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Protocol Title

A Randomized Phase 2 Study Comparing Docetaxel Alone to Docetaxel in Combination with OGX-427 in Patients with Relapsed or Refractory Metastatic Urothelial Carcinoma after Receiving a Platinum-containing Regimen
HCRN GU12-160; The Borealis-2 Clinical Trial

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Hoosier Cancer Research Network, Inc.

Trial Support and OGX-427 (IND# 71,700) Provided by
OncoGenex Technologies, Inc.

Investigational New Drug (IND) Application 117,291

Protocol Version 7 Date: 15OCT2014

PROTOCOL SIGNATURE PAGE

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a record for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

PLEASE COMPLETE & EMAIL COPY TO HCRN

SYNOPSIS	
TITLE	A Randomized Phase 2 Study Comparing Docetaxel Alone to Docetaxel in Combination with OGX-427 in Patients with Relapsed or Refractory Metastatic Urothelial Carcinoma after Receiving a Platinum-containing Regimen HCRN GU12-160; The Borealis-2 Clinical Trial
STUDY PHASE	II
OBJECTIVES	**Primary Objective:** • To determine whether docetaxel administered in combination with OGX-427 provides a survival benefit compared to docetaxel alone. **Secondary Objectives:** • To compare the safety and tolerability of OGX-427 in combination with docetaxel to that of docetaxel alone. • To compare overall response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (CR+PR+stable disease), duration of response, and progression-free survival (PFS) between the treatment arms. • To evaluate the effect of therapy with docetaxel and OGX-427 on serum Hsp27 levels and other serum proteins and explore their relation with clinical outcomes. • To evaluate the association of urothelial carcinoma expression of Hsp27 measured by immunohistochemistry (IHC) in archival tissue with clinical outcomes. • To evaluate the effect of therapy on peripheral blood circulating tumor cells (CTC) enumeration and expression of Hsp27 and other relevant proteins via immunoflourescence and levels of telomerase by quantitative polymerase chain reaction (PCR), and explore their relation with clinical outcomes. • Somatic (tumor) and germ-line DNA/ RNA will be isolated to allow future approved investigations to determine if somatic mutations in Hsp27, ABCB1, ABCG2, TUBB4 and other relevant genes of interest are associated with treatment outcome (optional informed consent).
STUDY DESIGN	This is a randomized, open-label trial to evaluate whether suppression of Hsp27 production using OGX-427, a second-generation antisense oligonucleotide (ASO), in combination with docetaxel can prolong survival time compared to docetaxel alone in participants with locally-advanced or metastatic urothelial carcinoma (UC) that are relapsed or refractory after receiving a platinum-containing regimen. A

	total of 200 subjects will be enrolled. One interim analysis will occur to determine whether to stop study enrollment based on survival futility. The trial will not be stopped early based on efficacy.
NUMBER OF PARTICIPANTS	N = 200
ELIGIBIILTY	Inclusion Criteria: 1. Participants must have a diagnosis of metastatic or inoperable, locally-advanced urothelial carcinoma (bladder, urethra, ureter and renal pelvis) (T4b, N2, N3, or M1 disease). NOTE: Mixed histological differentiation such as squamous, glandular (adenocarcinoma), and micropapillary are eligible unless the tumor is considered a pure histological variant according to the pathology report. Participants with any small cell features (mixed or pure histology) are not eligible. 2. Participants must have measurable disease defined as at least one target lesion that can be accurately measured in at least one dimension by RECIST v1.1 criteria (see Appendix A). Lesions in previously irradiated areas should not be selected as target lesions, unless there is demonstrated progression in the lesion. 3. Participants must have received prior systemic platinum-based chemotherapy for urothelial carcinoma. Specifically, participants must also meet one or more of the following criteria: • Initial metastatic recurrence < 1 year after the completion of perioperative therapy (i.e. neoadjuvant or adjuvant setting) and no more than one chemotherapy regimen administered in the metastatic or inoperable, locally advanced setting. OR • Initial metastatic recurrence > 1 year after the completion of perioperative therapy (i.e. neoadjuvant or adjuvant setting) with disease progression after the completion of at least one but no more than two chemotherapy regimens administered in the metastatic or inoperable, locally-advanced setting. OR • Disease progression after the completion of therapy administered in the metastatic or inoperable, locally advanced setting with no prior history of perioperative platinum-based therapy and no more than two chemotherapy regimens administered in the metastatic or inoperable, locally advanced setting. 4. Participants must be ≥ 18 years since no dosing or adverse event data are currently available on the use of OGX-427 in participants < 18 years of age. 5. Life expectancy of greater than 3 months.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix B).

7. Participants must have adequate organ and marrow function as defined below:
   - ANC ≥ 1,500/mcL
   - Hemoglobin ≥ 8 g/dL
   - Platelets ≥ 100,000/mcL
   - Total bilirubin ≤ 1.1 X ULN (≤ 2.0 X ULN if secondary to Gilbert's disease)
   - SGOT (AST)/SGPT (ALT) ≤ 1.5 X ULN
   - Serum creatinine ≤ 1.5 X ULN

8. Minimum of 21 days have elapsed since prior major surgery, with recovery from any adverse events.

9. Minimum of 14 days have elapsed since any prior radiation therapy, with recovery from any adverse events.

10. The effects of OGX-427 on the developing human fetus are unknown. For this reason, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment and for three months after completion of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

11. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria:

1. History of treatment with docetaxel or cabazitaxel in any setting. Participants treated with prior paclitaxel are eligible.

2. Prior enrollment in the OncoGenex Phase 2 Study OGX-427-02.

3. Participants may not be receiving other investigational agents.

4. Participants with known brain or spinal cord metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. NOTE: Brain imaging is not required unless the participant has symptoms or physical signs of central nervous system (CNS) disease.

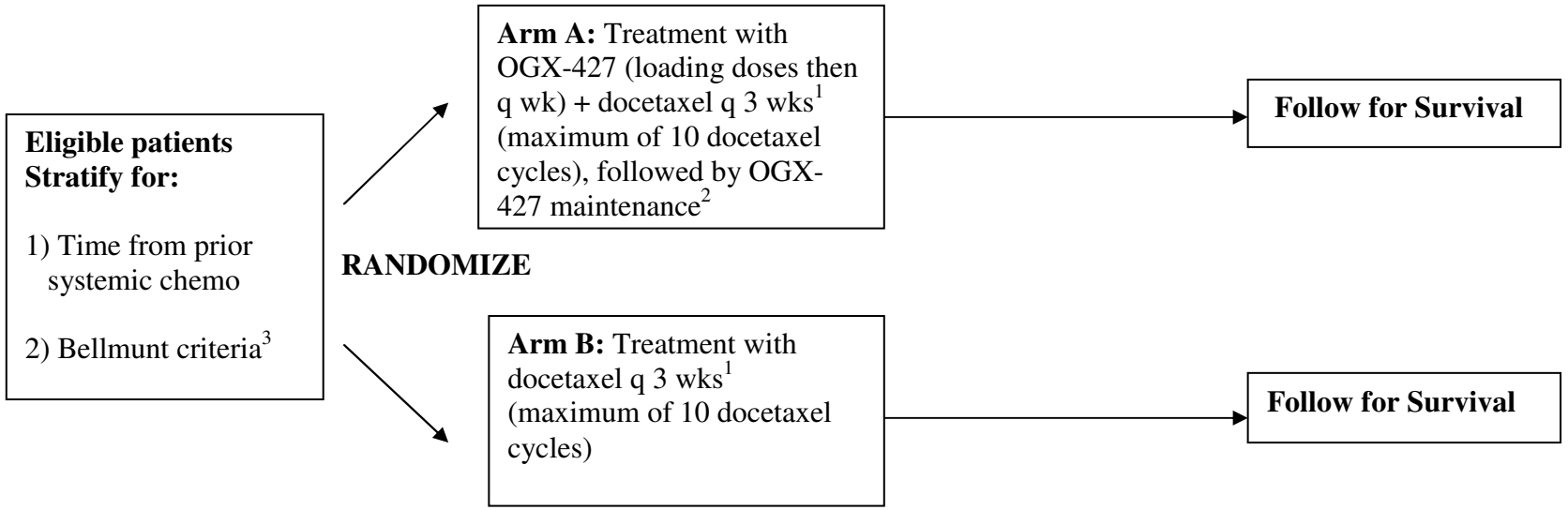
5. History of allergic reactions or severe hypersensitivity reactions to drugs formulated with polysorbate 80 or antisense oligonucleotides.

6. Peripheral neuropathy ≥ Grade 2.

	7. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. 8. Cerebrovascular accident, myocardial infarction or pulmonary embolus within 3 months of randomization. 9. Pregnant women and breast-feeding women are excluded from this study because of the risk to a fetus due to docetaxel chemotherapy and OGX-427 systemic treatment (fertility toxicology studies have not been completed for OGX-427). 10. Active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): active secondary malignancy is defined as a current need for cancer therapy or a high possibility (> 30%) of recurrence during the study.
EVALUATION CRITERIA	**NOTE:** Although response is not the primary endpoint of this trial, participants with measurable and/or non-measurable disease will be assessed by RECIST v1.1. For the purposes of this study, participants should be reevaluated every 6 weeks. **Primary:** • Overall survival (OS) is defined as the duration of time from randomization until death due to any cause, or censored at the date last known alive. **Secondary:** • Toxicity measured using NCI CTCAE v4.0 • RECIST v1.1 response criteria will be used to compare overall response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (CR+PR+stable disease), duration of response, and progression-free survival (PFS) between the treatment arms. • Descriptive measures to assess the effect of therapy with docetaxel and OGX-427 on serum Hsp27 levels and other serum proteins and their relation with clinical outcomes. • The association of urothelial carcinoma expression of Hsp27 will be measured by immunohistochemistry (IHC) in archival tissue with clinical outcomes. • Descriptive measures to assess the effect of therapy with docetaxel and OGX-427 on peripheral blood circulating tumor cells (CTCs) and their relation with clinical outcomes.

STATISTICAL CONSIDERATIONS	Participants will be randomized with 1:1 allocation to receive docetaxel ± OGX-427 using permuted blocks methods within strata.[39] Overall survival is defined in Section 10.4. Based on the docetaxel plus vandetanib vs. docetaxel trial[33] in a similar patient population, the median OS on the docetaxel control arm is expected to be 6 months (hazard rate of 0.1155). This study is designed to have adequate power to detect a 33% reduction in the OS hazard rate (to 0.0770) on the docetaxel + OGX-427 arm corresponding to a hazard ratio (docetaxel + OGX-427/ docetaxel) = 0.667. If OS follows an exponential distribution, then this difference corresponds approximately to a 50% improvement in median OS (to 9 months on the docetaxel + OGX-427 arm). The null hypothesis is no difference in treatment effect. The primary analysis is a superiority test of OS, performed at one-sided 0.10 significance level using a stratified logrank test.[40] There will be 90% power to detect this OS difference assuming 200 participants are enrolled over 31 months with 8 months of additional follow-up (39 months/3.25 years total duration). Full information under the alternative hypothesis will occur at 162 deaths. The Kaplan-Meier (KM) method will be used to estimate OS distributions by treatment arm.[41] A stratified Cox proportional hazards (PH) regression model will estimate the OS treatment hazard ratio and 80% 2-sided confidence intervals in unadjusted and adjusted models.[42] Exploratory subgroup analyses will investigate heterogeneity of treatment effects according to subgroups defined by the stratification factors, estimating hazard ratios within subgroups and testing for treatment-by-subgroup interaction in Cox PH regression models. The study will also be monitored for futility with one interim analysis, planned prior to completion of accrual at approximately 50% information (approximately 81 deaths). The decision for early rejection of the experimental therapy will be guided by a hazard ratio boundary using the spending function methodology of Lan and DeMets with O'Brien-Fleming parameter to adjust the boundary for the actual interim analysis time. If conducted precisely at 50% information, the cut-off hazard ratio is 1.052 corresponding to a z-scale value of -0.227. If the hazard ratio estimate lies above 1.052, the study may be stopped early. Under the null hypothesis, the boundary crossing probability is 0.41. The futility rule with a beta spent of 0.020 at the one interim analysis is incorporated in the power calculation for efficacy and has negligible impact on sample size. Sample size and interim monitoring considerations used East version 5.2 (Cytel Inc.).
ENROLLMENT PERIOD	Approximately 31 months
FOLLOW-UP PERIOD	Duration of study treatment will depend on evidence of disease progression and tolerance. Participants will be followed until death. The primary analysis can be completed an estimated 8 months following enrollment of the last participant.

SCHEMA



[1] Treatment cycles will continue until disease progression by RECIST v1.1, unacceptable toxicity, completion of 10 cycles, or voluntary withdrawal.
[2] OGX-427 maintenance will continue in participants who do not have disease progression or who discontinue docetaxel due to toxicity but who do not have documented disease progression and have completed disease assessments following at least 2 cycles of chemotherapy. Maintenance treatment will continue until documented disease progression or unacceptable toxicity due to OGX-427
[3] The "Bellmunt criteria" are outlined in Section 5.6.

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1. OBJECTIVES

1.1 Study Design

This is a randomized, open-label Phase 2 clinical trial to evaluate whether suppression of Hsp27 production using OGX-427, a second-generation antisense oligonucleotide (ASO), in combination with docetaxel can prolong survival time compared to docetaxel alone in participants with metastatic or inoperable, locally-advanced urothelial carcinoma (UC) that relapsed after, or is refractory to a platinum-containing regimen. A total of approximately 200 subjects (100 in each arm) will be stratified (see Section 5.6) and randomized to a 1:1 ratio to one of two arms. One interim analysis will occur to determine whether to stop study enrollment based on survival futility. The trial will not be stopped early based on efficacy.

1.2 Primary Objective

- To determine whether docetaxel administered in combination with OGX-427 provides a survival benefit compared to docetaxel alone.

1.3 Secondary Objectives

- To compare the safety and tolerability of OGX-427 in combination with docetaxel to that of docetaxel alone.
- To compare overall response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (CR+PR+stable disease), duration of response (see Section 10.3.7), and progression-free survival (PFS) between the treatment arms.
- To evaluate the effect of therapy with docetaxel and OGX-427 on serum Hsp27 levels and other serum proteins and explore their relation with clinical outcomes.
- To evaluate the association of urothelial carcinoma expression of Hsp27 measured by immunohistochemistry (IHC) in archival tissue with clinical outcomes.
- To evaluate the effect of therapy on peripheral blood circulating tumor cells (CTC) enumeration and expression of Hsp27 and other relevant proteins via immunoflourescence and levels of telomerase by quantitative PCR, and explore their relation with clinical outcomes.
- Somatic (tumor) and germ-line DNA/ RNA will be isolated to allow future approved investigations to determine if somatic mutations in Hsp27, ABCB1, ABCG2, TUBB4 and other relevant genes of interest are associated with treatment outcome (optional informed consent).

