– platelet count
– hemoglobin

5 mL of blood for serum chemistry to include:

– electrolytes (Na, K, Cl, and CO_2)
– serum creatinine
– SGOT (AST)
– SGPT (ALT)
– alkaline phosphatase
– bilirubin (total)
– glucose

3 mL of blood for PSA (sent to Local Laboratory)

7 mL of blood (red topped tube) and **7 mL** of blood (EDTA tube) for assays evaluating Hsp27, clusterin, and other relevant protein levels (see Section 14.3) Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.

6.2.6.1. CTCs *for Both Arms* at Weeks 1, 5, 9, 13 only (Day 1 of each)

7.5 mL of blood for CTCs must be collected in a CellSave Preservative Tube™ supplied by Sponsor and shipped on the same day (see Section 14.3).

For patients on the Experimental Arm, blood samples for CTC assessment must be collected prior to the infusion of OGX-427.

6.2.6.2. Disease Assessments *for Both Arms*

For this study, disease will be assessed according to criteria in Section 6.4.1 and Section 6.4.2.

Any patient who develops new clinical signs or symptoms of disease progression at any time should have a chest, abdominal, and pelvic CT scan and a bone scan to assess for disease progression.

All patients will be assessed for disease status with a chest, abdominal, and pelvic CT scan and a bone scan at the milestone Day 60 assessment (expected to occur at the end of Week 8, prior to Week 9), and at 16, 24, 32, 40, and 48 weeks (i.e., every 8 weeks) until disease progression.

6.2.7. Milestone Day 60 Disease Assessment

The objective of the milestone Day 60 disease assessment will be to evaluate for any previously undiscovered evidence of progression. This assessment will be conducted approximately 60 calendar days following randomization and is expected to occur after Week 8 and prior to Day 1, Week 9. The milestone Day 60 disease assessment must be

completed within the inclusive window of Day 53 to Day 67 post-randomization, regardless of the timing of Week 8 treatment (i.e., whether treatment scheduling at any time has been delayed). All living patients who have not had documented disease progression prior to the milestone Day 60 disease assessment will be assessed for evidence of disease progression. For patients who had criteria possibly indicating disease progression on or after Week 4 (i.e., appearance of 2 or more new bone lesions), the milestone Day 60 disease assessment will be the confirmation scan that disease progression has occurred (see Section 6.4.1.2).

The milestone Day 60 disease assessment must be scheduled in the inclusive window of Days 53 to 67 following randomization. This assessment may be conducted in conjunction with procedures scheduled for Day 1, Week 9 (as detailed in 6.2.6) if that visit occurs within the specified timeframe (Days 53 to 67). **Milestone Day 60 disease assessments done outside of this window are protocol violations. Please note that the rules for scheduling the milestone Day 60 disease assessments apply even if the patient was recently evaluated according to the study calendar just prior to Day 53, or would be evaluated according to the study calendar shortly after Day 67.** Clinical site personnel are encouraged to contact the Sponsor (or a designated representative) to discuss options for scheduling of the milestone Day 60 disease assessment in cases where other evaluations would precede or follow closely.

For the milestone Day 60 disease assessment, the following evaluations must be completed:

1. Record bisphosphonate or denosumab usage.
2. Obtain chest, abdomen and pelvic CT scans (MRI, if appropriate) and a bone scan. Note: MRI should only be performed if disease assessment at screening was assessed by MRI.
3. Collect approximately **3 mL** of blood for PSA (sent to Local Laboratory).

Refer to Section 6.4.1 for disease progression criteria.

6.2.8. End of Treatment (EOT) Visit [21 days (± 7 days) Following Withdrawal from Study Treatment]

The following patients who are withdrawing from study treatment for any reason (see Section 5.5) must have an EOT Visit:

- Patients who were randomized to the Experimental Arm
- Patients who were randomized to the Control Arm and will not cross-over to receive OGX-427
- Patients who have crossed over from the Control Arm and have received OGX-427

Note: Patients on the Control Arm who have disease progression and wish to cross over on the study to receive OGX-427 per the Experimental Arm Procedures will have a Screening Visit in the same time period rather than an EOT Visit (see Section 6.3.3).

The following will be documented/evaluated at the EOT Visit:

1. Record the reason for withdrawal from further treatment for patients on the Experimental Arm or from the study for patients on the Control Arm who are not eligible to cross-over or do not wish to cross-over to receive OGX-427 treatment.
2. Conduct physical exam limited to signs and symptoms of disease or toxicity.
3. Assess vital signs.
4. Document weight.
5. Record ECOG score (see Section 14.5).
6. Any patient who does not have documented disease progression must have a repeat chest, abdominal and pelvic CT scan and bone scan if not performed within the last 8 weeks.
7. Collect approximately **27 mL** of blood as follows:

   5 mL anticoagulated blood for CBC to include:

   - WBC count
   - absolute neutrophil and lymphocyte count
   - platelet count
   - hemoglobin

   5 mL blood for serum chemistry to include:

   - electrolytes (Na, Cl, K, and CO_2)
   - serum creatinine
   - SGOT (AST)
   - SGPT (ALT)
   - alkaline phosphatase
   - bilirubin (total)
   - glucose

   3 mL of blood for PSA (sent to Local Laboratory)

   7 mL of blood (red topped tube) and **7 mL** of blood (EDTA) for assays for evaluating Hsp27, clusterin, and other relevant protein levels (see Section 14.3). Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.

9. Update and record adverse events since last assessment. All previous and new adverse events are to be followed to at least 30 days following last dose of OGX-427 (for Experimental Arm, including cross-over patients) or until the End of Treatment Visit for the Control Arm. All SAEs and Grade 3 or higher adverse events that are ongoing must be followed until each event resolves or is assessed as chronic. Follow-up can be accomplished via an additional clinic visit or telephone contact with patient.

10. Update and record concomitant medications since last assessment. All concomitant medications are to be followed for at least 30 days following last dose of OGX-427 (for Experimental Arm, including cross-over patients) or until the End of Treatment Visit for patients on the Control Arm. Follow-up can be accomplished via an additional clinic visit or telephone contact with the patient.

6.2.9. Off Treatment Follow-up Period [Every 4 weeks (± 5 days)]

Patients will have study visits and evaluations every 4 weeks after the End of Treatment Visit, and continuing until disease progression is documented.

The following evaluations will be performed unless otherwise specified:

1. Physical exam limited to signs and symptoms of disease or toxicity.
2. Record weight.
3. Record ECOG score (see Section 14.5).
4. Collect approximately **3 mL** of blood for PSA (sent to Local Laboratory).
5. Collect approximately **7 mL** of blood (red topped tube) and **7 mL** of blood (EDTA tube) for assays for evaluating Hsp27, clusterin, and other relevant protein levels (see Section 14.3). Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.
6. Update and record all adverse events for 30 days following last dose of OGX-427 or until the End of Treatment Visit for the Control Arm. All SAEs and grade 3 or higher adverse events that are ongoing need to be followed until each event resolves or is assessed as chronic.
7. Repeat chest, abdominal and pelvic CT scans, and bone scan every **8 weeks**. (Note: Patients who develop new clinical signs or symptoms of disease progression at any time should have a repeat chest, abdominal, and pelvic CT scan and a bone scan).

After 30 days following the last dose of OGX-427 or End of Treatment Visit for the Control Arm, record only concomitant medications associated with SAEs and grade 3 or higher adverse events that have not resolved or have not been assessed as chronic. Subsequent anti-cancer therapy administered during the Off-Treatment Follow-up Period should be recorded.

6.3. Cross-over OGX-427 Treatment for Control Patients

6.3.1. Procedures for Control Patients to be Eligible for Cross-over Treatment

Patients in the Control Arm with documented disease progression will be allowed to cross-over to receive OGX-427 treatment per the Experimental Arm schedule, providing the patient is eligible for treatment with OGX-427 (i.e., fulfills all inclusion and exclusion criteria below) and continues to receive abiraterone acetate and prednisone. **Note:** Crossover must occur within 48 weeks of study randomization.

Only patients on the Control Arm who remain on study treatment until documented disease progression will be allowed to cross-over. Control Arm patients who have disease-related deterioration in ECOG performance status to Grade 2 or higher are not eligible to cross-over. Sponsor (or delegate) approval of eligibility for cross-over is required.

Screening for eligibility criteria will begin following the date of documented disease progression (see Section 6.3.3). The first loading dose of OGX-427 must be administered within 8 weeks of the date of documented disease progression and will be considered Day 1, Week 1 for OGX-427 treatment.

OGX-427 treatment, study evaluations, and disease assessments will occur in the same manner as defined for the Experimental Arm in Sections 6.2.3 through 6.2.7 until further disease progression is documented or the patient meets another End of Study Treatment criterion for withdrawal (see Section 5.5). Patients who are withdrawn from study treatment for a reason other than documented disease progression or patient withdrawal of consent to participate in the study should be followed until further disease progression is documented, if possible.

6.3.2. Eligibility Criteria for Cross-over Treatment

To be eligible for cross-over treatment, subjects must meet ALL of the following inclusion criteria and not meet any of the exclusion criteria.

Inclusion criteria:

1. Has met one or more of the criteria for disease progression as outlined in Section 6.4.1.2 (other than disease related deterioration in ECOG performance status to Grade 3 or higher; initiation of any cytotoxic, systemic anti-cancer therapy; or cancer pain requiring initiation of chronic opiate analgesia (oral or parenteral) or a consistent increase >33% in daily opioid use from baseline) within 48 weeks from study randomization

   Note: If disease progression is by PSA or bone scan only, confirmation of progression must be documented prior to first dose of OGX-427.
2. ECOG performance status of 0 or 1
3. Currently receiving and tolerating abiraterone acetate (1000 mg oral daily) and prednisone (10-20 mg oral daily)
4. No evidence of other symptomatic or radiographic progression that would require alternative therapy
5. All patients who have not had a surgical orchiectomy must continue treatment with LHRH agonist or antagonist to maintain a castrate level of testosterone.
6. Prior radiation therapy for disease progression is permitted if a minimum of at least 14 days have passed since completing radiotherapy at the time of the first dose of OGX-427 (exception for radiotherapy: at least 7 days since completing a single fraction of ≤800 cGy to a restricted field or limited-field radiotherapy to non-marrow bearing area such as an extremity or orbit)

7. At least 14 days has passed since any major surgery and 5 days for minor surgery (i.e. port placement)
8. Baseline laboratory values as stated below:
    a. ANC ≥ 1.5 x 10^9 cells /L, platelet count ≥ 100 x 10^9 /L, and hemoglobin ≥ 9 g/dL without transfusion
    b. Creatinine ≤ 1.3 x upper limit of normal (ULN)
    c. Total bilirubin ≤ 1.1 x ULN (unless elevated secondary to conditions such as Gilbert's disease, in which case a direct bilirubin ≤ ULN is required)
    d. SGPT (ALT) and SGOT (AST) ≤ 3.0 x ULN
    e. Castrate serum testosterone level (< 50 ng/dL **or** < 1.7 nmol/L)
    f. Potassium within normal limits
9. Recovery from all toxicities of prior therapy to ≤grade 2 by NCI CTCAE, version 4.0
10. Must be willing to continue use of effective contraception throughout study treatment and for 3 months after completion of study treatment if able to father a child.
11. Must continue to be willing not to change (add or subtract) bone protecting therapy (bisphosphonates and/or denosumab) during the study unless changed for toxicity.