2. BACKGROUND

2.1 Hsp27 as a Therapeutic Target for Cancer

Recent technological developments have opened new avenues to identify and validate target genes involved in oncogenesis and disease progression, especially in the area of treatment resistance. Several proteins have been identified and fully characterized at the Vancouver Prostate Centre that promote tumor progression and development of resistance by inhibiting apoptosis. This includes clusterin, a heat shock-like protein, and heat shock protein 27 (Hsp27).

Heat shock proteins are a family of highly conserved proteins whose expression is induced by cell stressors such as hyperthermia, oxidative stress, cytotoxic chemotherapy, and radiation. Heat shock proteins such as Hsp27 potently inhibit amorphous aggregation of target proteins under stress conditions, acting on the slow, off-folding protein pathway to play a key role against harmful protein accumulation.

Hsp27 has a multiplicity of cellular and molecular functions, including transcription factors, signal-transducing receptor kinases, cell-cycle regulators, steroid hormone receptors, and delivery of ubiquitin-proteasomal degradation pathway.1,2 Cells recovering from stress contain elevated levels of Hsp27 and consequently are in a cytoprotected state against a subsequent exposure to a normally lethal stress exposure.3 Although an important modulator of the stress response in normal cells, in cancer Hsp27 also stabilizes mutated or inappropriately activated oncoproteins that contribute to the initiation, growth, and metastasis of human cancers.4-8 Cancer cells express high levels of Hsp27, in part a consequence of mutated, misfolded protein load and are, therefore, pre-adapted to resist treatment-induced cell death.

Hsp27 interacts with many key apoptosis-associated proteins to regulate a cell's apoptotic rheostat, including the intrinsic and extrinsic pathways. The intrinsic pathway primarily functions through intracellular death signals, which trigger outer mitochondrial membrane permeabilization, leading to the release of cytochrome-c. Cytochrome-c interacts with Apaf-1 and caspase-9 to form the "apoptosome" which activates caspase-3, leading to an activation cascade of downstream caspases, the so called "effectors" of cell death. The extrinsic pathway is activated through cell membrane-associated proteins of the TNF receptor family (such as Fas, Trail-R1, Trail-R2 and others) which can trigger caspase-independent apoptosis or directly activate caspase-8, which leads to activation of the downstream effector caspases. Hsp27 inhibits apoptotic cell death by a variety of mechanisms involving both pathways. Hsp27 can inhibit apoptosis by preventing release of mitochondrial cytochrome-c,[9] by directly interacting with caspase-3,[10] inhibiting Fas-induced caspase-independent apoptosis,[10,11] counter-acting reactive oxygen species[12] and by stabilizing and accelerating recovery of actin filaments, thus preventing disruption of the cytoskeleton.[13] Hsp27 is also involved in regulation of AKT[14] and enhances NF-kB activity by increasing degradation of I-κBα.[15] Hsp27 also chaperones and shuttles stat3 into the nucleus, enhancing transcription of several stat3-regulated survival genes.[16]

This brief review illustrates that Hsp27 may serve as a therapeutic 'hyper-node,' a target situated as a 'hub" at the center of many pathways regulating response of a cell to therapeutic stress. Targeting Hsp27 is attractive as it would affect multiple pathways implicated in cancer progression and resistance, as opposed to targeting a single pathway, a strategy that might have limited benefits in the face of the redundant signaling pathways and heterogeneity characteristic of cancer.

2.2 The Role of Hsp27 in Bladder Cancer

Many tumors have been shown to express Hsp27 including bladder, prostate, breast, ovarian, lung, endometrial, gastric and hepatic cancers, as well as leukemia and osteosarcoma.[17] The role of Hsp27 in bladder cancer is summarized below.

Hsp27 is expressed in low levels in normal bladder epithelium,18 but expression is increased in bladder cancer. Storm et al. were among the first to demonstrate by immunohistochemistry

(IHC) that Hsp27 was overexpressed in bladder cancers in > 50% of 23 patients who underwent radical cystectomy, with no expression in adjacent normal urothelium.[19] Another analysis of 42 patients with superficial bladder cancer showed that Hsp27 was highly expressed in over 50% of cells in 83% of tumors.[20] Kassem et al. investigated the expression-profile of stress-related and DNA repair genes by cDNA microarray analysis with qRT-PCR confirmation in both a radioresistant bladder carcinoma cell line (MGH-U1) and a radiosensitive cell line (S40b) both pre and post 2 Gy irradiation.[21] Only three genes, including Hsp27, showed consistent down regulation in the radiosensitive cell line, suggesting Hsp27 plays a role in radioresistance and might be a potential target for cancer therapy.

2.3 Antisense Oligonucleotide Strategies to Target Relevant Genes

Targeted therapies that have been approved for use in the clinical setting typically involve the use of small molecule inhibitors or antibodies. Unfortunately, many potential therapeutic targets are not amenable to such tactics, and, therefore, strategies to inhibit these targets at the gene expression level are an attractive concept. Antisense oligonucleotide (ASO) therapy is one such strategy to specifically target functionally relevant genes. ASOs are chemically modified stretches of single-strand DNA complementary to the mRNA regions of a target gene that inhibit translation by forming RNA/DNA duplexes, thereby reducing mRNA and protein levels of the target gene.[22,23] Expression of specific proteins can be reduced by blocking this translation, and subsequent cascades of protein-protein signaling control of cellular proliferation, differentiation, homeostasis and apoptosis can be altered. The specificity and efficacy of an ASO relies on the targeting afforded by Watson-Crick strand hybridization, where only a match between the target sequence and the ASO will lead to efficient hybridization and inhibition of translation. The ASO technology platform provides powerful tools to specifically target genes of importance in a number of human diseases, including cancer.

Various antisense chemistries have been evaluated to date. The most widely studied are phosphorothioate ASOs, water soluble agents designed to resist nuclease digestion through substitution of the non-bridging phosphoryl oxygen of DNA with sulfur.[24] As a class, phosphorothioate ASOs have been well tolerated, and, for the most part, toxicity has been non-sequence specific and attributable to the phosphorothioate backbone. However, in clinical trials with phosphorothioate “first generation” ASOs, continuous or frequent intravenous (IV) infusions were required because of their relatively short plasma half-lives and rapid degradation. Therefore, considerable effort has been made to improve the stability and potency of ASOs by modifications of the phosphodiester-linkages or alterations to the ring structure or the ribosugars.

Advances in nucleic acid chemistry have yielded ASO modifications such as the 2´-O-(2-methoxyethyl) or 2´-MOE modification to selected ribosugars that make an oligonucleotide more resistant to nuclease degradation.[25,26] The 2´-MOE modification is incorporated at the 2´-position of the ribosugar moiety at selected portions of the oligonucleotides. 2´-MOE ASOs form duplexes with RNA with a significantly higher affinity relative to unmodified phosphorothioate ASOs, which results in improved antisense potency both in cell culture systems and in animals. In addition, 2´-MOE ASOs display significantly improved resistance against nuclease-mediated metabolism relative to earlier types of phosphorothioate ASOs,[25,26] resulting in significantly improved tissue half-life *in vivo*, which produces a longer

duration of action and allows for a less frequent dosing regimen.[25] Finally, 2´-MOE ASOs have shown a more attractive safety profile than unmodified phosphorothioate ASOs.

2.4 OGX-427 as a Therapeutic Product

OGX-427 is an ASO 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. OGX-427 is a 4-12-4 MOE gapmer oligonucleotide with phosphorothiolated internucleotide linkages.

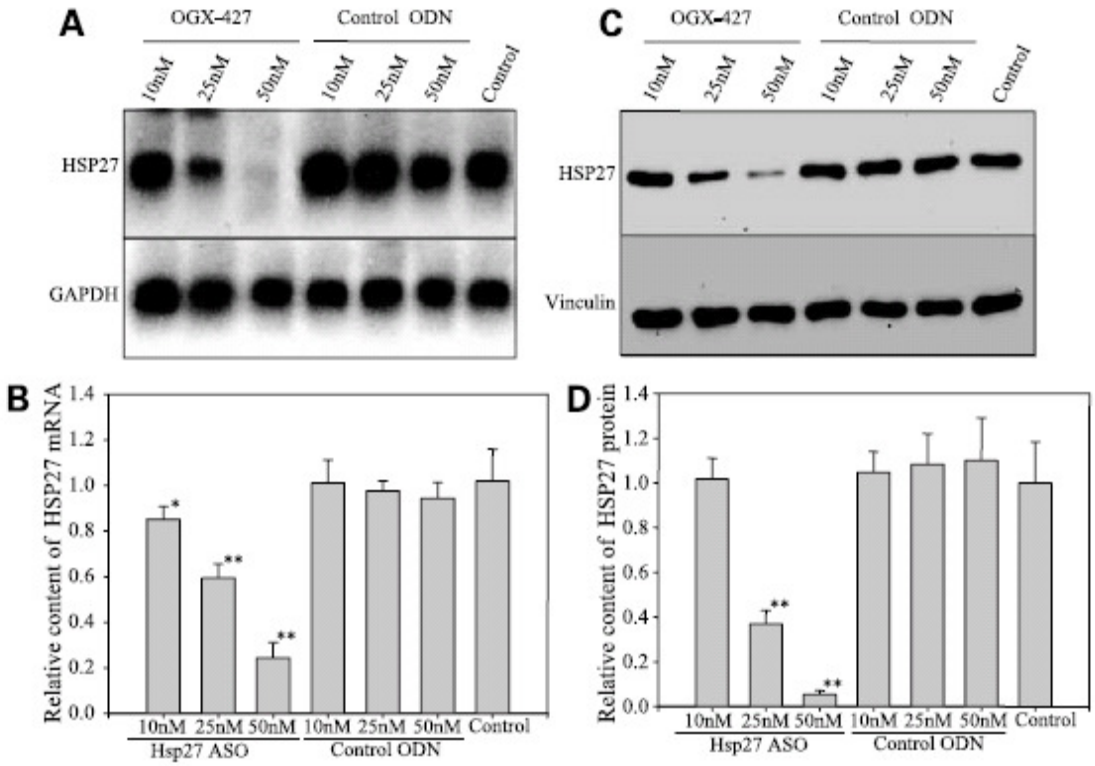
In preclinical studies, OGX-427 or an Hsp27 ASO was tested alone or in combination with other drugs in various animal tumor models. Studies were conducted with a control group administered a mismatched-sequence control ASO to the target mRNA. Reported below are representative experiments in bladder cancer. Other representative experiments in other cancer models such as prostate, lung, ovarian, pancreas and breast can be found in the Investigator's Brochure (IB).

2.4.1 *In Vitro* Preclinical Pharmacology Studies

Kamada et al. analyzed the functional significance of Hsp27 expression in bladder cancer cell growth, cancer progression, and treatment resistance to cytotoxic chemotherapy *in vitro* and *in vivo* using the human UMUC-3 bladder cell-line.[27] *In vitro*, they found that Hsp27 overexpression in UMUC-3 cells accelerated cell growth and increased resistance against paclitaxel by greater than 90%. Hsp27 knockdown by OGX-427 or Hsp27 siRNA reduced Hsp27 mRNA levels by up to 80% and Hsp27 protein levels by 95% in a dose- and sequence-specific manner. In addition OGX-427 enhanced the induction of apoptosis and chemosensitized cells to paclitaxel by greater than two-fold, reducing the IC50 by > 50%.

Figure 1 below demonstrates suppression of Hsp27 mRNA and protein expression levels by OGX-427.

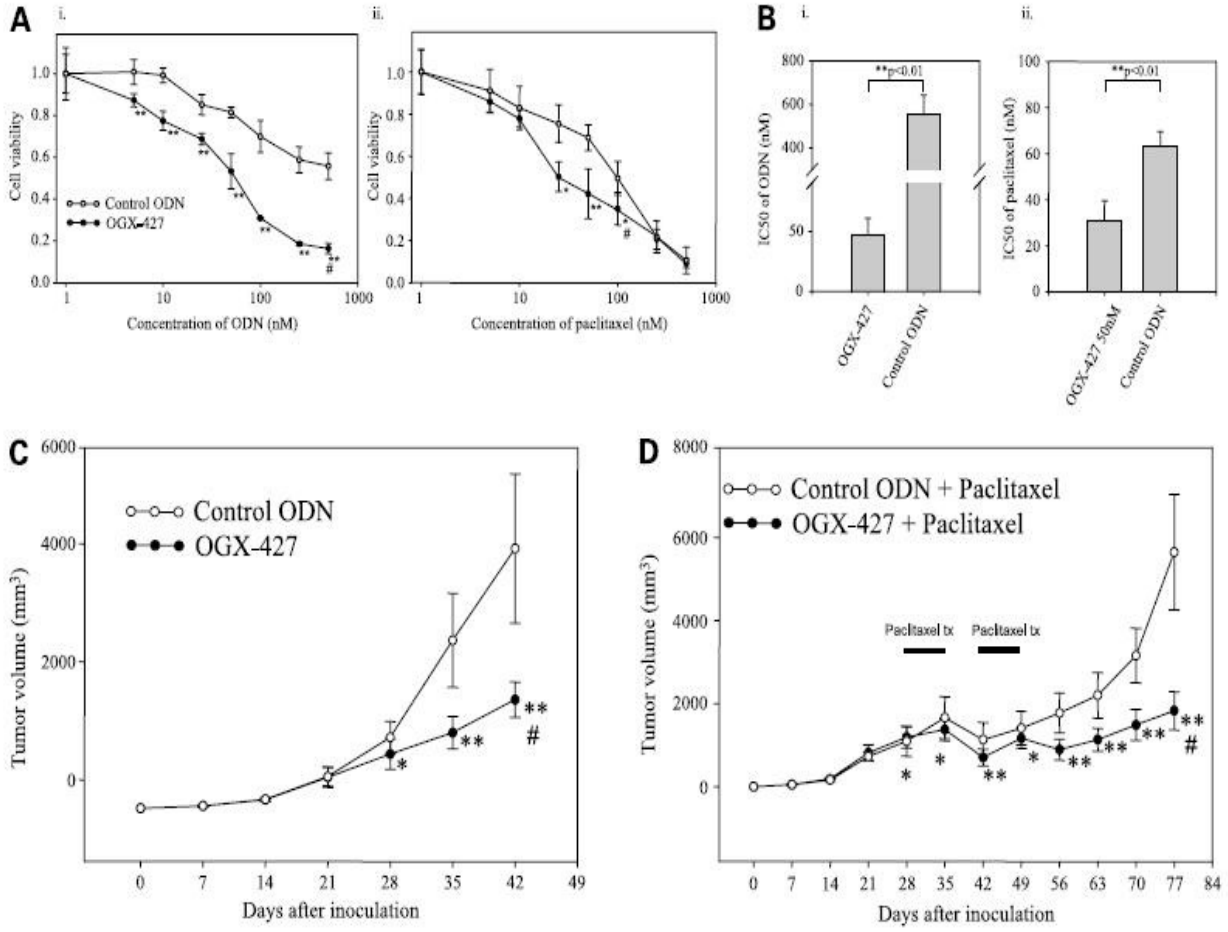
Figure 1: Sequence-Specific and Dose-Dependent Suppression of Hsp27 mRNA and Protein Expression Levels by OGX-427 in UMUC-3 Cells



A. UMUC-3 cells were treated with 10, 25, and 50 nmol/L OGX-427 or control ODN for 2 days. One day after treatment, total cellular RNA was extracted, and Hsp27 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA expression were analyzed by Northern blotting. Control cells treated with OligofectAMINE only. **B**. Quantitative analysis of Hsp27 mRNA levels from A after normalization to GAPDH by densitometric analysis. **C**. UMUC-3 cells were treated with various concentrations of OGX-427 and control ODN for 2 days. Two days after treatment, cellular proteins were extracted from cultured cells and Hsp27 and vinculin protein levels were analyzed by Western blotting. **D**. Quantitative analysis of Hsp27 protein levels from C after normalization to vinculin by densitometric analysis. *, $P < 0.05$; **, $P < 0.01$ differ from control ODN by Student's *t* test.