Exclusion criteria:

Subjects meeting ANY of the following exclusion criteria will NOT be eligible for cross-over treatment:

1. Documented brain metastases or carcinomatous meningitis while on abiraterone treatment, treated or untreated (Brain imaging for asymptomatic patients is not required.)
2. Cord compression requiring surgery or radiation therapy while on abiraterone treatment
3. Any new uncontrolled medical condition that would preclude protocol therapy
4. Active second malignancy (including lymphoid malignancies such as chronic lymphocytic leukemia or low grade lymphoma) defined, in general, as requiring anticancer therapy or at high risk of recurrence during the study; not including adequately treated non-melanomatous skin cancer or other solid tumors curatively treated with no evidence of disease in > 3 years
5. Active autoimmune disease requiring treatment
6. Known LVEF <50% or NYHA Class III or IV heart failure

6.3.3. Screening Procedures for Cross-over Treatment

Note: The date of cross over is considered the last day all screening procedures are confirmed completed and the patient is deemed eligible to cross over. The Day 60 evaluation should be scheduled for 60 days after the date of cross over.

Screening for cross-over patients will include:

1. Record the reason for ending Control Arm treatment.
2. Perform a complete physical examination.
3. Assess vital signs (temperature, heart rate, blood pressure).
4. Document weight.
5. Record ECOG performance status.
6. Obtain chest/abdomen/pelvic CT scans and a bone scan for disease assessment if not obtained within 28 days. CT scans should be performed per RECIST 1.1 criteria (see Section 6.4).
7. Record concomitant medications.
8. Collect approximately **34.5 mL** blood as follows: (all CBCs, serum chemistries, and PSA assays will be performed in the local laboratory; the remaining assays will be performed at the Central Laboratory).

   5 mL of anticoagulated blood for a CBC to include:

   - white blood cell (WBC) count
   - absolute neutrophil and lymphocyte count
   - platelet count
   - hemoglobin

   5 mL of blood for serum chemistry testing**:**

   - electrolytes (Na, K, Cl, and CO_2)
   - serum creatinine
   - SGOT (AST)
   - SGPT (ALT)
   - alkaline phosphatase
   - bilirubin (total)
   - glucose
   -

   3 mL of blood for PSA within 14 days prior to cross-over

   A separate blood draw of approximately **21.5 mL** for Hsp27, clusterin, other relevant proteins, and CTCs is to be obtained during screening to better assess the levels at time of cross-over. It is preferred that this blood draw occur within 14 days of cross-over, i.e., close to the time of OGX-427 treatment.

- **7 mL** of blood (red topped tube) and **7 mL** of blood (EDTA tube) for assays evaluating Hsp27, clusterin, and other relevant proteins (see Section 14.3). Serum and plasma will be divided into three aliquots and sent to a Central Laboratory.
- **7.5 mL** of blood for CTCs collected in a CellSave Preservative Tube™ supplied by the Sponsor (see Section 14.3) and shipped to the Central Laboratory on the same day.

6.4. Study Outcome Definitions

6.4.1. Disease Progression

In addition to disease assessments every 8 weeks, all patients should be evaluated for disease progression at the time of any new signs or symptoms of cancer during the study. Disease progression is defined in Section 6.4.1.2.

6.4.1.1. Evaluation of Baseline Target and Non-Target Lesions

Measurable Disease (Target Lesions)

Measurable lesions include all soft-tissue lesions. Visceral lesions must be able to be accurately measured in at least one dimension with the longest diameter ≥ 10 mm using CT scans or MRI. For pathological lymph nodes to be measureable, a node must by ≥ 15 mm in the short axis.

Previously irradiated lesions should not be considered measurable.

CT scans with contrast (unless contraindicated, i.e., especially for patients with increased risk of contrast related nephropathy) should be performed with slice thickness no greater than 5 mm. The same method of assessment should be used at baseline and during follow-up assessments for each lesion, i.e., conventional vs. spiral CT or MRI.

At baseline, measurable lesions representing overall tumor burden, up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as "target lesions" and recorded and measured. **Lesions that are unsuitable for accurate, repeated measurements should not be selected as target lesions.** A sum of the diameters (long axis for non-nodal and short axis for nodal lesions) of all target lesions at baseline will be calculated and reported as the baseline sum diameter. This will be used as reference to characterize disease response. Lesions should be recorded in the same order on sequential examinations.

Non-Measurable Disease (Non-Target Lesions)

All other lesions or sites of disease (**including lesions on bone scan)** should be identified as "non-target lesions" and should also be recorded at baseline. This includes measurable lesions smaller than dimensions defined above or lesions in excess of 2 per organ or 5 in total. Worsening (increase in intensity or size of a lesion) of pre-existing non-target lesions, including bone lesions, may be difficult to interpret and therefore will not be considered evidence of progressive disease. Measurement of these lesions is not required;

however the **presence or absence of each should be noted**. **Do not record "increased", "decreased" or "stable."**

6.4.1.2. Criteria for Disease Progression

Patients will be assessed as having Disease Progression if one or more of the following criteria have been met:

a. PSA: If a decline from baseline: an increase of ≥ 25% and ≥ 2 ng/mL above the on-study nadir confirmed by a second value 3 or more weeks later. If no decline from baseline: an increase of ≥ 25% and ≥ 2 ng/mL from baseline confirmed by a second value 3 or more weeks later

   Note: Disease progression based on PSA cannot be confirmed prior to Day 60 (8 weeks).

b. Measurable disease: Progression of measurable disease has occurred if any of the criteria below are met on CT scan:

   – The appearance of one or more new lesions

   – At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

c. Bone scan: ≥ 2 new lesions (if the first on study bone scan at Day 60 shows ≥ 2 new lesions, this requires confirmation on a second scan ≥ 4 weeks later which shows ≥2 additional new lesions)

d. Non-measurable disease (non-target lesions on CT scan): Progression of disease has occurred if the criteria outlined below for "unequivocal progression" of existing non-target lesions on CT scan has been met. To achieve unequivocal progression on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease (SD) or partial response (PR) in measurable disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare. When the patient has only non-measurable disease, the same general concepts apply as noted above, however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. A useful test that can be applied is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).

e. Disease related deterioration in ECOG performance status to Grade 3 or higher. Note: Patients whose ECOG performance status decreases to Grade 2 during the study should be assessed by the Investigator for their need for systemic chemotherapy or other non-study therapies. **Note:** Patients on the Control Arm

with an ECOG Grade 2 or higher are not eligible to cross-over to the Experimental Arm.

f. Need for palliative radiation therapy
g. Initiation of any cytotoxic, systemic anti-cancer therapy
h. Surgery for any complication due to disease progression
i. Cancer pain requiring initiation of chronic opiate analgesia (oral or parenteral) or a consistent increase >33% in daily opioid use from baseline. Note: Any patients with cancer pain who require increasing narcotics for relief of cancer pain should be assessed by the Investigator for the need to initiate systemic chemotherapy or other non-study therapies.

6.4.2. Response Definitions

6.4.2.1. Objective Response

Objective Response takes into account both measurable and non-measurable lesions by CT (or MRI, if applicable), bone lesions, and tumor markers.

Complete Response (CR): Disappearance of all measurable and non-measurable lesions on CT scan and bone scan, with no new lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. All tumor markers must have normalized, as have disease-related symptoms. Confirmatory scans are required.

Partial Response (PR): At least a 30% decrease in the sum of diameters (long axis for non-nodal lesions, short axis for nodal lesions) of measurable lesions on CT scan, taking as reference the baseline sum diameters, with no "unequivocal progression" of non-measurable lesions on CT scan or bone scan and no new lesions.

Stable Disease (SD): Neither sufficient shrinkage of measurable lesions on CT scan to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. There may be persistence of one or more non-target lesions on CT scan or bone scan, and/or maintenance of tumor marker level above the normal limits.

Disease Progression (PD): See Section 6.4.1.2 subpoints b, c, and d.

Not Evaluable (NE): When no imaging/measurement is performed at a particular time point, the patient is NE at that time point. If only a subset of lesion measurements are made at an assessment, the patient is NE at that time point, unless PD is otherwise determined. Every attempt should be made to perform an imaging evaluation prior to initiating any new anticancer therapy.

6.4.2.2. PSA Response

A PSA response is defined as a post-treatment decline in PSA from baseline. The response must be confirmed by a second value 3 or more weeks later.

≥50% response: A PSA decline of 50% or more from baseline, confirmed by a second value 3 or more weeks later.

≥30% response: A PSA decline of 30% or more from baseline, confirmed by a second value 3 or more weeks later.

PSA progression: See Section 6.4.1.2 subpoint a.

6.5. Protocol-Specific Samples for Correlative Studies

Details regarding processing, labeling, and shipping of samples can be found in Section 14.3. Following completion of all correlative analysis, any remaining research samples will be destroyed within 3 years following completion of the study.

6.5.1. Blood Collection for Assays Evaluating Hsp27, Clusterin, and Other Relevant Proteins

Blood for assays for evaluating Hsp27, clusterin, and other relevant proteins will be collected, processed at the local site and shipped to a central laboratory for analysis (see Section 14.3). Baseline and changes in Hsp27 protein levels will be explored in relation to patient outcomes as a possible prognostic and predictive biomarker for OGX-427 biologic activity. Clusterin, a cytoprotective chaperone protein similar to heat shock proteins, will be measured as clusterin protein levels may change in response to Hsp27 inhibition.