Figure 2 below demonstrates the cytotoxic effect of both OGX-427 monotherapy and combination therapy with OGX-427 and paclitaxel.

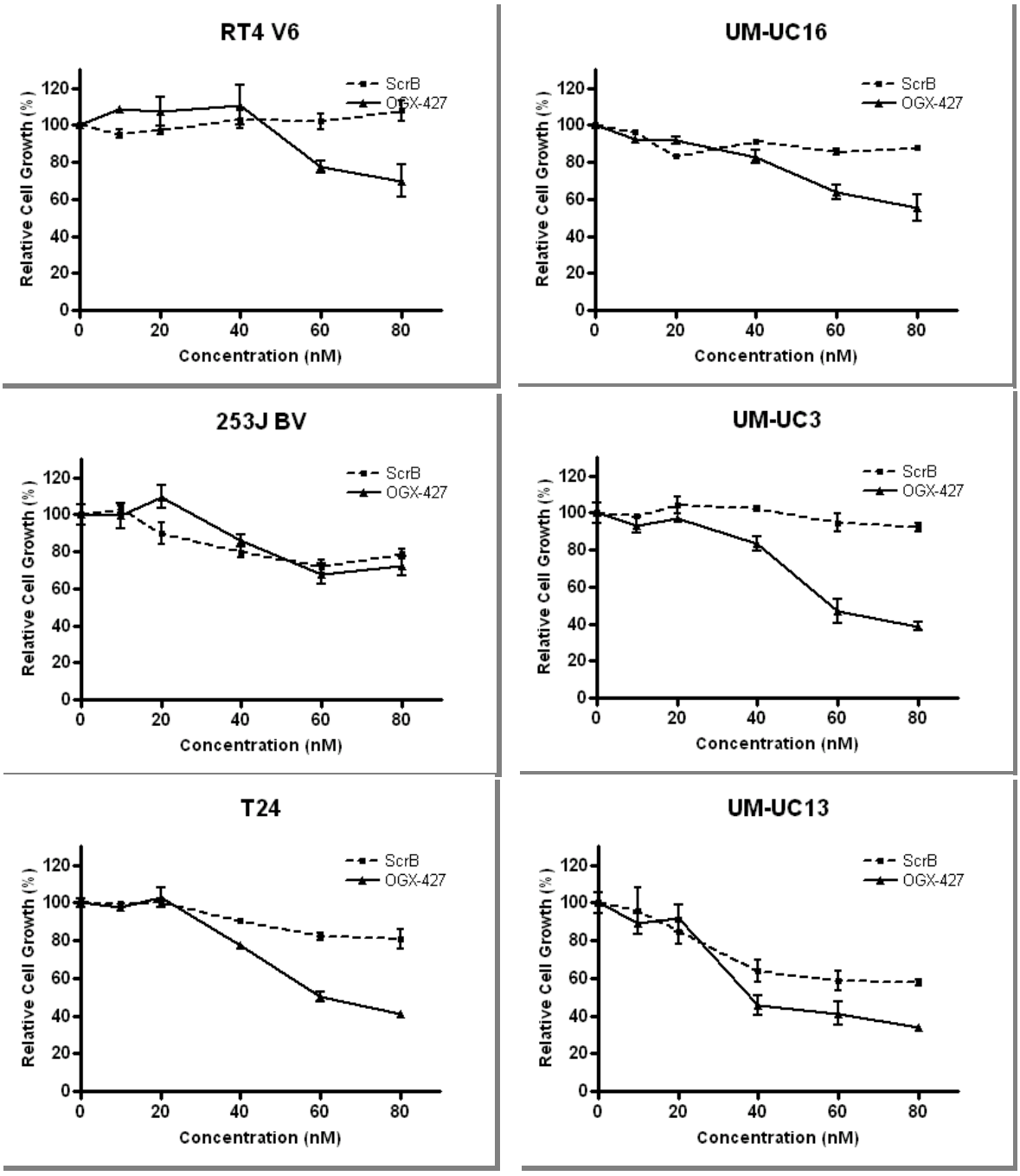
Figure 2: Cytotoxic Effect of both OGX-427 Monotherapy and Combination Therapy with OGX-427 and Paclitaxel



A. UMUC-3 cells were treated with various concentration of OGX-427 or control ODN for 2 d F paclitaxel. i, cells treated with increasing concentrations of ODN alone; cell viability determined by MTT assay after 48 h of treatment. ii, cells treated with ODN and paclitaxel; cells were initially treated with 50 nmol/L of ODN (either OGX-427 or control ODN). Chemotherapy of increasing concentrations was added after 2 d of treatment with respective ODN. After 24 h of incubation, cell viability was determined by MTT assay. **B.** IC50 was calculated from cell viability plots. The difference in each IC50 (i, ODN monotherapy; and ii, combination therapy of ODN + paclitaxel) was analyzed by Student's t test. **, $P < 0.01$; #, $P < 0.01$ (ANOVA-repeated measurement). **C.** Effects of OGX-427 monotherapy in vivo. When tumor volume was f100 mm3 (day 14), OGX-427 treatment was started. After 1 wk of an induction daily dose of 12 mg/kg/mouse OGX-427 or control ODN given i.p., mice were injected with the same dose thrice per week. Tumors were measured weekly. **D.** Effects of combination therapy in vivo. Combination treatment was started when tumor volume reached f500 mm3 (day 21). After 1 wk of a daily induction dose of either OGX-427 or control ODN at 12 mg/kg/mouse, mice were injected with similar doses thrice a week. Two cycles of i.v. paclitaxel treatment were given on days 28 to 35 and 42 to 49 at 0.5 kg/mg/mouse. *, $P < 0.05$, **$P < 0.01$ (Student's t test); #, $P < 0.01$ (ANOVA-repeated measurement).

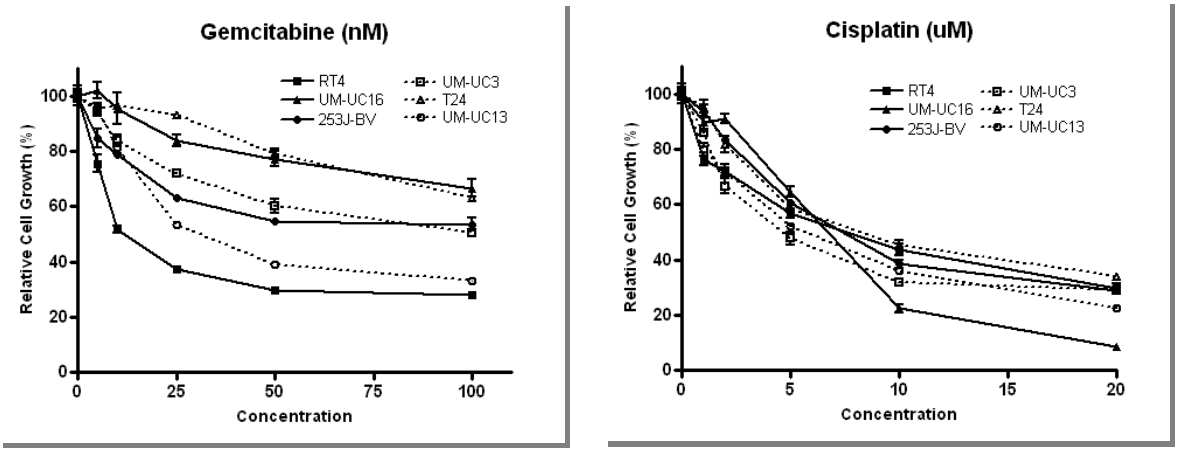
Gleave and colleagues have shown that OGX-427 demonstrated potent *in vitro* activity against four of six human bladder cancer cells lines, with IC50 below 100 nM, as shown in Figure 3 below (unpublished data).

Figure 3: Treatment with OGX-427 in Human Bladder Cancer Cell Lines



The IC50 values for gemcitabine (25-100 nM) and cisplatin (5-10 µM) monotherapy are illustrated in **Figure 4** below.

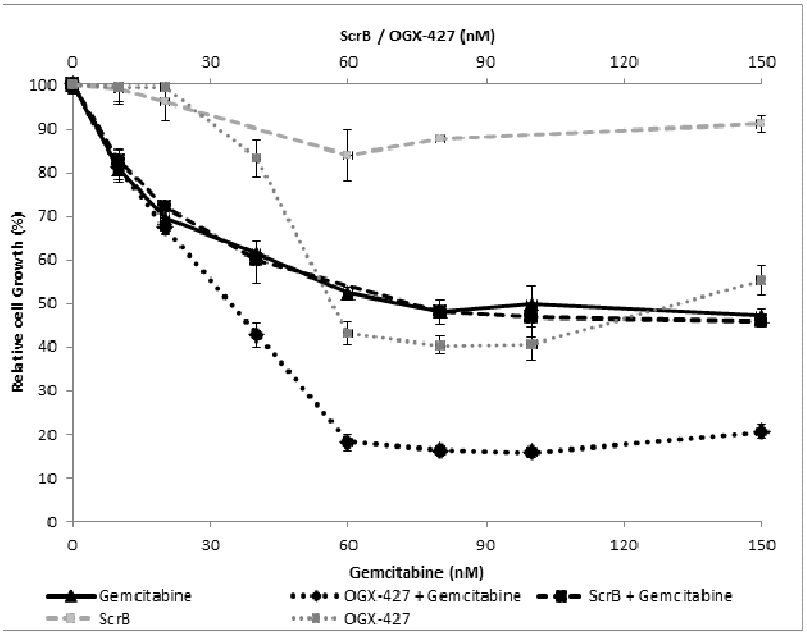
Figure 4: Treatment with Gemcitabine and Cisplatin in a Panel of Human Bladder Cancer Cells



OGX-427 synergistically sensitized gemcitabine cytotoxicity *in vitro* in several bladder cancer cell lines.

Error! Not a valid bookmark self-reference. below shows the combination of gemcitabine and OGX-427 cell growth assays in UM-UC16 human bladder cancer cells using the crystal violet staining assay. Cells were treated with two transfections 24 hours apart using oligofectamine plus OGX-427 or scr control oligo and then treated with indicated concentration of gemcitabine for 48 hours. The data illustrate dose dependent decreases in UM-UC16 bladder cancer cell growth with OGX-427 or gemcitabine monotherapy.

Figure 5: Treatment with OGX-427 and Gemcitabine in UM-UC16 Cells



P < 0.01 vs. Gemcitabine
P < 0.01 vs. ScrB + Gemcitabine

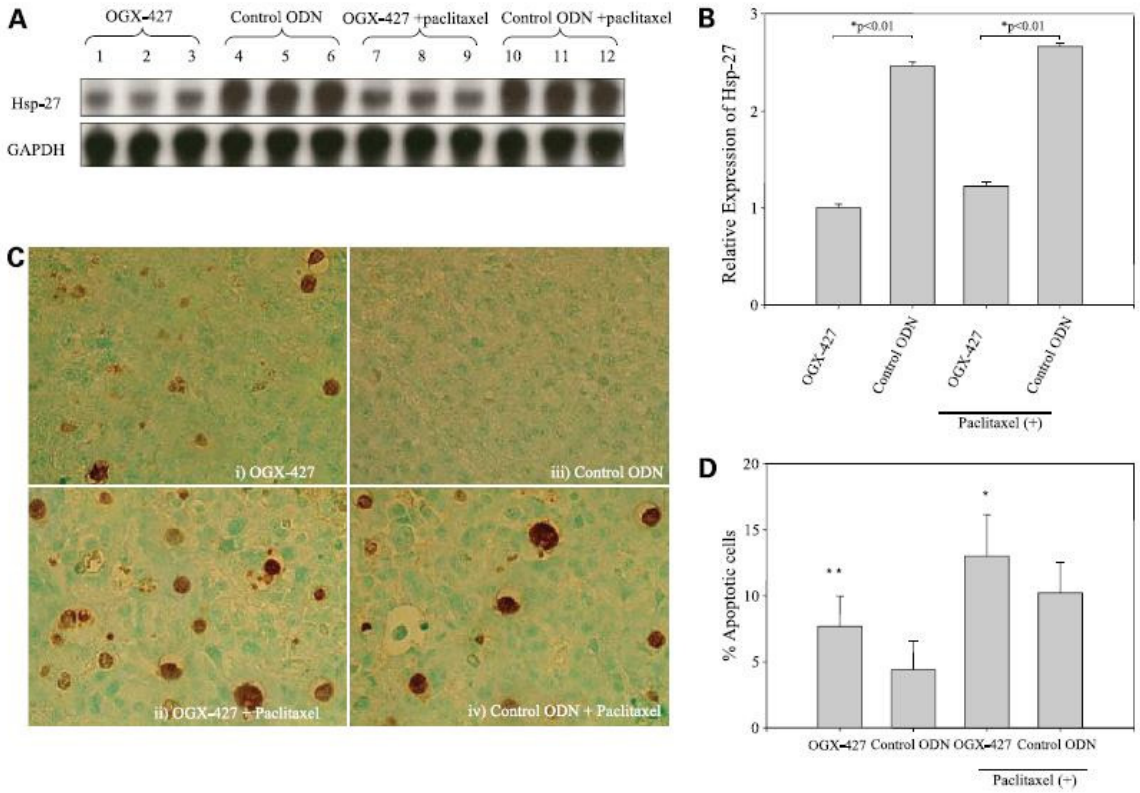
2.4.2 *In Vivo* Preclinical Pharmacology Studies

The effects of Hsp27 ASO on the growth of human tumors *in vivo* have been examined. Outlined below are representative experiments in bladder cancer. Other representative experiments in other cancer models can be found in the Investigator's Brochure.

OGX-427 significantly inhibited bladder tumor growth *in vivo* in mice, enhanced sensitivity to paclitaxel, and induced significantly higher levels of apoptosis compared to xenografts treated with control ASOs.

OGX-427 significantly inhibited bladder tumor growth *in vivo* in UMUC-3 xenografts.[27] OGX-427 combined with paclitaxel significantly inhibited tumor growth and enhanced apoptosis compared with tumors treated with paclitaxel plus control ASO.[27] Figure 6 below shows the effect of OGX-427 treatment on Hsp27 expression.