6.5.2. Circulating Tumor Cells

Baseline and changes in circulating tumor cells (CTCs) after treatment have been correlated with prognosis in CRPC. CTCs will be collected at screening and weeks 1, 5, 9 and 13. Blood for CTCs will be collected, processed at the local site, and shipped to a central laboratory for analysis using the Immunicon/Veridex system (see Section 5.5).

6.5.3. Tissue for PTEN

Hsp27 is involved in regulation of the serine/threonine kinase AKT, and AKT is constitutively activated by loss of the PTEN tumor suppressor gene, which frequently occurs in prostate cancer.[63] Furthermore, pre-clinical data suggest that loss of PTEN may be a potential predictive factor for response to Hsp27 inhibition. Original biopsy/prostatectomy specimens (tissue is preferred however unstained slides are acceptable) and redacted pathology reports from all patients randomized to study will be sent to a central laboratory for evaluation of PTEN deletion status using a FISH assay[63] (see Section 14.3). Tissue will be returned if requested. Slides will not be returned.

6.6. Dose Modifications for Toxicity

Toxicities will be graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0. In general, the need for dose modifications of OGX-427, abiraterone acetate, and/or prednisone will be assessed based on laboratory values or physical signs obtained within 48 hours prior to treatment.

Treatment delays, for experimental arm, for any reason, not made up in the same calendar week of the scheduled dose will be considered ‘missed’ doses. Treatment may not be missed for more than three weeks (4 missed doses). If treatment must be delayed longer than three weeks for any reason, the patient will be removed from protocol treatment but will continue to be followed for safety and disease progression.

No dose reductions of the 600 mg dose will be performed during the three OGX-427 loading doses. However, any grade 3 or 4 adverse events occurring during the loading dose period must resolve to ≤ Grade 1 before the next loading dose or before the first weekly dose of 800 mg OGX-427 can be administered.

The OGX-427 weekly dose of 800 mg should be administered starting at Week 2. After Week 2, dose modifications may occur as indicated in this section.

The dose of OGX-427 or abiraterone will not be re-escalated once the dose is reduced. If more than two dose reductions of OGX-427 or abiraterone are required, the patient should be removed from study treatment. If OGX-427 or abiraterone is discontinued due to toxicity, the patient will be removed from study treatment. Patients should have an End of Treatment Visit and then should enter the Off-Treatment Follow-up Period until disease progression.

If prednisone is reduced due to toxicity, the patient may continue on study treatment with abiraterone (with or without OGX-427, dependent on randomization). However, abiraterone should not be administered without some form of steroid coverage. If serious side effects develop related to mineralocorticoid excess, stress doses of steroids can be given.

Reasons for modifying the dose of OGX-427, abiraterone acetate, or prednisone must be recorded in the source documents and the eCRF.

6.6.1. Dose Modifications for OGX-427

Table 5: Dose Level Modifications for OGX-427

Dose Level	Study agent
100%	800 mg
First dose reduction	700 mg
Second dose reduction*	600 mg

* Requirement for a third dose reduction will lead to discontinuation from study treatment.

6.6.2. Dose Modifications for Abiraterone Acetate

Dose modifications for abiraterone are noted below. For more information refer to the Package Insert for abiraterone acetate provided in the Study Procedure Manual.

Table 6: Dose Level Modifications for Abiraterone Acetate

Dose Level	Study Agent
100%	1000 mg
First dose reduction	750 mg
Second dose reduction*	500 mg

* Requirement for a third dose reduction will lead to discontinuation from

study treatment.

6.6.3. Hepatic Toxicity for OGX-427 and Abiraterone Acetate

Modification for hepatic toxicity should be based on AST, ALT, and bilirubin values. The dose adjustments are shown in the table below.

Table 7: Dose Modifications of OGX-427 for Hepatic Toxicity

	Transaminase AST and ALT levels			
	≤3.0 x ULN (Grade 1)	**>3.0 and ≤5.0 x ULN (Grade 2)**	**>5.0 x ULN (Grade 3)**	**>20 x ULN (Grade 4)**
Bilirubin ≤1.1 x ULN	**100%** of dose	**Hold** **Resume** when both AST and ALT ≤3.0 x ULN	**Hold** **Resume** when both AST and ALT ≤3.0 x ULN; **Decrease** OGX-427 by 1 dose level	**Remove** from protocol treatment
Bilirubin >1.1 x ULN	**Hold** **Resume** when bilirubin to ≤1.1 x ULN	**Hold** **Resume** when bilirubin to ≤1.1 x ULN and both AST and ALT ≤3.0 x ULN; **Decrease** OGX-427 by 1 dose level	**Remove** from protocol treatment	**Remove** from protocol treatment

Table 8: Dose Modifications of Abiraterone Acetate for Hepatic Toxicity

	Transaminase AST and ALT levels			
	≤3.0 x ULN (Grade 1)	**>3.0 and ≤5.0 x ULN (Grade 2)**	**>5.0 x ULN (Grade 3)**	**>20 x ULN (Grade 4)**
Bilirubin ≤3.0 x ULN	**100%** of dose	**Hold** Monitor liver tests at least weekly **Resume** when bilirubin <1.5 x ULN and both AST and ALT ≤3.0 x ULN	**Hold** Monitor liver tests at least weekly **Resume** when bilirubin <1.5 x ULN and both AST and ALT ≤3.0 x ULN **Decrease** abiraterone by 1 dose level	**Remove** from protocol treatment
Bilirubin >3.0 x ULN Any AST/ALT	**Hold** Monitor liver tests at least weekly **Resume** when bilirubin **≤**1.5 x ULN and both AST and ALT ≤3.0 x ULN **Decrease** abiraterone by 1 dose level			**Remove** from protocol treatment

6.6.4. Hematological Toxicity for OGX-427

Table 9: Dose Modifications for Hematologic Toxicity

Toxicity	**Dose Modification***
ANC ≥1.5 x10^9 cells /L **and** platelet count ≥100 x 10^9/L,	**100%** of present dose
ANC <1.5 x10^9 cells /L **AND/OR** platelet count <100 x 10^9/L	**Hold** OGX-427: Repeat counts weekly When ANC ≥1.5 x10^9 cells /L **and** platelet count ≥100 x 10^9/L, resume at 100% of present dose If held for more than 1 week, **resume** but **decrease** OGX-427 by one dose level following the recovery of the ANC to ≥1.5 x10^9 cells/L and the platelet count to ≥100 x 10^9/L **Remove** patient from protocol treatment if the ANC has not recovered to ≥1.5 x10^9 cells /L and/or platelet count to ≥100 x 10^9/L **within 3 weeks** (4 missed doses)

***Note:** Grade 3-4 lymphopenia is a known class effect of ASOs; dose modifications are not required.

6.6.5. Renal Toxicity for OGX-427

Table 10: Dose Modifications of OGX-427 for Renal Toxicity

Toxicity	Dose Modification
Creatinine level increase of >0.3 mg/dL above baseline; creatinine 1.5 - 2.0 x above baseline (Grade 1)	**100%** of present dose
Creatinine 2 - 3 x above baseline (Grade 2)	**Hold** **Resume** OGX-427 at 100% of present dose when creatinine ≤2.0 x above baseline (Grade 1)*
Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated (Grade 3)	**Hold** **Resume** OGX-427 when creatinine ≤2.0 x above baseline (Grade 1)*; **decrease** OGX-427 by 1 dose level
Life-threatening consequences; dialysis indicated (Grade 4)	**Remove** from protocol treatment

***Note:** Repeat creatinine assessment at least weekly until resolution to grade 1.

6.6.6. Acute Infusion Reactions: Dose Modifications for OGX-427

In the event of an acute infusion reaction (e.g., flushing, rash, fever, urticaria, dyspnea, bronchospasm, and/or hypotension) during the OGX-427 infusion, follow the Institutional Guidelines of each site and the recommendations shown in the table below based on the grade of the reaction. There will be no dose reductions of OGX-427 during the Loading Dose Period, but loading doses must be held until resolution of any toxicity to ≤ Grade 1. In addition, dosing of OGX-427 at Cycle 1, Day 1, will be held until resolution of any infusion reactions to ≤ grade 1 following the last loading dose.

To identify the grade of a reaction, refer to the list below adapted from the NCI CTCAE Version 4.0 dated May 28, 2009 (under the terms “Infusion related reaction” and “Cytokine release syndrome”):

- **Grade 1:** Mild reaction; infusion interruption not indicated; intervention not indicated.
- **Grade 2:** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.
- **Grade 3:** Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. **Note:** any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated

Table 11: Dose Modifications for Acute Infusion Reactions with OGX-427

Toxicity	Dose Modification
Any Grade 1 infusion reaction	Slow the rate of infusion of the drug until resolution of symptoms, then resume at the planned infusion rate.
First Grade 2 infusion reaction	Stop the infusion. Give dexamethasone 8 mg IV, diphenhydramine 50 mg IV, and/or an H2 antagonist (e.g. Ranitidine 50 mg IV), after consultation with the attendant physician. Resume infusion after recovery of symptoms to grade ≤1 at a slower rate and increase incrementally toward the initial rate. If the reaction recurs, stop the infusion and do not administer the remaining volume.
Second Grade 2 infusion reaction, or first Grade 3 infusion reaction	Stop the infusion. Give dexamethasone 8 mg IV, diphenhydramine 50 mg IV, and/or an H2 antagonist (e.g. Ranitidine 50 mg IV), after consultation with the attendant physician. Resume accordingly after recovery of symptoms to grade ≤1. **Add 8 mg dexamethasone to the premedication regimen (H2 antagonist and antihistamine) for a minimum of 12 weeks.**
Grade 2 or Grade 3 infusion reaction in the presence of steroid prophylaxis	Stop the infusion. Give dexamethasone 8 mg IV, diphenhydramine 50 mg IV, and/or an H2 antagonist (e.g. Ranitidine 50 mg IV), after consultation with the attendant physician. **Grade 2 or 3 infusion reaction in the presence of steroids: reduce subsequent administration of OGX-427 by one dose level (a maximum of two dose reductions are allowed after Week 2). Any patient experiencing a second grade 3 infusion reaction to OGX-427 despite adequate steroid prophylaxis will be discontinued from study treatment.**
Any Grade 4 infusion reaction	Discontinue OGX-427 infusion. Follow Institutional Guidelines for treatment. Discontinue all study treatment.

6.6.7. Management of Hypertension

Table 12: Dose Modifications of Abiraterone Acetate for Hypertension

Toxicity	Dose Modification
Grade 1 or 2 hypertension	Institute or increase anti-hypertensive measures while continuing abiraterone
Grade 3 hypertension for >24 hours (BP≥160/100 or, if previously normal, symptomatic increase by >20 mm Hg [diastolic] or BP>160/100) or, requires more than one drug than previously used	Hold abiraterone Institute or increase anti-hypertensive measures Abiraterone may be restarted when blood pressure values on hypertensive therapy return to ≤grade 1 (140/90) Resume abiraterone at the same dose
If grade 3 toxicity recurs in spite of adequate antihypertensive	Hold abiraterone

regimen	Continue medical management for hypertension Abiraterone may be restarted when blood pressure values return to ≤grade 1 (140/90) Reduce the dose of abiraterone by one dose level
Grade 4 (life-threatening, malignant hypertension, or any hypertension with a neurologic deficit)	Patient should be removed from study therapy.

6.6.8. Management of Hypokalemia

Table 613: Dose Modifications of Abiraterone Acetate for Hypokalemia

Toxicity	Dose Modification
Grade 1 asymptomatic hypokalemia (<LLN to 3.0 mmol/L)	Hold abiraterone; initiate oral K+ supplement or increase dose up to a maximum oral dose of 80 mEq/day. Abiraterone can be reinstituted at the same dose once the K+ is normal.
Grade 2 hypokalemia (symptomatic <LLN to 3.0 mmol/L) or grade 3 hypokalemia (<3.0-2.5 mmol/L)	Hold abiraterone; initiate oral K+ supplement or increase dose up to a maximum oral dose of 80 mEq/day. Resume abiraterone when three consecutive K+ are normal; decrease abiraterone by one dose level.
If serum K+ cannot be corrected with 80 mEq of daily K+ dosing by oral supplementation	Administer IV K+. Resume abiraterone when three consecutive K+ are normal; decreased abiraterone by one dose level.
Grade 4 hypokalemia (<2.5 mmol/L)	Remove patient from protocol therapy.

Note: While making changes to potassium supplementation, the K+ should be repeated at least weekly (or more frequently per investigator) until three consecutive values are in the normal range.

6.6.9. Management of Rash

- For any grade 3 rash covering >30% body surface area (BSA), abiraterone should be held until resolution to grade 1 and the dose of abiraterone should be reduced by one dose level. Weekly OGX-427 infusions may continue.
- If grade 3 rash does not resolve to grade 1 within 3 weeks, the patient will be removed from protocol therapy.

6.6.10. Grade 3 or 4 Non-Hematological Toxicities for OGX-427 and Abiraterone Acetate Not Discussed Above

Discontinue OGX-427 and abiraterone therapy for the following reasons:

- Any Grade 4 non-hematological AE with the following exceptions: alopecia, anemia, pain, fatigue (asthenia, lethargy, malaise), insomnia, nail changes, arthralgia and myalgia.
- Any Grade 3 non-hematological AE which is felt by the principal investigator (PI) to be clinically relevant and which does not resolve to ≤ Grade 2 within 48 hours of the initiation of standard therapy or supportive care, (e.g. antiemetics for nausea or vomiting, antidiarrheal for diarrhea, insulin for hyperglycemia or IV fluids for renal compromise secondary to dehydration).

Decrease the dose of OGX-427 and abiraterone by one dose-level for the following reasons:

- Grade 4 fatigue (asthenia, lethargy, malaise), arthralgia and myalgia occurring for more than 3 weeks.
- Any Grade 3 non-hematological AE which is felt by the PI to be clinically relevant and which resolves to ≤ Grade 2 within 48 hours of standard therapy or supportive care but reoccurs.

6.6.11. Onset of either ≥Grade 2 Motor Neuropathy or ≥Grade 2 Muscle Weakness

Any onset of ≥grade 2 motor neuropathy or ≥grade 2 muscle weakness should be evaluated by EMG to rule out the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP). With a diagnosis of CIDP the patient should be discontinued from study treatment.

6.6.12. Dose Modifications for Prednisone

Prednisone can be held or decreased for adverse events per investigator standard of care. Examples of prednisone side effects that an investigator may consider decreasing or discontinuing prednisone dosing include onset or exacerbation of diabetes mellitus, hypertension, gastrointestinal ulceration or bleeding, severe neurological side effects, or other serious adverse events. Prednisone may be reinstituted with the resolution of the adverse event at the discretion of the Investigator. The reason for altering the dose or discontinuing prednisone should be documented on the eCRF. Abiraterone should not be administered without some form of steroid coverage. If serious side effects develop related to mineralocorticoid excess, stress doses of steroids can be given.

6.7. Concomitant Medications/Therapy

6.7.1. Bisphosphonates and Bone Protecting Agents

Changes in bisphosphonate usage and/or bone protecting agents such as denosumab should not occur during the study treatment (unless the deletion or change is for toxicity associated with the baseline usage of these drugs). If the patient is not on a bisphosphonate or denosumab at study entry, they should not be initiated during study treatment. All

administration of bisphosphonates or denosumab (or any change in usage) during study treatment must be documented on the eCRF (including the reason for change if indicated).

6.7.2. Corticosteroids

Patients on both arms of the protocol will continue receiving prednisone, 10-20 mg/day PO. Patients who are intolerant of prednisone at a dose of 10 mg/day will **not** be eligible for the protocol. Changes in corticosteroid usage (except as premedication for infusion reactions [Section 6.7.3]) should not occur during the study treatment unless the deletion or change is for toxicity associated with the baseline usage. All administration of corticosteroids during study treatment, including premedications or treatment for infusion reactions, must be documented on the eCRF.

6.7.3. Premedication for OGX-427 Infusion-Related Adverse Events

All patients should be premedicated before each dose of OGX-427 with an H2 antagonist, e.g., ranitidine (Zantac) (50 mg IV or 150 mg PO) and an antihistamine e.g. diphenhydramine (25-50 mg IV or PO). It is recommended that these premedications be administered30-90 minutes prior to the infusion unless there is a medical reason the patient cannot receive one or more of the drugs. The type of H2 antagonist and antihistamine administered is at the discretion of the Investigator. For example, cimetidine (Tagament) could be substituted for ranitidine and/or loratadine (Claritin) for diphenhydramine (Benadryl).

Should a patient manifest a Grade 2 or greater adverse event(s) during or subsequent to an infusion of OGX-427 despite the above premedications, treatment should follow Institutional guidelines, however recommendations, including use of steroids, are available in Section 6.6.6/Table 11.

Following the need for treatment with steroids (8 mg of dexamethasone) on more than one occasion for a Grade 2 or greater adverse event associated with an infusion, the patient should receive prophylaxis with dexamethasone, 8 mg, in addition to continued premedication with an H2 antagonist and an antihistamine, for a minimum of 12 weeks, or longer if necessary.

6.7.4. Anti-emetics

Prophylactic or therapeutic treatment will be at the discretion of the Investigator.

6.7.5. Anticoagulation Therapy

Anticoagulation therapy for thrombosis with warfarin (Coumadin) is allowed, if required, during the study. The INR should be followed closely. In addition, low molecular weight heparins in a therapeutic dose are allowed, if clinically required, during the study. Platelets should be followed closely.

6.7.6. Growth Factors and Transfusions

Granulocyte-colony stimulating factor (G-CSF) is allowed. It is recommended that treatment with G-CSF follow the guidelines of the American Society of Clinical Oncology (ASCO), unless otherwise specified by Institutional standards. All other growth factors and

all transfusions will be at the discretion of the Investigator. Administration of all growth factors and transfusions must be documented on the Concomitant Medications eCRF.

6.7.7. Anticancer Therapies

Treatment with any other anticancer therapy (except steroids) is not allowed and is considered a protocol violation unless the patient has documented disease progression or has withdrawn from all further study evaluations. Anticancer therapies include, but are not limited to, other chemotherapy, immunotherapy, experimental therapy, or radiation therapy (except as indicated below). Patients who discontinue study treatment for disease progression should have documentation of any anticancer therapy administered.

6.7.8. Palliative Radiation Therapy

Patients will be removed from study treatment and will be considered to have disease progression for any cancer-related radiation therapy while on study. Lesions which are symptomatic or cause unstable bone should be irradiated before the start of study treatment. Previously irradiated lesions should not be considered measurable.

All radiation therapy must be completed at least 14 days before randomization (or following disease progression and prior to receiving OGX-427 therapy at the time of cross-over). Exception for radiotherapy: at least 7 days must have passed since completing single fraction of ≤ 800 cGy to a restricted field or limited-field radiotherapy to non-marrow bearing area such as an extremity or orbit) at the time of randomization.

7. STUDY AGENTS

7.1. OGX-427

OGX-427 will be supplied by OncoGenex Technologies Inc. OGX-427 Drug Product, 25 mg/mL injection is formulated as a mannitol-phosphate buffer solution (pH 7.4) for IV administration and is supplied as an 8-mL solution containing 200 mg OGX-427 in a single vial. The drug substance and active ingredient of OGX-427 is an antisense oligonucleotide (ASO).

Further information with regard to the drug product and drug substance may be found in the Investigator's Brochure for OGX-427 Injection, 25 mg/mL, and the Study Procedure Manual provided for this study.

7.1.1. Risks and Precautions

Safety data for OGX-427 have been compiled from the completed Phase I study OGX-427-01 and from the ongoing open-label Phase II study PR-01. Safety data from the ongoing placebo-controlled Phase II study OGX-427-02 is not included in this summary because these data are currently blinded. Only data on side effects experienced by the 76 patients receiving OGX-427 monotherapy (plus prednisone) are reported. Also included in these data is the one reported sudden unexpected serious adverse reaction (SUSAR) in the ongoing study PR-01

High levels of infusion reactions were observed in study OGX-427-01, especially at the highest doses tested (800 mg and 1000 mg) and during in the loading dose period and first weekly infusions, when OGX-427 concentrations are the highest. This observation prompted a reduction in the three loading doses from 1000 mg in study OGX-427-01 to 600 mg in study PR-01 and the addition of premedications (H2 antagonist and antihistamine). Because this study and subsequent studies will use the 600 mg loading dose, data on infusion-related reactions reported below reflect those observed among subjects in study PR-01, who received the 600 mg loading dose and prophylactic medications as outlined above.