Figure 6: Effect of OGX-427 Treatment on Hsp27 Expression



A. Mice were sacrificed after treatment with OGX-427 or control ODN and ± i.v. paclitaxel. Total RNA was extracted from tumor tissue, and then Hsp27 and GAPDH were analyzed by Northern blotting. Lanes 1 to 3, OGX-427 administered to UMUC-3 tumors in mice; lanes 4 to 6, control ODN administered to UMUC-3 tumors in mice; lanes 7 to 9, OGX-427 Hsp27 + paclitaxel administered to UMUC-3 tumors in mice; lanes 10 to 12, control ODN plus paclitaxel administered to UMUC-3 tumors in mice. **B.** Quantitative analysis of Hsp27 levels after normalization to GAPDH mRNA levels were determined by densitometric analysis. **C.** UMUC-3 tumors were harvested from each treatment group for detection of apoptosis using TUNEL staining. Sections of paraffin-embedded UMUC-3 tumors were stained with digoxigenin dUTP antibody to detect apoptotic cells and imaged at 40 x magnification. i, UMUC-3 tumor after treatment with OGX-427; ii, UMUC-3 tumor after treatment with control ODN; iii, UMUC-3 tumor after treatment with OGX-427 plus paclitaxel; iv, UMUC-3 tumor after treatment with control ODN plus paclitaxel. **D.** After TUNEL staining, the number of apoptotic cells was counted and expressed as a proportion of the total number of cells in each microscope field at a magnification x 400. Ten fields were examined. Columns, means; bars, SD. *, $P < 0.05$, **$P < 0.01$ (Student's *t* test).

Collectively, these findings suggest that Hsp27 knockdown with OGX-427 and combined therapy with paclitaxel could be a novel strategy to inhibit progression of bladder cancer.[54]

2.4.3 Summary of Phase 1 and Phase 2 Clinical Studies Evaluating the Safety and Efficacy of OGX-427

A Phase 1 study evaluated patients with cancers that have been shown to over-express Hsp27 (breast, ovarian, prostate, non-small cell lung [NSCL], and bladder). Patients had to have metastatic disease and have failed all therapies felt to be curative or no curative therapy existed. OGX-427 was administered, initially as loading doses and then weekly, to 64 patients in 7

cohorts. The loading dose was the same as the weekly dose. In Cohorts 1 to 5, OGX-427 was administered as a single agent to 6 or more patients 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 OGX-427 in Cohort 5. OGX-427 plus docetaxel was administered to two subsequent cohorts, Cohorts 6 and 7, at 800 and 1000 mg of OGX-427, respectively.

OGX-427 appeared to be tolerated even at the highest dose of 1000 mg, both as a single agent and when combined with docetaxel. A maximum tolerated dose (MTD) was not reached at the doses tested. The major non-laboratory toxicity were infusion reactions (rigors, pruritus, flushing, pyrexia, arthralgia, hypertension, and erythema) which were seen in approximately 72% of patients and which appeared to be at increased frequency and severity at the highest doses (800 mg and 1000 mg). Patients received only acetaminophen or ibuprofen prophylaxis. The majority of the infusion reactions (93%) were grade 1 or 2 and mainly occurred during the loading doses and Cycle 1. Reactions were treated with antihistamines, H2 blockers, and steroids. Some patients required steroid prophylaxis for repeated infusion reactions. There was no evidence of prolongation of cardiac repolarization. Based on pharmacokinetic studies, although the half-life remained constant, there was a non-proportional increase in C_{max} and AUC_{inf} and a decrease in plasma clearance with increasing doses.

Twenty-two patients in this study were treated with OGX-427 plus docetaxel: 6 with 800 mg OGX-427 plus docetaxel and 16 with 1000 mg OGX-427 plus docetaxel.

Table 1 below summarizes the number of cycles administered, study disposition, and reasons for discontinuation for both cohorts receiving the combination. Two subjects received loading doses only, both at the 1000 mg OGX-427 dose. The remaining 20 patients (91%) received the 3 loading doses and started Cycle 1 treatment, completing a range of treatment from 1 to 10 cycles. The reasons for therapy discontinuation are shown in the table below. Two patients were discontinued from study therapy for an adverse event or treatment delay of > 3 weeks, and one patient withdrew consent.

Table 1: Disposition of Patients Treated with OGX-427 + Docetaxel (Study OGX-427-01)

	OGX-427 + Docetaxel (800 mg) (Cohort 6) (N=6)	OGX-427 + Docetaxel (1000 mg) (Cohort 7) (N=16)
No. of Treatment Cycles		
Loading Dose Only		2 (13%)
1 cycle		2 (13%)
2 cycles	2 (33%)	3 (19%)
3 cycles	1 (17%)	1 (6%)
5 cycles		1 (6%)
6 cycles		1 (6%)
7 cycles	1 (17%)	
8 cycles		2 (13%)
9 cycles	1 (17%)	1 (6%)
10 cycles	1 (17%)	3 (19%)
Reason for Discontinuation, n (%)		
Completed 10 cycles	1 (17%)	3 (19%)
Adverse event	1 (17%)*	
Investigator/DSM decision		2 (13%)
Treatment delay (>3w)		1 (6%)
Disease progression	3 (50%)	6 (38%)
Global deterioration	1 (17%)	1 (6%)
Withdrew consent		1 (6%)
Other		2 (13%)**

* Adverse event: fatigue/taste alteration
** Other: study drug availability (1 patient); fatigue/bone pain (1 patient)

Administration of OGX-427 plus docetaxel did not, in general, appear to have additive toxicity to the known docetaxel safety profile except possibly for Grade 3-4 neutropenia. No dose-limiting toxicities of OGX-427 were observed in either cohort in combination with docetaxel. Grade 3-4 non-laboratory and laboratory adverse events for the combination of OGX-427 and docetaxel were as expected for docetaxel, as shown below in

Table 2 and Table 3, respectively. Among subjects receiving OGX-427 plus docetaxel, the most frequent Grade 3 or higher non-laboratory adverse events were febrile neutropenia, dyspnea, fatigue, and arthralgia.

Table 2: Non-Laboratory Grade 3 or 4 Events by Decreasing Frequency Observed in More than One Patient Treated with OGX-427 + Docetaxel (Study OGX-427-01)

	OGX-427 + Docetaxel (800 mg) (Cohort 6) (N=6)	OGX-427 + Docetaxel (1000 mg) (Cohort 7) (N=16)
Febrile Neutropenia	0 (0%)	5 (31%)
Dyspnea	1 (17%)	2 (13%)
Fatigue	2 (33%)	1 (6%)
Arthralgia	1 (17%)	1 (6%)

Laboratory toxicity was determined based on laboratory data. The majority of laboratory toxicity events were Grade 1 or Grade 2. The most common (> 25% of subjects) Grade 3 or higher laboratory toxicities among subjects receiving OGX-427 plus docetaxel were neutropenia, lymphopenia, and prolonged aPTT, as shown in Table 3 below. Increases in lymphopenia and prolonged aPTT are known ASO-class effects but do not appear to have clinical sequelae. More detailed safety information on patients receiving this combination is available in the OGX-427 Investigator Brochure.

Table 3: Treatment-Emergent Laboratory Grade 3 or 4 Events Observed in Patients Treated with OGX-427 + Docetaxel (Study OGX-427-01)

	OGX-427 + Docetaxel (800 mg) (Cohort 6) (N=6)	OGX-427 + Docetaxel (1000 mg) (Cohort 7) (N=16)
Hematology		
Neutropenia	5 (83%)	13 (81%)
Lymphopenia	4 (67%)	11 (69%)
Anemia	1 (17%)	4 (25%)
Thrombocytopenia	0 (0%)	1 (6%)
Coagulation		
Prolonged aPTT	1 (17%)	10 (63%)
Elevated INR	0 (0%)	1 (6%)
Serum Chemistry		
Hyponatremia	1 (17%)	4 (25%)
Hypokalemia	0 (0%)	1 (6%)
Elevated Serum Creatinine	0 (0%)	1 (6%)
Hyperkalemia	0 (0%)	1 (6%)

Reductions in tumor markers were observed in patients with both prostate (PSA) and ovarian (CA-125) cancer. Declines of 50% or greater in both total CTCs & $Hsp27^{+}$ CTCs were observed in over half the patients. These results were observed in each of the 7 cohorts and each disease category enrolled.

Thirty of the 64 patients had baseline and at least one post-baseline assessment of measurable disease. A total of 8 of 30 patients (27%) had a decrease in measurable disease from baseline of at least 15%. Two heavily pretreated patients with metastatic bladder cancer and visceral metastases were treated with docetaxel and OGX-427 at the 1000 mg dose. One patient survived 8 months and the other survived 20 months.

A Phase 2, open-label, randomized, cross-over study is currently underway (Study PR-01). This study is designed to evaluate the anti-tumor effects of OGX-427 with prednisone compared to prednisone alone in men with CRPC who have not previously received chemotherapy for metastatic disease. 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; and circulating tumor cells counts pre- and post-study drug.

In the PR-01 study, subjects are randomized to a Treatment Arm, which starts with three loading doses of 600 mg OGX-427 within 10 days, followed by weekly doses of 1000 mg of OGX-427 IV along with prednisone, or to a Control Arm with prednisone alone. After documentation of disease progression, subjects on the Control Arm have the option to cross over to receive OGX-427 plus prednisone (designated as the Crossover Arm).

As of the cutoff date of April 26, 2012, safety data are available for 56 randomized subjects (27 in the Treatment Arm and 29 in the Control Arm). The most frequently reported non-laboratory AEs among subjects treated with OGX-427 (Treatment and Crossover Arms) were chills, diarrhea, nausea, and fatigue; the majority of AEs were Grade 1 or Grade 2. The most common laboratory AEs among subjects treated with OGX-427 were anemia, lymphopenia, and hyperglycemia. Because of the high frequency of infusion reactions in the Phase 1 study, especially at the higher OGX-427 doses, the loading dose for all subjects in study PR-01 was decreased to 600 mg. In addition, subjects in study PR-01 received both an antihistamine and a histamine antagonist as prophylaxis. Infusion reactions were seen in 52% of subjects.
Efficacy data are available on a subset of 42 subjects as of May 15, 2012 (22 in the Treatment Arm and 20 in the Control Arm). Twelve of 22 (55%) subjects in the Treatment Arm and 6 of 20 (30%) in the Control Arm had no documented disease progression at 12 weeks. Thirteen of 22 (59%) subjects on the Treatment Arm had a > 30% decrease in PSA compared to 6 of 20 (30%) on the Control Arm. Nine subjects in the Treatment Arm and 12 in the Control Arm had measurable disease at baseline. One subject in the Treatment Arm (11%) had a complete response based on measurable disease. Also in the Treatment Arm, 3 subjects (33%) achieved a partial response, 1 (11%) had stable disease, and 4 (44%) did not have a post-baseline assessment at the time of this analysis. In the Control Arm, 7 subjects (58%) achieved stable disease, 2 (17%) had disease progression, and 3 (25%) did not have a post-baseline assessment at the time of analysis.

Another Phase 2 study (Study OGX-427-02) is currently underway evaluating gemcitabine and cisplatin in combination with OGX-427 or placebo. This randomized, double-blind Phase 2 study is being conducted in patients with advanced transitional cell carcinoma who have not previously received chemotherapy for metastatic disease and are not candidates for potential curative

surgery or radiotherapy. The primary endpoint is overall survival (OS). The study also assesses safety and tolerability of OGX-427 in combination with gemcitabine and cisplatin; objective response; levels of Hsp27, clusterin, and CTCs; and pharmacokinetic parameters.
As of the cut-off date of April 26, 2012, 16 subjects have been randomized and 12 subjects have been treated in this study. Four serious adverse events have been reported to date in 4 subjects, including pneumonia, pulmonary emboli, renal failure, and pancreatitis. Safety data are currently blinded.

A fourth study with OGX-427 is ongoing at a single medical center in Canada (Study BL-01) as an Investigator-sponsored study. In this study, OGX-427 is administered by intravesical instillation (directly into the bladder) in subjects with bladder cancer prior to transurethral resection of the bladder tumor or radical cystectomy. In this Phase 1 study, subjects are treated with intravesical OGX-427 on days 1, 3, 5, and 8 and then undergo surgery on days 9-12. The dose of OGX-427 is being escalated after tolerability and safety assessment for each cohort (20uM, 50uM, 100uM, 250uM, 500uM, and 750uM). Objectives include safety and pharmacokinetics, pharmacodynamics, and biologic effects of intravesical OGX-427. Currently, 13 subjects have been enrolled in the trial, and the 250uM cohort has been completed. No significant drug-related adverse events have been reported and no dose limiting toxicity (DLT) has been observed. To date, pathological staging of surgical specimens revealed that 5 of the 13 patients (38%) had complete responses.

Please refer to the Investigator's Brochure for more detailed information on the safety and clinical trial results for OGX-427.

2.5 Metastatic Urothelial Carcinoma

Urothelial carcinoma is the fifth most common malignancy in the United States and accounts for 13,000 deaths yearly.28 Yet metastatic urothelial cancer has seen few significant advances in the last decade. Standard of care in the United States consists of a cisplatin-based upfront therapy (gemcitabine plus cisplatin [GC] or methotrexate, cisplatin, doxorubicin, and vinblastine [MVAC]). Once patients progress through one of these regimens, there is no second-line standard of care. Many agents, including docetaxel, paclitaxel, and ifosfamide, have shown single agent responses (between 10-20%, which improve with combination therapy),29-32 yet no randomized trial has shown the benefit of one over another. In fact, no second-line trial has demonstrated improved survival with any chemotherapy agent. Because of this lack of a gold standard, practice patterns differ, although taxane therapies are the most commonly used (either in combination or as single agents).

Relevant to this protocol, docetaxel (Taxotere) is a commonly used chemotherapeutic agent in urothelial carcinoma, both as a single agent and in combination with other therapies. In a Phase 2 study of single agent docetaxel in second-line or later metastatic urothelial carcinoma, the response rate was 13%, with a median survival of 9 months.29 This response rate and median survival is in line with other single agent chemotherapy Phase 2 trials in this patient population. The addition of vandetanib to docetaxel in the second, third, or fourth line did not result in improved overall survival (OS), progression-free survival (PFS), or overall response rate (ORR) among patients with metastatic urothelial cancer pretreated with platinum-based therapy. In this

randomized, double-blind, Phase 2 trial (n=142), patients receiving docetaxel plus vandetanib had a median PFS of 2.56 months, median OS of 5.85 months, and ORR of 7%; patients receiving docetaxel plus placebo had a median PFS of 1.58 months, median OS of 7.03 months, and ORR of 11%.33 In addition, patients on this trial did not show differences in PFS and OS based on prior history of paclitaxel treatment.

New agents or combination treatments that prolong survival in the second-line setting are urgently needed. In an effort to identify clinical and laboratory pretreatment factors that predict OS among second-line patients, Bellmunt et al. prospectively analyzed patients with metastatic transitional cell carcinoma of the urothelial tract who had treatment failure following first-line, platinum-based therapies and were enrolled in a Phase 3 clinical trial of vinflunine and best supportive care versus best supportive care alone.34 Three adverse risk factors were prognostic of OS: Eastern Cooperative Oncology Group (ECOG) performance status > 0, hemoglobin level < 10 g/dL, and the presence of liver metastases. A scoring system was developed to classify second-line urothelial cancer patients into four risk groups based on the presence of 0, 1, 2, or 3 of these prognostic risk factors. Application of this scoring system to the 370-patient cohort resulted in median OS times for these groups of 14.2, 7.3, 3,8, and 1.7 months (P<0.001), respectively.

In addition, time from prior chemotherapy has been shown to be important in determining outcomes in previously treated urothelial carcinoma patients.35 Patients with less than 3 months since the last date they received prior chemotherapy to the date of initiation of subsequent chemotherapy had significantly worse outcomes compared to those that initiated subsequent therapy 3 months or later.

2.6 Rationale

Current treatments for urothelial carcinoma have limited success in preventing tumor recurrence and/or progression, and overall mortality rates have remained fairly constant. The prognosis of patients with invasive or metastatic disease is extremely poor. Cisplatin-based chemotherapy regimens, such as gemcitabine and cisplatin, are the mainstay of treatment for patients with advanced disease. However, twenty years of experience have failed to make much progress in improving patient outcomes. Although urothelial carcinoma is considered to be a chemotherapy-sensitive neoplasm, the efficacy of combination chemotherapy has been restricted because of de novo drug resistance and acquired resistance. Thus, there is a need to identify mechanisms by which cancer cells inhibit the effects of chemotherapy and to develop novel treatments that, hopefully, improve survival, especially in relapsed or refractory urothelial carcinoma after receiving platinum-based chemotherapy.

Heat shock proteins such as Hsp27 play a crucial role in regulating the balance between cell survival and death by acting as molecular chaperones to facilitate transport, folding, and assembly of polypeptides. Hsp27 expression is increased in many cancers including bladder cancer. Overexpression has been associated with inhibition of apoptosis, increased cytoprotection, and the development of treatment resistance by inhibition of apoptotic cell death induced by chemotherapeutic agents. ASOs specifically hybridize with complementary mRNA regions to form RNA/DNA duplexes to inhibit target gene expression. OGX-427 is a second-

generation ASO that effectively targets and down-regulates Hsp27 mRNA and has been shown to increase apoptosis, inhibit tumor growth, and sensitize cells to chemotherapy in a variety of malignancies including bladder cancer. These findings provide preclinical proof of principle for its use in the treatment of this disease.

A Phase 1 study in patients with prostate, breast, ovarian, lung, and bladder cancer has shown tolerable doses of OGX-427 up to 1000 mg when administered alone or with docetaxel chemotherapy. Biological activity as monotherapy was observed by measurable disease response, decreases in tumor markers, and circulating tumor cell (CTC) responses. Another Phase 1 study evaluating OGX-427 by intravesical instillation (directly into the bladder) in subjects with bladder cancer prior to transurethral resection of the bladder tumor or radical cystectomy has shown 38% complete pathological responses.

Given the poor outcomes for patients with advanced, refractory metastatic urothelial carcinoma, the preclinical rationale for the addition of OGX-427 to reduce treatment resistance, and the Phase 1 study demonstrating that combination with docetaxel is safe, we propose a trial considering docetaxel plus OGX-427 in previously treated urothelial carcinoma with a platinum-based regimen. Docetaxel is a relevant control arm as there is no standard of care in relapsed, refractory metastatic urothelial carcinoma, and docetaxel is a widely-used option in this situation.

Dramatic differences in results between Phase 2 studies testing the same treatment regimen have been observed in urothelial cancer. This is largely due to varying ratios of good, intermediate, and poor prognosis patients enrolled on those studies.36 Therefore, a randomized and appropriately stratified design affording a comparison of an investigational therapy against a control is ideal to investigate the activity of docetaxel and OGX-427. Improved OS compared to a contemporaneous control (rather than an historical control, which could suffer from many biases) would provide a strong rationale to move forward with Phase 3 testing in this patient population. The use of objective response as the primary endpoint is not an ideal surrogate for clinical benefit. Median OS in patients with metastatic urothelial cancer previously treated with chemotherapy is only 6-7 months. The recent contemporary Phase 2 study of taxane chemotherapy demonstrated a median OS of 6.7 months.33 Since survival time is so short, using OS as a screen for clinical benefit in this context is appropriate. This study will stratify patients based on the presence of 3 known adverse prognostic factors: hepatic metastases, anemia, and impaired performance status, which have been identified as driving outcomes in previously-treated patients with advanced bladder cancer.37 In addition, time from prior chemotherapy has been shown to be important in predicting outcomes and adds significance to the second-line prognostic factors.

Therefore, there will be two stratification factors. Randomization will be stratified based on the risk categories: presence of 0 or 1-3 adverse prognostic factors (liver metastases, hemoglobin < 10 g/dL, ECOG PS 1) and time from prior systemic chemotherapy < 3 months vs. ≥ 3 months (as defined in Section 5.6).

2.7 Correlative Studies Background

This study will assess the effect of study treatment on serum Hsp27 levels and may evaluate other proteins (e.g., other Hsp family members and their client proteins) as biomarkers that may emerge as prognostic or predictive factors in urothelial cancer. Archival tumor tissue will be collected to assess Hsp27 IHC staining to determine whether tissue levels of Hsp27 are associated with outcome in patients treated with OGX-427. It is hypothesized that elevated baseline Hsp27 levels will have improved outcomes when treated with OGX-427 both in the tumor tissue and serum. In addition, to facilitate future research and better understand the mechanism of treatment sensitivity, somatic (tumor) and germ-line DNA/RNA will be isolated from archival tumor tissue for use in future approved investigations to determine if somatic mutations are associated with treatment outcome.

2.8 Microfilter Platform for Circulating Tumor Cell Capture and Analysis

Even in the presence of more effective regimens to treat advanced malignant cancers, there still exists a crucial need to predict and monitor therapeutic efficacy in real time. The biologic heterogeneity of cancer and the large populations afflicted pose the pivotal questions of whom to treat, with which therapies and how to monitor the efficacy of therapy, challenges that can only be addressed through the development of more accurate and informative biomarkers. This need is evident for other malignancies where useful predictors of treatment response have provided a major advance, such as in breast cancer (Herceptest) or colorectal cancer (K-Ras mutations). Peripheral blood circulating tumor cells (CTCs) recently have been shown to have prognostic and predictive value in metastatic breast, colon and prostate cancer. In prostate (as well as in breast and colon) cancer, quantification of CTCs before and after therapy has been shown to predict overall disease response, and the CellSearch assay has been approved by FDA to assess such response. This assay, nevertheless, has limitations. Aside from associated costs, the assay depends on enrichment of CTCs based on their expression of EpCAM, a variably expressed cell surface marker, adversely affecting CTC enrichment. It is also likely that enumeration of CTC alone may be inadequate as prognostic and predictive marker for therapeutic response; particular biomarkers expressed on CTCs may provide a wealth of additional information about clinical outcome and response to therapy. Finally, although the utility of CTC analysis in other common malignancies has been widely demonstrated, few studies have investigated the utility of CTCs to predict therapeutic response in bladder cancer, and there are currently no studies that directly evaluate the expression of a therapeutic target on CTCs to predict and monitor treatment efficacy.

In response to these unmet clinical needs, collaborators at the University of Miami – Miller School of Medicine have developed a microfabricated parylene membrane-based device capable of capturing CTCs based on their larger size relative to hematopoietic cells, and have shown its utility in capturing CTC in cancer patient blood samples with high efficiency and with enhanced ease and speed.[43] Briefly, 7.5-10 ml blood samples are drawn from participants by standard phlebotomy measures into anticoagulant tubes. Immediately upon receipt, the blood is diluted 1:1 in 1x PBS, and briefly fixed in 1% formalin at room temperature for 10 minutes. Following fixation, the blood samples are passed through the microfilter device at low, steady pressure

using syringe pump. Following filtration the microfilter is disengaged from its housing cassette and placed onto a glass microscope slide for downstream molecular analyses. There is evidence that not only the capture, but also the characterization of CTC can provide additional information regarding optimal therapeutic efficacy, as demonstrated by the evaluation of EGFR mutations in lung cancer CTCs from patients who are candidates for anti-EGFR therapy.[44] We have further enhanced our microfilter devices by incorporating the capability for downstream molecular characterization, such as on-chip multi-marker immunohistochemistry and genetic tests, which adds a useful dimension besides CTC quantification.

Molecular Characterization of CTCs by Immunoflourescence: Recently, the microfilter device for CTC capture and molecular analysis was used in the SWOG S0421 phase III double-blind clinical trial to evaluate the efficacy of Atrasentan, an endothelin-1 A receptor (ETAR) inhibitor, in combination with docetaxel versus docetaxel + prednisone to treat metastatic castration-resistant prostate cancer (mCRPC). Preliminary analysis of 456 blood samples total from 152 mCRPC patients taken at three timepoints during treatment enrolled and randomized into the treatment arms of the study indicates that the microfilter device successfully captures CTCs to predict therapeutic efficacy, and evaluation of ETAR expression directly on CTCs demonstrates the potential of captured CTCs to be characterized for expression of therapeutic targets and markers of response [unpublished data]. In the current study, we plan to evaluate our ability to predict the therapeutic efficacy of OGX-427 in combination with docetaxel versus docetaxel alone in metastatic bladder cancer as a second line therapy through CTC enumeration, as well as evaluate expression of the OGX-427 drug target, Hsp27, directly on CTCs to predict and monitor treatment efficacy.

Molecular Characterization of CTCs by Quantitative Measurement of Telomerase Expression: Telomerase is an enzyme which lengthens and protects telomeres, the tandem repetitive DNA sequences that cap the ends of human chromosomes. Whereas benign, terminally differentiated tissues have extremely low telomerase level, malignant cells from a variety of cancers have significantly elevated telomerase expression and telomerase activity levels. The robust presence of telomerase in cancer cells and its relative absence from benign tissues has led to a profusion of studies to assess its biomarker utility for diagnosis and prognosis. Telomerase has emerged as a cancer-specific biomarker that is consistently detected in primary tumors, metastases, and circulating tumor cells. In multiple studies over the past decade, telomerase activity was shown to provide significant diagnostic and prognostic utility across numerous cancer types.

As described in above, telomerase is a ribonucleoprotein complex that synthesizes 6 base telomeric repeats (TTAGGG) onto the 3' end of existing telomeres. This mechanism of action led to the development of the TRAP (Telomeric Repeat Amplification Protocol) assay, a two-step PCR-based method to detect telomerase activity *in vitro*. Briefly, a cell or tissue sample is lysed in CHAPS-based lysis buffer and the cell lysate, which contains telomerase, is collected and analyzed in 2 steps: In the first step, called the extension step, an aliquot of cell lysate is mixed with a telomerase substrate oligonucleotide (TS) in the presence of dNTPs. Telomerase catalyzes the addition of telomeric repeats onto the 3' end of TS. The amount of extended telomeric repeats is directly proportional to the amount of telomerase present in the cell lysate. In the second step, called the amplification step, the products of the extension reaction (step 1) are amplified by PCR using a reverse primer and are subsequently visualized and quantified by gel

electrophoresis. More recently, variety of real-time quantitative PCR (qPCR) detection methods have been developed in order to make the amplification (second) step simpler, faster and more reliable. After the extension (first) step is completed (as per classical TRAP assay), a reverse "ACX" primer is used in the second step for amplification by real-time PCR. The ACX primer contains mismatches which prevent primer-dimer formation while still enabling amplification of the extension products. Prior to starting every qPCR-TRAP assay, cell numbers and protein levels in cell lysates are measured and equalized to ensure that results reflect equal input amounts. Ultimately, qPCR-TRAP produces a SYBR green curve from which the threshold cycle of detection (Ct – inversely proportional to starting amounts) is calculated for each sample. Standard control samples are run with every qPCR-TRAP reaction to generate a standard curve. This curve serves both as a control for the efficiency of the real-time PCR reaction and for normalization and comparison of the unknown samples to the known standard controls.

qPCR-TRAP has also been used to detect changes in cancer cell telomerase activity when inhibiting proliferation, as well as telomerase activity levels from prostate cancer cells derived from freshly resected primary prostatectomy specimens. Most recently, as part of the SWOG S0421 phase III double-blind clinical trial described previously above, blood samples were evaluated from 262 mCRPC patients being treated with Atrasentan in combination with docetaxel versus docetaxel + prednisone, the standard of care for this diagnosis. Results from this study demonstrate that telomerase activity measured from CTCs captured by the microfilter device constituted the first-ever CTC-derived biomarker prognostic of overall survival in a large prospective clinical trial. In the current study, we plan to use our previously optimized protocols to predict the therapeutic efficacy of OGX-427 in combination with docetaxel versus docetaxel alone in metastatic bladder cancer as a second line therapy through the measurement of telomerase activity in CTCs.

3. PARTICIPANT SELECTION

Each participant will be provided an informed consent form. A copy of the signed informed consent will be provided to the participant.

Each participant will undergo screening procedures as outlined in Section 0. Participants meeting all inclusion/exclusion criteria will be randomized to treatment and begin the study procedures. All participants are considered enrolled once randomized.

3.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. Participants must have a diagnosis of metastatic or inoperable, locally-advanced urothelial carcinoma (bladder, urethra, ureter and renal pelvis) (T4b, N2, N3, or M1 disease).

   NOTE: Mixed histological differentiation such as squamous, glandular (adenocarcinoma), and micropapillary are eligible unless the tumor is considered a pure

histological variant according to the pathology report. Participants with any small cell features (mixed or pure histology) are not eligible.

2. Participants must have measurable disease defined as at least one target lesion that can be accurately measured in at least one dimension by RECIST v1.1 criteria (see Appendix A). Lesions in previously irradiated areas should not be selected as target lesions, unless there is demonstrated progression in the lesion.

3. Participants must have received prior systemic platinum-based chemotherapy for urothelial carcinoma. Specifically, subjects must also meet one or more of the following criteria:
    - Initial metastatic recurrence < 1 year after the completion of perioperative therapy (i.e. neoadjuvant or adjuvant setting) and no more than one chemotherapy regimen administered in the metastatic or inoperable, locally advanced setting.
      OR
    - Initial metastatic recurrence > 1 year after the completion of perioperative therapy (i.e. neoadjuvant or adjuvant setting) with disease progression after the completion of at least one but no more than two chemotherapy regimens administered in the metastatic or inoperable, locally-advanced setting.
      OR
    - Disease progression after the completion of therapy administered in the metastatic or inoperable, locally advanced setting with no prior history of perioperative platinum-based therapy and no more than two chemotherapy regimens administered in the metastatic or inoperable, locally advanced setting.

4. Participants must be ≥ 18 years of age at time of consent since no dosing or adverse event data are currently available on the use of OGX-427 in participants < 18 years of age.