The risks and side effects documented in patients who have been treated with **OGX-427 plus prednisone only** that have been identified as possibly, probably, or definitely related to study drug are defined below:

Very likely (>20% of patients):

- Anemia (83%) which can cause tiredness, shortness of breath, and a possible need for red blood cell transfusions
- Lymphopenia (79%) which in rare circumstances could lead to uncommon but serious infections
- Transient prolongation of PTT (55%) which in rare circumstances could lead to serious bleeding
- Infusion reactions during or soon after the infusion of OGX-427 have occurred in approximately 52% of patients. The most common symptoms have been chills (33%), flushing (19%), diarrhea (15%), nausea (11%), and vomiting (11%). The majority of the reactions occurred during the first three loading doses and during the first weekly infusions of therapy. However, reactions have continued to occur with further infusions in some patients.
- Decrease in kidney function (41%), which could require dialysis
- Decrease in liver function (reversible) (37%)
- Hyponatremia (37%) which could cause a seizure
- Thrombocytopenia (36%) which in rare situations could lead to an increased risk of bleeding and/or need for platelet transfusions
- Hypokalemia (36%)
- Hyperglycemia (26%)
- Diarrhea (24%)
- Fatigue (21%)

Less likely (5-20% of patients):

- Elevated international normalized ratio (INR; 20%)
- Nausea (20%)
- Pyrexia (16%)

- Decreased appetite (13%)
- Vomiting (13%)
- Blood creatinine increased (12%)
- Numbness, tingling, stabbing pains in the hands and/or feet (10%)
- Arthralgia (9%)
- Dizziness (9%)
- Hypertension (9%)
- Neutropenia (9%)
- Hyperkalemia (9%)
- Cytokine release syndrome (8%)
- Headache (8%)
- Myalgia (8%)
- Elevated bilirubin (8%)
- Difficulty walking and/or weakness of the arms and/or legs (8%)
- Hematuria (7%)
- Influenza like illness (7%)
- Urticaria (7%)
- Dyspnea (5%)
- Abdominal pain (5%)
- Erythema (5%)
- Chest pain (5%)
- Rash (5%)

Rarely (but may be serious) (< 5% of patients):

- Cerebral hemorrhage
- Thrombosis which in rare cases can lead to a pulmonary embolus
- Vascular purpura
- Hemolytic uremic syndrome (HUS)
- Chronic Inflammatory Demyelenating Polyneuropathy (CIDP), which has led to the inability to walk

7.1.2. Supply, Packaging, Labeling, Storage of OGX-427

All clinical trial material will be labeled in accordance with local and federal regulations, stipulating that the product is for investigational use only. The drug product OGX-427 is

provided at a concentration of 200 mg/vial (25 mg/mL in 8 mL) in a USP Type 1 glass vial with a coated butyl rubber closure and aluminum seal with plastic flip-off button. The vials containing OGX-427 are to be stored in a secure, temperature monitored refrigerator at 2-8 °C until the time of use. OGX-427 vials require withdrawal and injection into an IV diluent solution (Dextrose in Water: D5W) using aseptic technique. Each vial will contain at least 8 mL fill volume. The contents of each vial will be a clear, colorless to slightly yellow liquid by visual inspection. OGX-427 diluted in D5W is stable for 24 hours when stored at room temperature.

At the completion of the study, all unused vials of OGX-427 must be returned to the Sponsor, unless there is a written Institutional procedure that calls for immediate disposal of unused drug product vials or the site is instructed otherwise by the Sponsor. All materials released for human clinical trials will be periodically tested and monitored for their acceptable shelf life for at least the duration of the study. Any material that fails to comply with the manufactured specifications will be promptly removed from the Investigative site and replaced with new clinical supplies by the Sponsor.

7.1.3. Administration

OGX-427 should be added to 250 mL 5% Dextrose in Water (D5W) as close to the time of administration as possible (see Pharmacy Manual for more details). The dose will be administered using either a peripheral or central indwelling catheter intravenously as an infusion over 2 hours. An infusion pump should be used. (See 14.1 for more detailed instructions).

7.1.4. Accountability

The Investigator or designee will maintain records of product delivery to the trial site, product inventory at the site, the dose given to each patient and the return of unused doses to OncoGenex (or where otherwise mandated, the destruction of unused doses).

7.2. Abiraterone Acetate

Abiraterone acetate is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

Based upon experience from clinical trials, abiraterone acetate is generally well tolerated. The most common adverse events related to abiraterone acetate monotherapy include fatigue, hypertension, fluid retention, and hypokalemia due to mineralocorticoid excess caused by compensatory adrenocorticotropic hormone (ACTH) drive. In this study, the concomitant administration of prednisone is expected to mitigate these side effects by supplementing cortisol and abrogating ACTH drive. When patients receive abiraterone acetate, they will also be prescribed prednisone (10-20 mg daily). If serious side effects develop related to mineralocorticoid excess, stress doses of steroids can be given.

Further information with regard to the drug product and drug substance may be found in the Package Insert for abiraterone acetate provided in the Study Procedure Manual for this study.

7.2.1. Risks and Precautions

Adverse reactions listed below were documented in a Phase 3 trial in patients who have been treated with **abiraterone acetate plus prednisone** (n=791); adverse events shown were due to abiraterone and occurred with either a ≥2% absolute increase in frequency compared to placebo or were events of special interest.

- Joint swelling/discomfort (29.5%)
- Edema (26.7%)
- Muscle discomfort (26.2%)
- Hot flush (19.0%)
- Diarrhea (17.6%)
- Urinary tract infection (11.5%)
- Cough (10.6%)
- Hypertension (8.5%)
- Arrhythmia (7.2%)
- Urinary frequency (7.2%)
- Nocturia (6.2%)
- Dyspepsia (6.1%)
- Fractures (5.9%)
- Upper respiratory tract infection (5.4%)
- Chest pain or chest discomfort (3.8%)
- Cardiac failure (2.3%)

7.2.2. Supply, Packaging, Labeling, Storage

Abiraterone acetate is commercially available in 250 mg tablets. Store at room temperature.

7.2.3. Administration

Abiraterone acetate will be administered orally at 1000 mg once daily in combination with oral prednisone taken twice daily. Abiraterone acetate must be taken on an empty stomach; no food should be consumed for at least 2 hours before and 1 hour after the dose. Please refer to the Package Insert for complete safety information and for administration directions. Missed doses are not made up.

7.2.4. Accountability

Evidence of prescription(s) as well as ongoing assessment of patient compliance with dosing regimen must be present in source documentation. Pill counts will not be conducted for this study.

7.3. Prednisone Treatment

Prednisone is a corticosteroid used for the treatment of many cancers and is usually given along with other anticancer drugs.

7.3.1. Risks and Precautions

Prednisone should be administered with fluids and food to decrease the risk of gastrointestinal complications. Prednisone can exacerbate diabetes mellitus, hypertension and chronic and acute infections. Prednisone can mask symptoms of infections.

Other Toxicities:

- Cardiovascular: fluid retention (common), hypertension, congestive heart failure.
- Gastrointestinal (GI): pain and/or ulcerations anywhere in the GI tract (common), weight increase (common), increased thirst, pancreatitis (rare).
- Infections: increased risk of acute and chronic infections (common).
- Metabolic: diabetes mellitus, fluid and electrolyte disturbances.
- Musculoskeletal: weakness (common), decrease in muscle mass (common), osteoporosis.
- Neurological: mood swings (common), depression, insomnia (common), dizziness, headache, confusion (rare), excitement (rare), psychosis (rare), seizures (rare).
- Ophthalmological: visual changes.
- Urological: increased frequency of urination.

Withdrawal of prednisone after prolonged therapy may result in symptoms such as fever, myalgias, and arthralgia which could be symptoms of adrenal insufficiency.

7.3.2. Supply, Packaging, Labeling, Storage

Prednisone is commercially available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets. Store at room temperature and away from heat, light and moisture.

7.3.3. Administration

Prednisone will be administered orally at 10-20 mg daily. Please refer to the Package Insert for complete safety information and for administration directions. Missed doses are not made up.

7.3.4. Accountability

Evidence of prescription(s) as well as ongoing assessment of patient compliance with dosing regimen must be present in source documentation. Pill counts will not be conducted for this study.

7.4. Other Risks and Precautions from Study Procedures

Other discomforts of this study are those of collecting blood, insertion of intravenous lines and lying in radiology machinery. Venipuncture causes transient discomfort and may cause temporary hypotension (e.g., fainting) from a vasovagal response. Bruising due to bleeding beneath the skin may occur if pressure is not applied long enough. Infection could occur at the site of needle insertion or insertion of an intravenous line. Edema, pain and/or phlebitis could occur at the site of an infusion if the drug leaks out into tissues. Back discomfort could occur when lying on hard tables while undergoing radiology assessments.

8. ADVERSE EVENTS

Safety will be assessed by consideration of all adverse events reported by or elicited from the patient and by abnormalities detected on hematology and serum chemistry tests and physical examination. All laboratory values will be separately graded for toxicity by the drug provider based on NCI CTCAE Version 4.0. Consequently, laboratory abnormalities do not have to be recorded on the Adverse Event eCRF unless they result in a dose modification or require treatment. Worsening of other pre-existing medical conditions and any changes to concomitant medications/treatments will also be taken into account in this evaluation.

All adverse events (serious and non-serious) beginning at the time of randomization and ending 30 days following the last dose of OGX-427 or at the End of Treatment Visit for the Control Arm will be recorded on the Adverse Event eCRF. Serious adverse events and grade 3 or higher adverse events that are ongoing at the end of study will be followed until each event resolves or is assessed as chronic.

8.1. Definitions

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration, at any dose, of a medicinal or therapeutic product whether or not considered related to that product.

Serious and severe are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that (at any dose):

- Results in death (death due to progressive disease will not be reported as an SAE)
- Is life-threatening (i.e., the patient was at risk of death at the time of the event)

- Requires inpatient hospital admission or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether or not reporting an SAE is 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 patient, or may require intervention to prevent one of the outcomes listed above. These should usually be considered serious (examples of such events are intensive treatment for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

8.2. Reporting of Adverse Events

All adverse events occurring during the study, whether or not attributable to the study treatment, observed by the Investigator or reported by the patient spontaneously or in response to a direct question, will be recorded in the patient's source documents and eCRFs. Adverse events will be graded in accordance with NCI CTCAE Version 4.0. (See Section 14.2.)

The nature of each event, start and end date, action taken in response to the event, outcome, NCI CTCAE toxicity grade, relationship to OGX-427, relationship to abiraterone acetate, relationship to prednisone treatment, and whether the event is serious should be established and recorded on the Adverse Event eCRF. All entries must be clearly documented in the source documents and the source documentation should be signed and dated by an Investigator.

Adverse events documented in the eCRF without a stop date should be reviewed at subsequent visits. Documentation regarding adverse events should be updated as necessary.

Adverse events changing in severity will be recorded as new adverse events**.**

Laboratory normal values used for the analyses and laboratory certification accreditation(s) will be provided for each site-specific laboratory and updated as required, at least yearly.

8.3. Reporting of Serious Adverse Events

Any SAE occurring in this study on or after the time of randomization must immediately be reported to both the Sponsor-Investigators and OncoGenex Pharmaceuticals Inc and/or others as described below.

The SAE Report Form (see Study Procedure Manual) should be faxed or emailed by the study site within 24 hours of initial knowledge of the event at the site. The form should be sent to Hoosier Cancer Research Network. Additional details are available in the Study Procedure Manual.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

All SAEs including those that are ongoing at the end of study will be followed until each event resolves or is assessed as chronic. The Investigator should provide conventional medical treatment if necessary and monitor the patient's condition until the event resolves or becomes chronic.

The SAE Report should be completed using standard medical terms and in English, to the best extent possible given the time constraints.

An adequate SAE Report includes the following minimum information:

- Study number
- Patient I.D. number and initials
- Event description including date of onset, outcome and reason for the event to be considered serious
- Name of investigational product including drug dose and administration dates
- Assessment of causality (none, possible, probable, definite)
- Person reporting event including site name or number

A follow-up report with additional information (e.g., duration of event with event outcome [resolution, ongoing, fatal], laboratory tests performed, other diagnostic tests performed and treatments) should be faxed in a timely manner to Hoosier Cancer Research Network, using a new SAE Report form stating this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation. Additional reports should be provided as soon as further information becomes available.

When all information has been obtained, and whenever possible, an SAE should be recorded as the diagnosis (e.g., small bowel obstruction) not as a series of signs and symptoms (e.g., abdominal pain, fever, vomiting).

OncoGenex (or delegate) will notify Investigators of other reportable SAEs occurring at other sites through "Dear Doctor" letters. The Investigator is responsible for informing the local IRB/REB of SAEs that occur at the site and reportable SAEs communicated by the Sponsor in compliance with local requirements.

Detailed instructions for reporting serious adverse events are available in the Study Procedures Manual.

8.4. Hoosier Cancer Research Network Requirements for Reporting SAEs

Hoosier Cancer Research Network will report any SAE to OncoGenex **within one working day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal requirements.

Hoosier Cancer Research Network will fax the SAE form to OncoGenex and will provide follow-up information as reasonably requested.

8.5. Assessment of Causality

The causal relationship between an adverse event and OGX-427, abiraterone acetate, and/or prednisone will be determined and documented separately by the responsible Investigator, or designee, according to best medical judgment as follows:

Table 7: Assessment of Causal Relationship to OGX-427, Abiraterone Acetate, or Prednisone

Category	Description
None	The event is definitely not associated with the OGX-427, abiraterone, or prednisone.
Possible	The event may be related to OGX-427, abiraterone, or prednisone. The event follows a reasonable temporal sequence following OGX-427, abiraterone, or prednisone administration but could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Probable	The event is likely related to OGX-427, abiraterone, or prednisone. The event follows a reasonable temporal sequence following the administration of OGX-427, abiraterone, or prednisone, abates upon discontinuation of OGX-427, abiraterone, or prednisone, and cannot be *reasonably* explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
Definite	The event is related to OGX-427, abiraterone, or prednisone. The event follows a reasonable temporal sequence following OGX-427, abiraterone, or prednisone administration, abates upon discontinuation of OGX-427, abiraterone, or prednisone and cannot be explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

9. SAFETY MONITORING

9.1. Data Safety Monitor

Safety monitoring will be performed by an independent data safety monitor (DSM) who will be appointed for this study.

Although OGX-427 was tolerable at 1000 mg doses in combination with docetaxel and an MTD was not reached in the Phase 1 study, this will be the first evaluation of OGX-427 in combination with abiraterone acetate. Thus, there will be a scheduled complete DSM safety review after the first 20 patients have been enrolled (10 patients per treatment arm) and treated for at least one cycle to assess the frequency of ≥ Grade 3 adverse events and serious adverse events. In addition, the independent DSM will perform real-time monitoring of serious adverse events for the first 20 patients. Frequency of further safety reviews will be determined by the DSM based on this early safety review.

The primary responsibility of the DSM will be overall safety for patients on the protocol. The DSM will monitor the safety of individual patients during the entire adverse event reporting period (i.e., from the first administration of Study Drug through 30 days after completion of study treatment). The DSM will:

- The sponsor will provide the DSM with a copy of any unexpected Study Drug-related SAE Report Form within 15 business days of receipt by the sponsor. The Medical Monitor will also provide the DSM with copies of all expedited SAE reports submitted to regulatory agencies.
- Perform periodic reviews of all safety data for individual patients. These listings would be based on the available safety data in the clinical study database and will include: demographic characteristics, general medical history (including concurrent illnesses), disease history, Study Drug administration, vital signs during infusion, clinical laboratory data (serum chemistry, hematology), and reported adverse events.
- Perform continued monitoring of Grade 3 and higher adverse events and SAEs on an ongoing basis for all patients.

9.2. Study Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The investigator/institution guarantees access to source documents by the Sponsor or its designee and appropriate regulatory agencies.

The trial site may also be required to participate in a quality assurance audit by OncoGenex or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigators and his/her relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

9.3. Data and Safety Monitoring Plan

Hoosier Cancer Research Network data safety monitoring activities include:

- Review of clinical trial conduct for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator and funding company of recommended action
- Notification of sites coordinated by the Hoosier Cancer Research Network of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

See Section 9.1 for additional details.

9.4. Data/Safety Monitoring and Reporting Guidelines

Hoosier Cancer Research Network will compile data summary reports for this trial and submit these reports monthly to the Sponsor-investigator. Hoosier Cancer Research Network will submit data summary reports a minimum of twice a year to a DSMC for review.

10. STATISTICAL CONSIDERATIONS

This section describes the sample size calculation and the planned statistical analyses for the primary and secondary efficacy endpoints and for safety.

10.1. Sample Size

The planned sample size is 74 patients. Patients will be randomized with equal probability to the two treatment arms.

Overall study success is defined as the primary endpoint meeting statistical criterion. The one-sided type I error probability for the outcome is specified to be 10%, giving an overall type I error probability for the primary endpoint of 20%.

For this endpoint, if it is assumed that the control arm success probability is 5% then there will be 90% power to detect a hypothesized 25 %-point increment in the success probability, with an increment of 12.9% or more defining the region of success for that outcome. If the control arm success probability is greater than 5%, the power will be less. For example, for a control arm success probability of 20% the power will be 78%, and for a control arm success probability of 40% the power will be 74%.

10.2. Analysis Sets

The All Randomized Analysis Set (ARAS) is defined as all subjects who are randomized. Subjects in the ARAS will be analyzed according to the arm into which they are randomized ("intent-to-treat" analysis).

The Safety Analysis Set is defined as all patients who were randomized and received at least one dose of study drug (OGX-427) plus continued treatment with abiraterone and prednisone on Arm A or were randomized and continued to receive abiraterone and prednisone only on Arm B. Subjects in the Safety Analysis Set will be analyzed according to the treatment actually received.

10.3. Efficacy Endpoints

10.3.1. Primary Endpoint

The primary objective of this study (Section 3.1) is to ascertain whether Arm A has a greater proportion of patients observed to be alive without progression at the milestone Day 60 assessment as compared to Arm B. The status of each patient at approximately Day 60 (window of Day 53-67) post-randomization is to be recorded as alive without disease progression or not (binary outcome) in order to compute the arm-specific proportion of patients who are alive without disease progression at approximately Day 60. This binary endpoint is called the milestone Day 60 status. Patients without an event prior to Day 60 post-randomization are to have a thorough disease assessment at Day 60 (window of Day 53-67) in order to establish the milestone Day 60 status. Day 60 as measured from the date of randomization will normally occur after completion of Week 8 treatment. However, the milestone Day 60 disease assessment must be completed within the inclusive window of Day 53 to Day 67 post-randomization, regardless of the timing of Week 8 treatment (i.e., if

treatment scheduling at any time has been delayed). An event is defined as evidence of disease progression on or before Day 60. Patients without events prior to Day 60 but who do not have the milestone Day 60 disease assessment (and are therefore protocol violations) will be classified as not being alive without disease progression at Day 60 (a conservative assumption relative to efficacy and enabling an intent-to-treat analysis for this endpoint).

This alive without disease progression endpoint is being evaluated as a milestone binary outcome in order to overcome potential bias associated with unequal between-arm progression assessment schedules in an open-label trial. Unequal assessment schedules are likely because the planned interventions in the two treatment arms are dissimilar.

The primary objective will be met if the proportion of patients in Arm A meeting the success criterion is significantly greater than the proportion of patients in Arm B meeting the success criterion at the milestone Day 60 assessment.

The primary analysis for this endpoint is Fisher's exact test for the 2x2 frequency table created by the combination of treatment arm (A, B) and endpoint (success, non-success). This Fisher's exact test can be regarded as a one-sided test of the between-arm difference in the proportion of successes. The null hypothesis of Arm A having an equal or inferior outcome relative to Arm B will be evaluated using the one-sided P value.

The statistical analyses for the primary efficacy endpoint will be performed for the set of all randomized subjects. Efficacy summary tables for the primary efficacy endpoint will be provided for both the set of all randomized subjects and the safety analysis set. (See Section 10.2 for definitions of analysis sets.)

10.3.2. Secondary Endpoints

The secondary objectives of the study are described in Section 3.2. Summaries of the secondary efficacy endpoints will be provided for the Safety Analysis Set.

PSA Response

Baseline PSA is defined as the PSA result at the Day 1 Week 1 visit. If the Day 1 Week 1 PSA result is missing then baseline PSA is defined as the PSA result at the Screening visit. At visits after Day 1 Week 1, the percent change from baseline PSA will be calculated for each subject. Best PSA response is defined as the maximum percent decrease from baseline PSA, or the minimum percent increase if there is no decrease. Patients who do not have PSA data after baseline will have missing data for best PSA response.

Best PSA response will be categorized as '≥ 30% decline,' '< 30% decline,' or 'missing' and the number (%) of patients within each category will be summarized by treatment arm. Similar summaries will be provided for best PSA response categories of '≥ 50% decline,' '≥ 90% decline,' and 'any decline.' Best PSA response will be also be summarized by treatment arm using descriptive statistics (e.g., number of subjects, mean, standard deviation, median, minimum, and maximum).