5. Life expectancy of > 3 months.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix B).

7. Participants must have adequate organ and marrow function as defined below:
    - Absolute neutrophil count (ANC) > 1,500/mcL
    - Hemoglobin ≥ 8 g/dL
    - Platelets > 100,000/mcL
    - Total bilirubin ≤ 1.1 X ULN (≤ 2.0 X ULN if secondary to Gilbert's disease)
    - SGOT (AST)/SGPT (ALT) < 1.5 X ULN
    - Serum creatinine ≤ 1.5 X ULN

8. Minimum of 21 days have elapsed since prior major surgery, with recovery from any adverse events.

9. Minimum of 14 days have elapsed since any prior radiation therapy, with recovery from any adverse events.

10. The effects of OGX-427 on the developing human fetus are unknown. For this reason, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment and for three months after completion of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

NOTE: A woman of child-bearing potential is defined as a woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

11. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

1. History of treatment with docetaxel or cabazitaxel in any setting. Participants treated with prior paclitaxel are eligible.

2. Prior enrollment in the OncoGenex Phase 2 Study OGX-427-02.

3. Participants may not be receiving other investigational agents.

4. Participants with known brain or spinal cord metastases are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. NOTE: Brain imaging is not required unless the participant has symptoms or physical signs of central nervous system (CNS) disease.

5. History of allergic reactions or severe hypersensitivity reactions to drugs formulated with polysorbate 80 or antisense oligonucleotides.

6. Peripheral neuropathy $\geq$ Grade 2.

7. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

8. Cerebrovascular accident, myocardial infarction or pulmonary embolus within 3 months of randomization.
9. Pregnant women and breast-feeding women are excluded from this study because of the risk to a fetus due to docetaxel chemotherapy and OGX-427 systemic treatment (fertility toxicology studies have not been completed for OGX-427).

10. Active second malignancy (except non-melanomatous skin cancer or incidental prostate cancer found on cystectomy): active secondary malignancy is defined as a current need for cancer therapy or a high possibility (> 30%) of recurrence during the study.

4. REGISTRATION PROCEDURES

All participants must be registered through the Hoosier Cancer Research Network, Inc. (HCRN) Electronic Data Capture (EDC) system.

Detailed guidelines for participant registration and electronic case report form (eCRF) completion can be found in the Study Procedures Manual (SPM) associated with this protocol. Participants must be registered prior to starting protocol therapy and begin therapy within 5 working days of registration and randomization.

Randomization will occur immediately after registering a participant. See Section 5.6 for randomization procedures.

Blinding

The study treatment is not blinded to the participant or the investigator.

5. TREATMENT PLAN

This is a randomized, open-label Phase 2 clinical trial in participants with metastatic or inoperable, locally-advanced urothelial bladder cancer who require additional chemotherapy after receiving a platinum-based regimen. A total of approximately 200 participants (100 in each arm) will be stratified (see Section 5.6) and randomized in a 1:1 ratio to one of two arms:

Arm A [docetaxel + OGX-427] and
Arm B [docetaxel alone]

All participants will be evaluated for inclusion in the study during the Screening Period. Participants who are eligible for the study will be randomized as described in Section 5.6 and will start study treatment within 5 working days of registration and randomization. The general treatment plans for both arms are described separately below:

Participants in Arm A will receive 3 doses of 600 mg of OGX-427 during a Loading Dose Period and then weekly OGX-427 at a dose of 600 mg, as shown in Figure 7A below. Participants in Arm A will also receive docetaxel at 75 mg/M^2 once every 21-day cycle. Following the loading doses, participants will receive docetaxel and OGX-427 on 21-day cycles

during the Treatment Period until disease progression, unacceptable toxicity related to docetaxel, voluntary participant withdrawal, or a maximum of 10 docetaxel cycles (see Section 5.14). Arm A participants who have completed all 10 cycles of docetaxel, or those who are removed from docetaxel due to toxicity, have completed disease assessments after at least 2 cycles, and do not have disease progression or unacceptable toxicity related to OGX-427, should continue weekly OGX-427 infusions as maintenance treatment until disease progression or unacceptable toxicity related to OGX-427.

Participants in Arm B will receive docetaxel at 75 mg/M^2 once every 21-day cycle as shown in Figure 7B below during the Treatment Period until disease progression, unacceptable toxicity related to docetaxel, voluntary participant withdrawal, or a maximum of 10 docetaxel cycles (see Section 5.14).

Figure 7: Treatment Schema for Arm A and Arm B

Figure 7A: For Arm A Participants Only

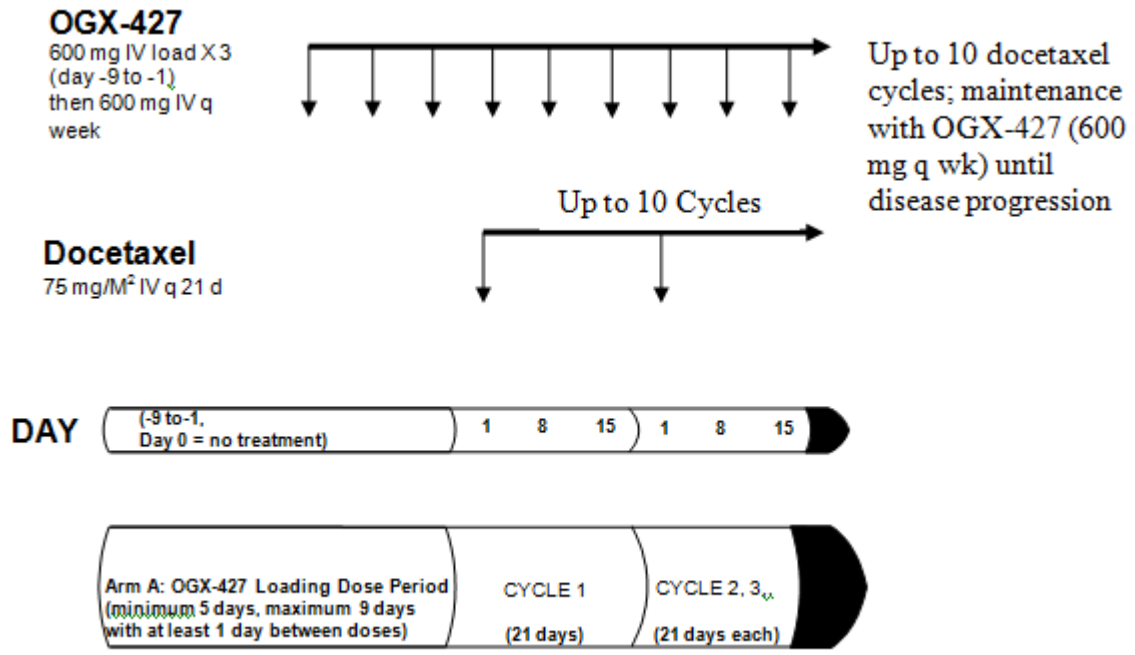
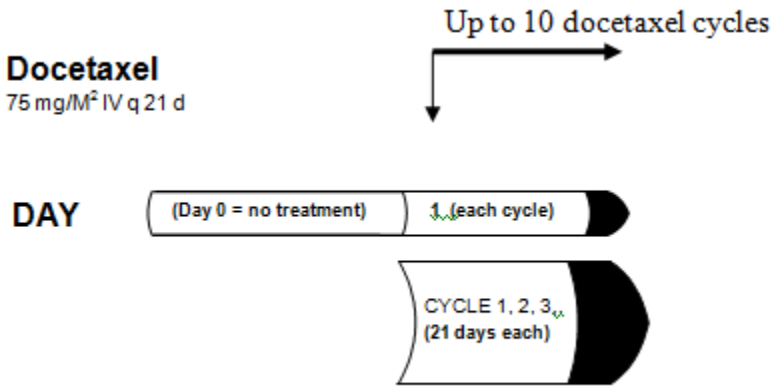


Figure 7B: For Arm B Participants Only



5.1 OGX-427 Loading Dose Period: Arm A Participants Only

Participants randomized onto the investigational arm (Arm A) are to receive OGX-427 beginning with a Loading Dose Period prior to the initiation of docetaxel treatment on Day 1 of Cycle 1. The first dose of OGX-427 for the Loading Dose Period must be administered within 5 working days of registration and randomization.

Three doses of 600 mg OGX-427 will be administered IV during the Loading Dose Period. Up to nine days are allowed for completing the three loading doses to account for clinic visits, weekends, and holidays. There must be at least one "non-infusion" day between each administration of OGX-427 (i.e., every other day) during the Loading Dose Period and between the third loading dose of OGX-427 and Day 1 of Cycle 1 (when docetaxel treatment will begin). More than one day can separate administrations, provided that all 3 doses are administered within the 9 days. A maximum of 7 days between the 3rd loading dose and Cycle 1, Day 1 is allowed. **A common schedule would be to give the three loading doses of OGX-427 on Monday, Wednesday, and Friday, with Cycle 1 Day 1 starting on the following Monday.** The day prior to Day 1 of Cycle 1 (identified as Day 0) should be a no treatment day (e.g., Sunday in the above example). Participants will receive each dose of OGX-427 as an approximately 2-hour infusion. Sites should make every effort to target infusion timing to be as close to 120 minutes as possible. However, given the variability of infusion pumps from site to site, a window of ± 10 minutes is permitted.

Because Grade 1 and 2 constitutional symptoms (e.g., chills, fever, pruritus, flushing) are seen in the majority of participants during the loading-dose infusions, all participants will be premedicated with a H2 blocker, antihistamine, and if needed corticosteroid during the loading doses and Cycle 1 (Days 1, 8, and 15), at a minimum.

If the participant has not manifested signs or symptoms of an infusion reaction during the loading doses and Cycle 1, participant may be treated in subsequent cycles without some or all of the premedications. Should Grade 2 or greater reactions occur, the participant should resume premedications, including dexamethasone, prior to Study Drug for the duration of the study. See Section 5.13.1.

5.2 21 Day Treatment Cycles (Beginning Day 1 of Cycle 1)

***Arm A Participants Only*:**
Following completion of the loading dose period, 600 mg OGX-427 will be given IV weekly on Days 1, 8, and 15 of each 21-day cycle. OGX-427 must be administered **prior to** docetaxel on Day 1 of each cycle. Docetaxel should be administered immediately following the completion of the OGX-427 infusion. Ensure that IV tubing and Y sites are flushed thoroughly with normal saline between administration of OGX-427 and docetaxel.

***Arm B Participants Only*:**
The first dose of docetaxel must be administered within 5 working days of registration and randomization.

Both Arm A and Arm B Participants:
Docetaxel (75 mg/M2) will be administered IV on Day 1 of each 21 day cycle.

Treatment cycles will continue until disease progression by RECIST v1.1, unacceptable toxicity, completion of 10 cycles, or voluntary withdrawal (see Section 5.14).

5.3 OGX-427 Maintenance: Arm A Participants Only

Following completion of 10 cycles of docetaxel, 600 mg OGX-427 will continue to be administered by IV weekly as maintenance therapy in Arm A participants who do not have disease progression (i.e., stable disease or better) (see Section 5.9). Participants without documented disease progression who have discontinued from docetaxel treatment not due to OGX-427-related toxicity can also continue to receive OGX-427 maintenance as long as they have completed disease assessments following at least 2 cycles of chemotherapy. Maintenance with OGX-427 will continue until disease progression or unacceptable toxicity.

5.4 Follow-up: All Participants

Imaging studies will be performed every 6 weeks (i.e., after completion of Cycles 2, 4, 6, 8 and 10) until disease progression and with any sign or symptom of new or worsening disease; CT of chest/abdomen/pelvis is preferred but MRI is acceptable, especially for participants with increased risk of contrast-related nephropathy or other contraindications. For Arm A, scans will be performed every 2 cycles (6 weeks) during the 21-day cycles of docetaxel administration and every 6 weeks during maintenance OGX-427 administration until disease progression; for Arm B, scans will be performed every 6 weeks during the 21-day cycles of docetaxel administration until disease progression. A window of ±1 week is allowed for scheduling, provided **all scans are completed before the subsequent cycle is scheduled to begin.** Bone scans will be repeated, if positive at baseline, every 6 weeks during the first 4 cycles of treatment (i.e., at the end of Cycles 2 and 4) and then every 12 weeks thereafter until disease progression (i.e., at the end of Cycle 8, at End of Treatment, and during maintenance with OGX-427 [Arm A only]).

If new clinical signs or symptoms of disease progression have developed, repeat imaging as clinically indicated, preferably using the same modality as baseline, when appropriate.

All participants will have an End of Treatment (EOT) visit when they discontinue study treatment. All participants will be followed until documented disease progression. Participants who discontinue study treatment for any reason, without documented disease progression, and who initiate other cancer treatment, will be followed for survival according to the Survival Follow-up Period outlined below.

Once disease progression is documented, participants will enter a Survival Follow-up Period. All participants must be followed for survival as the primary endpoint. During the Survival Follow-up Period, data will be collected every three months regarding further cancer therapy, secondary malignancy, and survival status.

Treatment Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
OGX-427	Pre-medicate 30-90 mins prior to OGX-427 infusion (unless intolerant) with antihistamine (diphenhydramine 25-50 mg or equivalent) and H2 antagonist (ranitidine 50 mg or equivalent)	600 mg loading then weekly doses	IV over approximately 2 hours per institutional standards prior to docetaxel	Three loading doses; Weekly dosing: q week	3-week cycles; Treatment for up to 10 docetaxel cycles (30 weeks) followed by weekly maintenance with OGX-427 until disease progression or unacceptable toxicity
Docetaxel	Premedicate with corticosteroids per institutional standards	75 mg/M^2	IV	q 21 days	

5.5 Screening Procedures to Assess Eligibility

Screening evaluations will occur during a period of up to 28 days from the first screening evaluation to randomization unless otherwise specified. The screening period may be extended 1-3 working days to accommodate the period ending on a weekend or holiday. The purpose of the screening period is to assure that subjects meet all entry criteria and that they adequately comprehend the protocol and its requirements. A screening log will document all participants 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.

The screening procedure will include the following assessments:

1. Collect signed and dated informed consent form. Provide a copy of the signed informed consent form to the participant.

2. Document disease history to include:
    - Histological diagnosis of urothelial carcinoma and documentation of mixed histology as required.
    - Date of initial diagnosis.
    - TNM stage at diagnosis.
    - Prior administration of all cancer therapy for bladder cancer including intravesicular, neo-adjuvant or adjuvant therapy, surgery, radiation therapy, hormonal therapy, chemotherapy, biologics and experimental agents.

3. Document demographics, concurrent illnesses, and medical history including significant historical events or findings and any pre-existing conditions.

4. Conduct complete physical examination and obtain weight and height, calculate BSA

5. Assess vital signs (blood pressure, heart rate, and temperature).

6. Document ECOG performance status (see Appendix B).

7. Obtain chest/abdomen/pelvic CT scans (CT abdomen preferred, but MRI abdomen acceptable especially for participants with increased risk of contrast-related nephropathy or other contraindications) plus bone scan, and any other imaging studies, as appropriate, for disease assessment. (A brain scan is not mandated by the study unless the participant has signs or symptoms of CNS disease). Baseline and subsequent imaging must be by the same type of procedure (e.g., CT/MRI scan/bone scan) whenever possible. Participants with any type of scan performed as standard of care prior to consent for this study within 28 days of study enrollment that is 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 v1.1 criteria (see Appendix A).