Objective Response

Objective response (see Section 6.4.2.1 for definition) will be assessed at Day 60, Week 16, Week 24, Week 32, Week 40, Week 48, End of Treatment, and at each visit during the

Off-Treatment Follow-Up Period. Best objective response is defined as the best response for each subject. The number (%) of patients in each best response category (CR, PR, SD, PD, NE) will be summarized by treatment arm.

For subjects with measurable disease at baseline, the baseline sum of lesion diameters and the percent change from baseline at each visit will be calculated. The best percent change from baseline will be summarized by treatment arm. The best percent change from baseline will be categorized as CR, PR, SD, PD, or NE and summarized by treatment arm. The definition for each of these categories follows:

- CR: A 100% decrease in the sum of diameters, taking as reference the baseline sum of diameters.
- PR: At least a 30% decrease (but < 100% decrease) in the sum of diameters, taking as reference the baseline sum of diameters.
- SD: Best percent change from baseline is defined, but does not meet criteria for CR, PR or PD.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- NE: No scans after baseline, or scans after baseline are not evaluable due to missing lesion measurements.

Progression-free Survival

Progression-free survival is defined as the time (weeks) from randomization to documented disease progression (see Section 6.4.1.2 for definition) or death from any cause. The following censoring rules will be applied to PFS:

- If there is no documentation of disease progression or death by the time of data cutoff, then PFS will be censored at the date of the last disease assessment before the data cutoff.
- Subjects who do not have any post-baseline disease assessments will be censored for PFS at the date of randomization.
- Subjects who initiate a new anticancer therapy will be censored for PFS at the date of the last disease assessment before the start of new anticancer therapy.

PFS will be summarized by treatment arm using Kaplan-Meier estimates, and Kaplan-Meier plots will be provided. Estimates of the median PFS and first and third quartiles will be provided using the Kaplan-Meier estimates along with two-sided 95% CIs. Estimates and 95% CIs will also be provided for the PFS probability at several time points based on the Kaplan-Meier estimates.

Time to Disease Progression

Time to disease progression will be summarized for the subset of patients who have documented disease progression (see Section 6.4.1.2 for definition). Time to disease progression will be summarized by treatment arm using Kaplan-Meier estimates, and

Kaplan-Meier plots will be provided. Estimates of the median PFS and first and third quartiles will be provided using the Kaplan-Meier estimates along with two-sided 95% CIs. Estimates and 95% CIs will also be provided for the PFS probability at several time points based on the Kaplan-Meier estimates.

CTC Counts

The baseline CTC count is defined as the CTC count at the Day 1 Week 1 visit. If the Day 1 Week 1 CTC count is missing then baseline CTC count is defined as the CTC count at the Screening visit.

The number of CTCs/7.5 mL will be summarized at baseline and at visits after baseline by treatment arm. The number (%) of patients with ≤ 5 CTCs/7.5 mL will also be summarized by treatment arm at baseline and at visits after baseline.

Levels of Hsp27 and Clusterin

The baseline result for each test is defined as the result at the Day 1 Week 1 visit. If the Day 1 Week 1 result is missing then the baseline result is defined as the result at the Screening visit.

Hsp27 and clusterin levels will be summarized at baseline and at visits after baseline by treatment arm using descriptive statistics (e.g., number of subjects, mean, standard deviation, median, minimum, and maximum). Similar summaries will be provided for change and percent change from baseline at visits after baseline.

10.4. Safety Summaries

Safety summaries will be provided for the safety analysis set (see Section 10.2 for definition).

Adverse events that occur multiple times for a subject will be counted only once per subject in summary tables. In tables that enumerate AEs by toxicity grade, only the worst toxicity grade for an AE occurring multiple times for a patient will be counted.

The number (%) of patients with at least one adverse event, at least one serious adverse event, and/or at least one Grade 3 or higher adverse event will be summarized by treatment arm.

Laboratory test results will be converted to standard international (SI) units and selected laboratory tests (lymphocytes, neutrophils, platelet count, hemoglobin, sodium, potassium, creatinine, bilirubin, AST, ALT) will be graded for toxicity using the criteria from CTCAE (Version 4.0) and normal ranges from the individual laboratories. If one or more normal ranges for a laboratory are missing then a standard normal range will be used to perform toxicity grading. The number (%) of patients with at least one laboratory toxicity and at least one Grade 3 or higher laboratory toxicity will be summarized by treatment arm and laboratory test. The incidence of laboratory toxicity will also be summarized for each laboratory test by toxicity grade and treatment arm. In these tables, only the worst toxicity grade for a patient will be counted for a toxicity occurring multiple times.

11. REGULATORY AND ETHICS CONSIDERATIONS

11.1. Informed Consent

The informed consent forms used for the study must comply with ICH E6 standard Good Clinical Practice (GCP), which is consistent with the principles that have their origin the Declaration of Helsinki and International Conference on Harmonization (ICH) Guidelines, and must have been approved by the Sponsor or Sponsor's representatives (prior to and after review by the site's IRB/REB) and the Investigator's IRB/REB. The Investigator or an authorized associate, who must be a physician, must explain the nature of the study and the treatment in such a manner that the patient is aware of his/her rights and responsibilities, as well as potential benefits and risks. The Investigator is also responsible for answering any questions the patient may have throughout the study and sharing any new information, in a timely manner, that may be relevant to the patient's willingness to continue his/her participation in the trial.

Patients must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent should be recorded in the patient's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, patients will be asked to sign and date the Informed Consent Form.

Patients, or their legally authorized representative, must give informed consent in writing prior to the performance of any protocol-specific procedure. Patients who cannot give informed consent (i.e. mentally incompetent patients or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients who are competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. A copy of the signed Informed Consent Form will be provided to the patient.

11.2. Institutional Review Board (IRB)/Research Ethics Board (REB)

Before the investigational product can be shipped to the investigative site and before the consenting and screening of patients at the site, the protocol, any protocol amendments, the consent form, any advertising materials, any materials to be provided to the subjects for the proposed clinical study and any other documents required by the local IRB/REB must be submitted by the Investigator for review and approval by the IRB/REB. The Investigator must also ensure that the IRB/REB reviews the progress of the study, if necessary, and renews its approval of the study on an annual basis. Any member of the IRB/REB who is directly affiliated with this study as an Investigator or as site personnel must abstain from the IRB/REB vote on the approval of the protocol.

All amendments or revisions to the protocol must undergo review by appropriate IRB/REBs. Amendments/revisions will be circulated to all participating sites with clear instructions regarding IRB/REB review. Amendments will be submitted by the Sponsor to the Therapeutic Products Directorate (TPD) and/or the Food and Drug Administration (FDA) and any other appropriate Regulatory Agencies prior to central implementation to the study, and by REBs prior to local implementation, EXCEPT when the amendment

eliminates an immediate hazard to clinical trial subjects or is of a purely administrative nature.

A copy of the IRB/REB approval letter must be forwarded to the Sponsor or Sponsor's representative before the study is implemented. The approval letter must clearly state the protocol title and version that was reviewed. The Investigator also must forward copies of subsequent amendment approval letters to the Sponsor upon receipt.

11.3. Patient Confidentiality

The Investigator must attempt to assure that the patients' confidentiality will be maintained within the limit of the law. Patients will be identified by patient number and initials (or other code) on all documents submitted to the Sponsor. Patients will not be identified by name.

All records will be kept in a secure place in the clinical research site. Computer data entry and data review programs will be done using patient numbers and initials (or other code) only. Clinical information will not be released without written permission of the patient, as outlined in the patient consent form.

The Investigator must maintain a separate screening log, including screen failures, of patient names and identification codes.

12. ADMINISTRATIVE PROCEDURES

12.1. Drug Provider Responsibilities

Following site initiation each study site will be provided with OGX-427 and study-related supplies. Upon completion of the study all unused supplies should be returned to OncoGenex or, upon notification from OncoGenex, destroyed according to local standard operating procedures, with documentation of the destruction.

All Investigators and their study personnel will receive training regarding the study procedures. This training will take place prior to enrollment of the first patient at each study site. Each study site will be provided with information regarding Good Clinical Practices and regulations specific to the conduct of clinical trials.

The study will be monitored by representatives of OncoGenex Technologies Inc. and/or designees. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol
- Verify that the research facilities, including laboratories and equipment, are adequate to safely and properly conduct the study
- Verify that the investigational product is stored properly and under the proper conditions, is in sufficient supply, and that receipt, use and return of investigational product at the study sites are controlled and documented adequately
- Verify that written informed consent was obtained before initiation of any screening procedures performed solely for the purpose of determining

eligibility for the clinical study and/or prior to the provision of study medication

- Review the patient eCRFs and source documents to ensure that reported study data are accurate, complete and verifiable from source documents
- Ensure that adequate records of clinical trial supplies are maintained
- Verify that the Investigator and study site personnel are adequately qualified throughout the study
- Verify that the safety information and amendments are submitted to the IRB/REBs

12.2. Investigator Responsibilities

All requested study data must be entered on the eCRFs for the study. For those patients who withdraw before completion of their specified treatment regimen, all available efficacy and safety data must be entered in the eCRF. The reason for withdrawal must be specified. Incomplete or inconsistent data on the eCRFs will result in data queries that will be returned to the Investigator for resolution.

The Investigator must maintain adequate and accurate source documents upon which eCRFs for each patient are based. The source documents are to be separate and distinct from the eCRF input data. An explanation should be provided for all missing data. The documents to be maintained must include, but are not limited to, detailed notes on:

- The medical history prior to participation in the study.
- The basic identifying information, such as demographics, that link the patient's source documents with the eCRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the patient.
- The patient's exposure to study treatment.
- All AEs.
- The patient's exposure to any concomitant therapy, including dates of administration.
- All relevant observations and data on the condition of the patient throughout the study.
- The oral and written communication with the patient regarding the study treatment, including the risks and benefits of the study. The date of informed consent must be recorded in the source documentation.

12.3. Regulatory Compliance

Quality Assurance representatives from OncoGenex or their delegate, the TPD, the FDA, and all other regulatory agencies as required will be allowed to periodically visit the Investigators/Investigative sites to discuss the conduct of the trial and, upon request,

inspect the records of the trial. These reviews are necessary to insure that the study is conducted according to standards consistent with the ICH Good Clinical Practice (GCP) Guideline.

The Investigator agrees to discuss and correct, if necessary, any problems or deficiencies that are found during the course of these reviews.