8. Record all sites of disease at baseline using RECIST v1.1.

9. Collect approximately 35 mL blood as follows:

   a. 5 mL anticoagulated blood for hematology to include:
      - WBC
      - hemoglobin
      - absolute neutrophils and lymphocytes
      - platelet count

   b. 5 mL blood for serum chemistries to include:
      - electrolytes (sodium, potassium, chloride, CO2, calcium and phosphorus)
      - serum creatinine
      - BUN
      - SGOT (AST) and SGPT (ALT)
      - alkaline phosphatase
      - total bilirubin
      - LDH
      - albumin
      - uric acid

NOTE: Samples for hematology and chemistry local laboratory testing may be collected at any time within 28 days prior to randomization, unless otherwise specified.

   c. 5 mL of blood for serum Hsp27 (see the SPM for detailed collection and central lab shipping guidelines).

   d. 20 mL of blood for CTC capture and analysis:10 mL in a CellSave Preservation Tube, 10 mL in an EDTA-coated (purple top) tube (see the SPM for detailed collection and central lab shipping guidelines).

10. Record current concomitant medications.

11. Serum pregnancy test for women of child-bearing potential (WOCBP)

5.6 Stratification Factors and Randomization Process Prior to Initiating Study Treatment

Randomization will take place following completion of the screening evaluations and eligibility assessment (See Section 5.5). Stratification factors will be employed in randomization in order to minimize between-arm assignment imbalance. Randomization cannot occur without adequate data for the following stratification factors:

1) Time from prior systemic chemotherapy (< 3 vs. ≥ 3 months). Time from prior systemic chemotherapy is defined as the date of last chemotherapy dose to the date of randomization and 3 months is defined as 90 days.

2) Number of adverse prognostic risk factors prior to randomization (i.e., "Bellmunt criteria," which include ECOG performance status > 0, hemoglobin <10 g/dL, and presence of liver metastases [0 versus 1-3 risk factors])[37]

(3) Within the strata, participants will be randomly assigned with equal probability to either the investigational arm (Arm A: docetaxel /OGX-427) or the control arm (Arm B: docetaxel).

5.7 OGX-427 Administration During Loading Dose Period, Arm A Participants Only

For Arm A participants only, three separate administrations of OGX-427 will be given during the Loading Dose Period. This period allows for variations in the treatment schedule due to clinic visits, weekends, and holidays. There must be at least one "non-infusion" day between each administration during the Loading Dose Period, and between the last loading dose and Day 1 of Cycle 1. More than one day can separate administrations, provided that all 3 doses are administered within the 9 days. A maximum of 7 days between the 3rd loading dose and Cycle 1, Day 1 is allowed. **An example of a schedule** would be to give the three loading dose administrations of OGX-427 on Monday, Wednesday, and Friday with Day 1, Cycle 1 starting on the following Monday. The day prior to Day 1 of Cycle 1 (identified as Day 0) should be a "no treatment" day (e.g., Sunday in the above example).

Additional Procedures Prior to Loading Dose 1

- Update concurrent illnesses prior to first loading dose.

- Collect approximately 20 mL blood as follows:
  a. 5 mL anticoagulated blood for hematology to include:
    - WBC
    - hemoglobin
    - absolute neutrophils and lymphocytes
    - platelet count

b. 5 mL blood for serum chemistries to include:
- electrolytes (sodium, potassium, chloride, CO2, calcium and phosphorus)
- serum creatinine
- BUN
- SGOT (AST) and SGPT (ALT)
- alkaline phosphatase
- total bilirubin
- LDH
- albumin
- uric acid

NOTE: Samples for hematology and chemistry local laboratory testing not required if performed within 14 days of the first loading dose.

c. 5-10 mL of blood for serum Hsp27 and other exploratory biomarker proteins (see the SPM for detailed collection and central lab shipping guidelines).

- **Only if missed during Screening** (see Section 5.5): Collect 20 mL of blood for CTC capture and analysis:10 mL in a CellSave Preservation Tube, 10 mL in an EDTA-coated (purple top) tube (see the SPM for detailed collection and central lab shipping guidelines).

Prior to Initiating the OGX-427 Loading Dose Infusions:

1. Participants should be premedicated 30-90 minutes prior to each of the three loading doses to reduce the risk and severity of infusion reactions with a minimum of the following (unless participant is intolerant):

   a. an antihistamine (diphenhydramine 25-50 mg or antihistamine equivalent)
   b. an H2 antagonist (ranitidine 50 mg or H2 antagonist equivalent)

Should a participant manifest a grade 2 or greater AE during or subsequent to an infusion reaction to OGX-427 despite the above premedications, treatment with steroids is recommended. Should the need for steroid treatment occur on more than 2 occasions, the participant should receive prophylaxis with steroids throughout OGX-427 therapy.

2. Infuse OGX-427 over approximately 2 hours per institutional standards, preferably using an infusion pump, on each of the 3 non-sequential days within the 9-day Loading Dose Period.

If any signs or symptoms of an infusion reaction (e.g. chills, vomiting, diarrhea,) occur during or immediately after the infusion, the following should be documented:

a. vital signs
b. AE(s) (signs and symptoms of reaction)
c. concomitant medications administered

5.8 21-Day Treatment Cycles with Docetaxel Beginning Day 1 of Cycle 1, All Participants

The study treatment and procedures listed are those performed for all participants during cycles 1-10, as well as Arm A- and Arm B-specific procedures. **NOTE:** ± 1 working day is allowed for each specified study visit.

5.8.1 For Arm A participants only: Prior to treatment on Day 1 of Cycle 1 only

1. Record adverse events that have occurred over the Loading Dose week.
2. Record concomitant medications taken over the Loading Dose week.

5.8.2 All participants: Assessments prior to treatment and on Day 1 of each cycle

1. Update concurrent illnesses prior to first dose Cycle 1 Day 1 (Arm B)

2. Update and record adverse events that have occurred during the previous cycle (i.e. Cycles 2-10).

3. Record concomitant medications taken during the previous cycle (i.e. Cycles 2-10).

4. Conduct limited physical exam (limited to signs and symptoms of disease or toxicity). \

5. Assess vital signs (blood pressure, heart rate and temperature).

6. Document weight, calculate BSA.

7. Record ECOG performance status.

8. Repeat chest, abdomen, and pelvic CT scans (MRI, if appropriate) every 6 weeks (i.e., after completing Cycles 2, 4, 6, 8 and 10). If positive at baseline, repeat bone scan for disease assessment every 6 weeks during the first 4 cycles of treatment (i.e., after Cycles 2 and 4) and then every 12 weeks thereafter until disease progression (i.e., after Cycle 8). There is a 5 day window for scans prior to Day 1 of each cycle. **All assessments should be performed in the same manner as the assessment at screening whenever possible**. Refer to **Section 10.3.4 for disease progression criteria.**

NOTE: If new clinical signs or symptoms of disease progression have developed during any treatment cycle, repeat imaging as clinically indicated, preferably using the same modality as baseline, when appropriate, prior to the next cycle.

9. Within 48 hours prior to Day 1 of each cycle collect approximately 20 mL blood as follows (Need not repeat if previously completed within 3 days of Cycle 1 Day 1):

    a. 5 mL anticoagulated blood for hematology to include:
    - WBC
    - hemoglobin
    - absolute neutrophils and lymphocytes
    - platelet count

b. 5 mL blood for serum chemistries to include:
- electrolytes (sodium, potassium, chloride, CO2, calcium and phosphorus)
- serum creatinine
- BUN
- SGOT (AST) and SGPT (ALT)
- alkaline phosphatase
- total bilirubin
- LDH
- albumin
- uric acid

c. 5-10 mL of blood for serum Hsp27 and other exploratory biomarker proteins (see the SPM for detailed collection and central lab shipping guidelines).

10. **Only if missed during Screening (Arm B only)** (See Section 5.5): Collect 20 mL of blood for CTC capture and analysis at pre-dose Cycle 1 Day 1:10 mL in a CellSave Preservation Tube, 10 mL in an EDTA-coated (purple top) tube (see the SPM for detailed collection and central lab shipping guidelines).

11. Collect 20 mL of blood for CTC capture and analysis:10 mL in a CellSave Preservation Tube, 10 mL in an EDTA-coated (purple top) tube at Cycles 2, 3 and 5 only (see the SPM for detailed collection and central lab shipping guidelines).

12. Evaluate above hematology and serum chemistry values and current adverse events, making any dose modifications as outlined in Section 6.2.1. Note: The laboratory results from the above hematology and serum chemistry testing should be available for review prior to the infusion on Day 1.

13. Initiate premedication with corticosteroids starting one day prior to docetaxel administration (refer to 5.13.2).

14. On Day 1 of each Cycle, administer docetaxel via IV infusion per package insert. For Arm A participants, docetaxel should be administered immediately following the completion of the OGX-427 infusion (see below). Ensure that IV tubing and Y sites are flushed thoroughly with normal saline between administration of OGX-427 and docetaxel.

15. On Days 8 and 15 of Cycle 1 only:
- Within 48 hours prior to study visit collect 5 mL blood for additional hematology assessments, to include:
  - WBC
  - hemoglobin
  - absolute neutrophils and lymphocytes
  - platelet count
- Record any adverse events

5.8.3 For Arm A participants only on Days 1, 8, and 15

Administer OGX-427 via IV infusion over approximately 2 hours per institutional standards, using an infusion pump whenever possible. Vital signs should be assessed for any signs or symptoms (i.e. flushing, chills, lightheadedness) that occur during or immediately after the OGX-427 infusion. Record any adverse events associated with the administration of OGX-427.

5.8.4 For Arm B participants only on Days 8 and 15 (Cycles 2-10)

Contact participants by telephone to record any adverse events or to assess for any change in participant's status that might warrant a clinic visit for further assessment. Document the phone call.

5.9 OGX-427 Maintenance Administration, Arm A Participants Only

Arm A participants who have completed all 10 cycles of docetaxel, or those who are removed from docetaxel due to toxicity, have completed disease assessments after at least 2 cycles, and do not have disease progression or toxicity related to OGX-427, should continue weekly OGX-427 infusions as maintenance treatment until disease progression or unacceptable toxicity.

1. Administer premedications 30-90 minutes prior to each OGX-427 infusion to reduce the risk of infusion reactions (unless participant is intolerant):
    - an antihistamine (diphenhydramine 25-50 mg or equivalent antihistamine)
    - an H2 antagonist (ranitidine 50 mg or H2 antagonist equivalent)

If the participant has not manifested signs or symptoms of an infusion reaction during the loading doses and Cycle 1, participant may be treated in subsequent cycles without some or all of the pre-medications. Should Grade 2 or greater reactions occur, the participant should resume premedications, including dexamethasone, prior to Study Drug for the duration of the study. In general, if the participant has required steroid prophylaxis during treatment, it should be continued during the maintenance period.

2. Administer OGX-427 by infusion over approximately 2 hours per institutional standards every week until disease progression.

    If any signs or symptoms occur during or immediately after the infusion, document the following:
    - vital signs
    - AE(s)

3. Perform a limited physical exam related to signs, symptoms and concurrent illnesses including vital signs every 3 weeks.

4. Record weight and ECOG performance status every 3 weeks.

5. AEs and concomitant medications documented weekly.

6. Collect approximately 15.0 mL blood every 3 weeks as follows:
   a. 5 mL anticoagulated blood for hematology to include:
   - WBC
   - hemoglobin
   - absolute neutrophils and lymphocytes
   - platelet count

   b. 5 mL blood for serum chemistries to include:
   - electrolytes (sodium, potassium, chloride, CO2, calcium and phosphorus)
   - serum creatinine
   - BUN
   - SGOT (AST) and SGPT (ALT)
   - alkaline phosphatase
   - total bilirubin
   - LDH
   - albumin
   - uric acid

   c. 5 mL of blood for serum Hsp27 (see the SPM for detailed collection and central lab shipping guidelines).

7. Every 6 weeks, participant should have repeat chest, abdomen, and pelvic CT scans (MRI, if appropriate); bone scan should be repeated every 12 weeks for disease assessment if positive at baseline. There is a 5 day window for scans prior to Day 1 of each cycle. **All assessments should be performed in the same manner as the assessment at screening whenever possible**. Refer to Section **10.3.4 for disease progression criteria. Note:** If any new clinical signs or symptoms of disease progression have developed during any treatment cycle, repeat imaging as clinically indicated, preferably using the same modality as baseline, when appropriate, prior to the next cycle.

5.10 End of Treatment Visit

All participants who received at least one dose of study treatment must have an End of Treatment Visit at least 30 days (+ 7 days) from the last dose of study treatment.

The following study procedures will be performed at the End of Treatment Visit.

1. Record the reasons(s) for withdrawal from further treatment on the eCRF.

2. Perform a limited physical examination related to signs, symptoms and concurrent illnesses and repeat of tumor measurements of palpable disease, if appropriate, including vital signs.

3. Record weight.

4. Record ECOG performance status.

5. Update and record changes in concomitant medications that occurred since the last visit through 30 days after the last dose of study treatment.

6. Update and record adverse events that occurred since the last visit through 30 days after the last dose of study treatment. NOTE: All SAEs and Grade 3 or higher adverse events and concomitant medications that are ongoing at the end of study treatment must be followed until each event resolves or is assessed as chronic.

7. Any participant who does not have documented disease progression must have chest, abdomen and pelvic CT scans (CT preferred, but MRI acceptable) and any other imaging studies performed at baseline, using the same technology as the screening scans, for disease status (if not performed within the last 6 weeks [42 days]). If the bone scan was positive at baseline, it should be repeated if not performed within the last 12 weeks. The schedule for subsequent scans during the Disease Progression Follow-up Period will be maintained (i.e. the assessment frequency does not 'reset' starting from the EOT visit).

8. Collect approximately 15 mL of blood as follows:

   a. 5 mL anticoagulated blood for hematology to include:
      - WBC
      - hemoglobin
      - absolute neutrophils and lymphocytes
      - platelet count

   b. 5 mL blood for serum chemistries to include:
      - electrolytes (sodium, potassium, chloride, CO2, calcium and phosphorus)
      - serum creatinine
      - BUN
      - SGOT (AST) and SGPT (ALT)
      - alkaline phosphatase
      - total bilirubin
      - LDH
      - albumin
      - uric acid

   c. 5 mL of blood for serum Hsp27 (see the SPM for detailed collection and central lab shipping guidelines).

5.11 Disease Progression Follow-up Period (Every 6 Weeks [± 7 Days])

All participants without documented disease progression who completed study treatment or withdrew from study treatment for a reason other than disease progression will have imaging evaluations during the Disease Progression Follow-up Period until disease progression is documented. The evaluation schedule start will be 6 weeks from the last on treatment assessment to maintain the every 6 weeks schedule.