12.4. Ethical Conduct of the Trial / Good Clinical Practice

The Sponsor(s) follows the ICH E6 standard for GCP which is consistent with the principles that have their origin in the Declaration of Helsinki. This trial will be conducted in accordance with the International Conference on Harmonization (ICH) Guidelines on GCP, the US Code of Federal Regulations, the Food and Drugs Act (Health Canada), and local requirements regarding IRB/REB committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

12.5. Protocol Modification or Premature Termination

All protocol amendments must be approved by OncoGenex Technologies Inc. Each IRB/REB will review and approve amendments prior to their implementation in the study. IRB/REB approval need not be obtained prior to removal of an immediate hazard to patients.

Individual patient protocol modifications may only be made with regard to the following and must be well documented:

- Patient safety (in consultation with the PI)
- Dose modification as described in Section 6.6 (must be well documented)

OncoGenex Technologies Inc. may terminate the protocol early for safety or if other issues occur.

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14. APPENDICES

14.1. Drug Formulation / Pharmacy Guideline for OGX-427

Drug: OGX-427 which is an Antisense Oligonucleotide (ASO)

How Supplied: 200 mg per 8 mL solution resulting in a 25 mg/mL concentration for OGX-427 in a 10 mL vial.

Appearance: Clear, colorless to slightly yellow solution.

Packaging: 10 mL USP Type I glass vial with a coated butyl rubber closure and aluminum seal with a plastic flip-off button. Vials are provided in cartons.

Storage: Undiluted concentrate vials to be refrigerated 2 – 8°C (36 -46°F). Protect from heat and direct sunlight. The drug product does not contain a preservative and is intended for single use only.

Handling: Per sterile treatment drug procedures at the study site.

Diluent/Dilution: Add the specified amount of OGX-427 to 250 mL of 5% Dextrose in Water for Injection, USP (D5W).

Stability: OGX-427 is stable for 24 hours when diluted in D5W.

Administration Route: Continuous intravenous infusion with infusion pump.

Dosage: See protocol for study-specific details.

Treatment Duration: 2 hour intravenous infusion.

Drug Re-supply: Please refer to the study-specific ***Clinical Supplies Shipment Request and Verification*** form, found in the Study Procedure Manual. For specific questions regarding re-supply, please contact OncoGenex Technologies Inc.

GENERAL INFORMATION

Detailed procedures for receipt and reorder of drug can be found in the Pharmacy Manual. All shipping and receipt documents found in each shipment should be filed in the pharmacy binder along with the accountability records.

OGX-427 Drug Product, 25 mg/mL, Injection is formulated as a mannitol-phosphate buffer solution (pH 7.4) for IV administration and is supplied as an 8 mL solution containing 200 mg OGX-427 in a single vial (10 mL clear glass). The drug substance and active ingredient of OGX-427 is an ASO. All vials of OGX-427 will be labeled as required by the relevant regulatory agencies and must be stored in a secure, temperature monitored refrigerator, at a temperature of 2 - 8° C (36-46° F) within the hospital pharmacy until the time of use. DO NOT FREEZE.

OGX-427 dosing solutions will be prepared and dispensed by the pharmacy according to the method of preparation described below. All OGX-427 dosing solutions will be administered intravenously using an infusion pump (preferably). Once mixed for administration, it is recommended that the OGX-427 dosing solution be administered within 24 hours if kept at room temperature or in a refrigerator (2-8° C, 36-46° F). The

pharmacist must maintain an accurate accountability record documenting the utilization of the investigational product at the clinical site.

DRUG DILUTION PROCEDURE

The OGX-427 drug dilution procedure should be performed according to the instructions below and following proper aseptic technique:

1. OGX-427 should be stored between 2 - 8° C (36 – 46°F) prior to use.
2. Once dose instructions have been received from the site Investigator, remove OGX-427 from the refrigerator and inspect the vials for particulate matter. Vials containing particulate matter should not be used.
3. Using proper aseptic technique withdraw the correct amount of OGX-427 from each vial using a syringe and a needle.

Dose Period	Dosage	# of vials	Volume of OGX-427
Loading Doses (Week 1)	**600 mg**	3	24 mL
Weekly Doses (Beginning Week 2)*	**800 mg**	4	32 mL

*Subtract 1 vial (200 mg) if a dose reduction of OGX-427 is required due to toxicity (A maximum of 2 dose reductions allowed after Week 2).

4. Add OGX-427 to 250 mL of intravenous 5% Dextrose in Water (D5W) solution. Attach the intravenous tubing to the bag and prime the IV line with the D5W solution.
5. Label the bag with appropriate identification.
6. OGX-427 can be administered via a central venous line for continuous intravenous infusion or a secure peripheral line may be used. This decision is at the discretion of the Investigator. The infusion should be administered over 2 hours using an infusion pump.

RE-SUPPLY OF INVESTIGATIONAL PRODUCT

Re-supply of investigational study agent, OGX-427, will be managed by OncoGenex Technologies Inc. or a designated drug management vendor. All re-supply requests should follow the instructions found in the Study Procedure Manual. Request for re-supply must originate with the clinical trial pharmacist at the site.

ACCOUNTABILITY/DISPOSAL OF INVESTIGATIONAL PRODUCT

Unless other procedures are agreed upon prior to study start, all used vials of OGX-427 must be maintained within the pharmacy for ongoing drug accountability, to be performed by the study monitor throughout the conduct of the trial. Any discrepancies in drug accountability must be explained in writing and filed in the Investigator Study File and with OncoGenex Technologies Inc.

All used and unused OGX-427 vials will undergo final reconciliation at the pharmacy at the end of the trial. Drug accountability and reconciliation will be performed by the CRA/monitor prior to the product destruction by the pharmacy. At the end of the study, sites will be informed whether unused drug will either be returned to OncoGenex or destroyed at the site. All product destruction must be done by incineration in accordance with the institution's Standard Operating Procedures. A copy of the Standard Operating Procedure for drug destruction should be collected and on file with the Sponsor.

14.2. Toxicity Grading Scale: NCI CTCAE Version 4.0

This information is also available on-line at: **NCI CTCAE Version 4.0**

14.3. Processing and Shipping of Study Samples

Specimen collection kits (containing all required blood collection tubes, storage vials and laboratory order form) will be provided to each of the participating clinical sites.

Following completion of all correlative analysis, any remaining research samples will be destroyed within 3 years following completion of the study.

Circulating Tumor Cell (CTC) Sampling:

CTC samples will be collected into a 7.5 mL CellSave® Preservative Tube (provided by the Sponsor). The samples must be collected and then shipped on the same day by an overnight courier. Samples will be processed on the CellTracks AutoPrep System® with the CellSearch Circulating Tumor Cell Kit®. Epithelial cells in the enriched sample will be characterized and counted (CK+/DAPI+/CD45-) with the CellTracks Analyzer II®.

All samples will be sent to:

Jenny Bazov

Analytical Pharmacology

Prostate Centre at Vancouver General Hospital

The Jack Bell Research Centre

2660 Oak Street

Vancouver, BC V6H 3Z6

(604) 875-4908

E-mail notification must be given prior to shipment of any samples addressed to:

hadomat@prostatecentre.com

eli@prostatecentre.com

jbazov@prostatecentre.com

All CellSave Preservative tubes for CTC analysis must be shipped at ambient temperature by express overnight delivery on the same day after they have been drawn. Collection of samples in CellSave preservative tubes should be coordinated with Jenny Baybik via e-mail or phone (604-875-4111 ext 68661) or Estelle Li via email or phone (604-875-4111 extension 63213) prior to sample collection.

Blood Collection for Assays for Evaluating Hsp27, Clusterin, and Other Relevant Proteins:

7 mL of blood for serum (red-top tube or equivalent, no additives) and 7 mL of blood for plasma (EDTA) will be collected. For serum, allow the blood to clot at room temperature for 20-30 minutes. For both serum and plasma, centrifuge samples at 4°C for 15 minutes at 3500 RPM. Serum and plasma will be removed and transferred into three polyethylene tubes (for a total of three aliquots of serum and three aliquots of plasma). These tubes should be labeled as serum or plasma with the date/time of collection and patient number indicated.

Note: hemolysis and platelets can affect the Hsp27 results. Hemolyzed samples should be redrawn. To assure that platelet contamination does not occur, please pipet the Hsp27 aliquot first (before the clusterin sample) from the upper half of the serum layer, making sure that the buffy coat is not disturbed.

Short term storage (less than 1 week) at -20 °C is acceptable; however, storage at -80 °C is recommended for longer storage if batch shipping.

All samples will be sent to:

Jenny Bazov

Analytical Pharmacology

Prostate Centre at Vancouver General Hospital

The Jack Bell Research Centre

2660 Oak Street

Vancouver, BC V6H 3Z6

(604) 875-4908

E-mail notification must be given prior to shipment of any samples addressed to:

hadomat@prostatecentre.com

eli@prostatecentre.com

jbazov@prostatecentre.com

Original Pathology Sample/Report for Evaluation of PTEN Deletion Status:

If available, all patients randomized to the study will have representative sections from a paraffin block of their primary diagnostic tumor specimen evaluated for PTEN deletion status by fluorescence in situ hybridization (FISH). After a patient is randomized to the study, obtain a section of the original paraffin tumor block (or unstained slides) and a copy of the original (redacted) pathology report. Prepare 3 slides with 6 µm thick sections from the archival paraffin blocks (known to contain cancer from prostatectomy or core biopsies) and send to the address below. Slide sets should be sent in batches upon notification from the sponsor and will not be returned.

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Sample Schedule for CTCs and Serum/Plasma for Hsp27, Clusterin, and Other Relevant Proteins

Sample Timepoint	Blood for CTC	Serum/Plasma for Hsp27, Clusterin, and Other Relevant Proteins
Screening Baseline	X	X
Week 1, Day 1	X	X
Week 5, Day 1	X	X
Week 9, Day 1	X	X
Week 13, Day 1	X	X
After Week 13	Stop collecting blood for CTC	Collect serum and plasma for Hsp27, clusterin, and other relevant proteins every 4 weeks until disease progression or Week 21, at EOT visit, and every 4 weeks during Off Treatment Follow Up until disease progression

Further details on sample preparation, labeling, storage and shipment will be provided in the Study Procedure Manual.

14.4. Guidelines to Evaluate the Response to Treatment in Solid Tumors (RECIST 1.1)

This information is available online at: **Revised RECIST Guideline (Version 1.1)**

14.5. ECOG Performance Status

This information is available at: **ECOG Performance Status**