The following evaluations will be performed every 6 weeks (± 7 days) unless otherwise specified:

1. Conduct limited physical examination related to signs, symptoms, and concurrent illnesses and including repeat measurements of palpable disease, if appropriate.
2. Record ECOG performance status.
3. Repeat chest, abdominal and pelvic CT scans (CT preferred, MRI acceptable) every 6 weeks. If the bone scan was positive at baseline, it should be repeated if not performed within the last 12 weeks.

NOTE: If any new clinical signs or symptoms of disease progression have developed, repeat imaging as clinically indicated, preferably using the same modality as baseline, when appropriate, for assessment of disease progression.

If the participant withdraws from study treatment for a reason other than disease progression and initiates other cancer treatment, discontinue follow-up for progression and follow for survival status only according to the Survival Follow-up Schedule below.

5.12 Survival Follow-up (Every 3 Months[± 7 Days])

Following disease progression, participants will be followed every 3 months for subsequent anticancer therapy, secondary malignancies, and survival status. Information on the start date, type and duration of any subsequent anticancer therapy will be collected. This follow-up may be accomplished through routine clinic follow-up visits, telephone contact with the participant or through contact with the primary practitioner or caregiver.

5.13 General Concomitant Medication and Supportive Care Guidelines

5.13.1 Premedications for OGX-427

Participants should be premedicated with a minimum of the following at 30-90 minutes prior to each OGX-427 infusion in an attempt to reduce the risk and severity of infusion reactions (unless participant is intolerant):

- an antihistamine (diphenhydramine 25-50 mg or equivalent antihistamine)
- an H2 antagonist (ranitidine 50 mg or H2 antagonist equivalent)

Should a participant manifest a grade 2 or greater AE during or subsequent to an infusion reaction to OGX-427 despite the above premedications, treatment with steroids is recommended. Should the need for steroid treatment occur on more than 2 occasions, the participant should receive prophylaxis with steroids throughout OGX-427 therapy.

If the participant has not manifested signs or symptoms of an infusion reaction during the loading doses and Cycle 1, participant may be treated in subsequent cycles without some or all of the premedications. Should Grade 2 or greater reactions occur, the participant should resume premedications, including dexamethasone, prior to Study Drug for the duration of the study.

5.13.2 Premedication for Docetaxel Chemotherapy

All participants should be premedicated with corticosteroids in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Refer to institutional standards for recommendations on premedication prior to docetaxel chemotherapy.

5.13.3 Growth Factors and Blood Products

Filgrastim (G-CSF), pegfilgrastim, sargramostim (GM-CSF), erythropoietin, and other growth factors may be utilized at the discretion of the Investigator. All growth factors must be recorded on the concomitant medication eCRF. American Society of Clinical Oncology (ASCO) guidelines should be followed.

The use of oprelvekin (IL-11, Neumega) is strongly discouraged.
All blood product transfusions will be at the discretion of the Investigator and must be recorded on the concomitant medication eCRF.

5.13.4 Anticoagulation

Participants on warfarin should have their international normalized ratio (INR) checked frequently to maintain a level between 2 and 3.

The use of low molecular weight heparin (LMWH) in participants with severe renal dysfunction will prolong the elimination half-life of LMWH and may increase bleeding risk. Renal function should be monitored and the dose of LMWH adjusted as required.

5.13.5 Anticancer Therapies

Treatment with any anticancer therapy, including radiation therapy, is not allowed while the participant is on study. Once the participant has documented disease progression or has terminated study treatment, further therapy is at the discretion of the Investigator. All anticancer therapy must be documented, including date of initiation.

5.14 Duration of Study Treatment

Duration of study treatment will depend on evidence of disease progression and tolerance. Study treatment may continue until one of the following criteria applies:

- Disease progression or death
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- More than a 4 week delay in any study treatment for any reason (i.e., 5 consecutive weekly doses of OGX-427 missed during chemotherapy or maintenance treatment). If there is more than a 4 week delay in docetaxel chemotherapy, the participant should be removed from further docetaxel chemotherapy and if receiving OGX-427 may continue on maintenance therapy (Refer to Section 5.9 for maintenance criteria)
- Inability or unwillingness to comply with the study treatment requirements
- Participant withdrawal from the study
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the opinion of the treating investigator
- Closure of the study by the drug sponsor, OncoGenex Technologies, or Regulatory Authorities
-

For Arm A participants, the maximum duration of study treatment could include 9 days for loading doses, 10 cycles at 3 weeks per cycle, and maintenance treatment until disease progression or unacceptable toxicity.

For Arm B participants, the maximum duration of study treatment could include 10 cycles at 3 weeks per cycle, for a total of approximately 30 weeks.

5.15 Duration of Follow Up

Participants will be followed for disease progression every 6 weeks (± 7 days) until disease progression is documented and then for survival status every 3 months until death. The exception is follow up for participants who discontinue study therapy for reasons other than progression and initiate other cancer treatment. They will be followed for survival status only according to the Survival Follow-up Schedule above.

NOTE: Participants removed from study for unacceptable adverse events will also be followed for resolution or stabilization of the adverse event as well as disease progression and survival status.

5.16 Criteria for Removal from Study Treatment

Participants will be removed from study treatment when any of the criteria listed in Section 5.14 applies. The reason for removal from study treatment and the date the participant discontinued study treatment must be documented in the study-specific electronic case report form (eCRF). Alternative care options will be discussed with the participant. Participants will be followed as described in Sections 5.11 and 5.12.

5.17 Criteria for Removal from Study Participation

Participants have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue to be evaluated in the trial. The investigator should ask the participant for his/her consent to continue to collect information on survival status.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dosing for docetaxel will be based on the participant’s height and actual body weight. Dosing for OGX-427 will be fixed at 600 mg.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Treatment delays not made up in the same calendar week for the scheduled dose, for treatment Day 1 will be 'made up' (i.e. if treatment for Day 1 is delayed, resume with Day 1 schedule once toxicity has resolved). Treatment delays not made up in the same calendar week for the scheduled dose, for treatment Days 8 or 15 will be 'skipped' and not made up (i.e., if treatment for Day 8 is delayed, resume with Day 15 schedule once toxicity has resolved).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study, and until the final study visit. Participants continuing to experience toxicity at the "End of Treatment Visit" may be contacted for additional assessments until the toxicity has resolved or is assessed as chronic.

In general, the need for dose modifications will be assessed based on laboratory values and/or physical signs obtained within 48 hours prior to treatment on Day 1 of each cycle. Modifications for toxicity are defined below for infusion reactions. Some dose modifications are specific for docetaxel only, for OGX-427 only, or for both docetaxel and OGX-427. In general, weekly administration of OGX-427 will continue when a cycle is delayed for toxicity felt to be due to docetaxel. The dose of OGX-427 or docetaxel will not be re-escalated once the dose is reduced. If more than two dose reductions of either OGX-427 or docetaxel are required, treatment with that study medication must be discontinued. Any participant requiring a toxicity-related dose delay of more than 4 weeks (5 consecutive OGX-427 doses missed) from the intended day of the next scheduled dose, for any reason, must be discontinued from study treatment. If there is more than a 4 weeks delay in docetaxel chemotherapy, the participant should be removed from further docetaxel chemotherapy. If the toxicity is not perceived as related to OGX-427, the patient may begin the OGX-427 maintenance phase, provided disease assessments were completed after at least 2 cycles of chemotherapy. Participants who discontinue study treatment will have an "End of Study Treatment" assessment (Section 5.10) and then enter the "Disease Progression Follow-up Period" until disease progression (Section 5.11).

The reason for modifying the dose of any study treatment (OGX-427 or docetaxel) must be recorded in the source documents and the eCRF.

6.1 Anticipated Toxicities

6.1.1 Anticipated Toxicities for OGX-427

As of the cutoff date of June 15, 2013, safety data when used as monotherapy has been compiled from a Phase I study (OGX-427-01) and from ongoing, open-label Phase II study, PR-01. The infusion reactions are based on PR-01 subjects who received 600 mg for each of 3 loading doses. Infusion reactions, which occur during or soon after the infusion of OGX-427, have occurred in approximately 67% of patients, including cytokine release syndrome. Patients were premedicated

with an H2 antagonist and antihistamine. The most common symptoms have been chills (46%), flushing (13%), diarrhea (20%), nausea (18%), and vomiting (10%).The majority of reactions occurred with the first three loading doses and during the first weekly infusions of therapy, but reactions have continued to occur with further infusions in some patients. Reactions may require treatment or prophylaxis with corticosteroids.

The risks and side effects that have been seen in patients who have been treated with **OGX-427 alone** that have been felt to be possibly, probably, or definitely related to OGX-427 are defined below.

Very likely (greater than 20% of patients):

- Anemia (88%) which can cause tiredness, shortness of breath, and a possible need for red blood cell transfusions
- Lymphopenia (77%) which in rare circumstances could lead to uncommon but serious infections
- Transient prolongation of aPTT (41%) which in rare circumstances could lead to serious bleeding
- Decrease in kidney function (45%) which could possibly require dialysis
- Elevated creatinine (45%)
- Decrease in liver function (reversible) (37%)
- Hyponatremia (42%) which in rare situations could cause a seizure
- Thrombocytopenia (39%) which in rare situations could lead to an increased risk of bleeding and/or need for platelet transfusions
- Elevated international normalized ratio (INR: 36%) (based on data from study 427-01 only, N=42)
- Hypokalemia (35%)
- Hyperglycemia (48%) (based on data from PR-01 only, N=61)
- Elevated ALT (31%)
- Diarrhea (28%)
- Fatigue (29%)
- Leukopenia (25%)
- Nausea (24%)

Less likely (5-20% of patients):

- Pyrexia (12%)
- Decreased appetite (14%)
- Vomiting (12%)
- Pruritis (16%)
- Arthralgia (9%)
- Dizziness (9%)
- Hypertension (9%)
- Neutropenia (9%)
- Hyperkalemia (9%)
- Headache (10%)
- Myalgia (8%)

- Elevated bilirubin (7%)
- Hematuria (5%)
- Influenza like illness (5%)
- Urticaria (5%)
- Dyspnea (7%)
- Cytokine release syndrome (6%)
- Abdominal pain (6%)
- Erythema (5%)
- Chest pain (6%)
- Rash (5%)
- Hyperhidrosis (5%)
- Hot flush (5%)
- Peripheral neuropathy (5%)
- Muscular weakness (5%)

Rarely (but may be serious) (less than 5% of patients) observed in any trial, with any causality:

- Cerebral hemorrhage
- Deep vein thrombosis
- Pulmonary embolus
- Vascular purpura
- Hemolytic uremic syndrome (HUS)
- Pancreatitis
- Bronchospasm
- Hemoptysis
- Hypovolemic shock
- Serious infection such as sepsis, pneumonia, abscess
- Arrhythmia
- Membranous nephropathy
- Anasarca
- Cardiac arrest
- Hemorrhage: gastrointestinal, urinary tract
- Atrial fibrillation
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Pyelonephritis
- Sudden death
- Intestinal obstruction
- Status epilepticus

The risks and side effects that have been seen in patients who have been treated with **OGX-427 and docetaxel** that have been felt to be possibly, probably, or definitely related to Study Drug are defined below.

Very likely (greater than 20% of patients):

- Infusion reactions, which occur during or soon after the infusion of OGX-427, have occurred in approximately 80% of patients, including cytokine release syndrome. The most common symptoms have been shaking chills (73%), itching (46%) and flushing (27%). The majority of reactions occurred with the first three loading doses and during the first weekly infusions of therapy, but reactions have continued to occur with further infusions in some patients. Reactions appear to be more frequent and more severe at higher doses of OGX-427 and may require treatment or prophylaxis with corticosteroids. In rare occasions, infusion reactions can be life threatening.
- Prolongation of PTT (100%) which in rare circumstances could lead to serious bleeding.
- Lymphopenia (100%) which in rare circumstances could lead to uncommon but serious infections.
- Anemia (100%) which can cause tiredness, shortness of breath, and a possible need for red blood cell transfusions.
- Neutropenia (91%) which can lead to serious infections.
- Low sodium (68%) which could cause a seizure.
- Decrease in kidney function (reversible) (50%)
- Thrombocytopenia (50%) which could lead to an increased risk of bleeding and/or require platelet transfusions.
- Fatigue/tiredness (46%)
- Decreased liver function (reversible) (41%)
- Nausea (36%)
- Decreased potassium (36%)
- Diarrhea (32%)
- Anorexia (23%)
- Dyspnea (23%)
- Abdominal pain (23%)
- Back pain (23%)

Less likely (5-20% of patients):

- Weight loss (18%)
- Sweating (18%)
- Erythema of the skin (18%)
- Decreased taste (14%)
- Chest pain (14%)
- Fever (14%)
- Myalgia or muscle weakness (10%)
- Oropharyngeal pain (9%)
- Vomiting (9%)
- Pain (9%)
- Mouth sores (9%)

- Wheezing (9%)
- Bronchospasm (9%)
- Peripheral edema (9%)
- Arthralgia (9%)
- Dehydration (9%)
- Hypoxia (9%)
- Oral candidiasis (9%)

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

- Atrial fibrillation
- Deep vein thrombosis
- Febrile neutropenia
- Delirium
- Sinus tachycardia
- Anaphylaxis or severe infusion reaction which can cause symptoms such as bronchospasm (narrowing of the airways causing breathing distress), hypotension (abnormally low blood pressure), and acute kidney failure which can be life threatening.

6.1.2 Anticipated Toxicities for Docetaxel

The risks and side effects observed with docetaxel when used as monotherapy in a population of patients previously treated with a platinum-based chemotherapy are summarized below. For more detailed information on docetaxel anticipated toxicities, please refer to the package insert for docetaxel.

Myelosuppression, predominately neutropenia, is the DLT of docetaxel with a nadir at days 7-10 and recovery by approximately day 14. CBCs with differential and platelet count should be monitored.

Docetaxel is hepatotoxic and should be used with caution in patients with abnormal liver function.

Docetaxel is contraindicated in patients with known hypersensitivity to docetaxel or to polysorbate 80. Reactions (flushing, fever, rigors, rash, hypotension, dyspnea, and/or bronchospasm) usually occur within the first few minutes of the first or second administrations and almost all occur within the first 10 minutes. Severe reactions occur in < 5% of patients. Patients should be closely monitored during infusions. Resuscitation equipment should be ready at the bedside.

Fluid retention is seen in around 25-50% of patients and can be severe (ascites, pleural, or pericardial effusions) in around 7% of patients.

All participants should receive corticosteroid premedication before docetaxel administration to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Refer to institutional standards for recommendations on premedication prior to docetaxel administration.

Very likely (greater than 20% of patients):

- Neutropenia (84%)
- Anemia (91%)
- Alopecia (56%)
- Asthenia (53%)
- Respiratory problems (41%)
- Nausea (34%)
- Infection (33%)
- Fluid retention (33%)
- Mucositis (26%)
- Sensory neuropathy (23%)
- Diarrhea (23%)
- Vomiting (22%)

Less likely (5-20% of patients):

- Rash (20%)
- Motor neuropathy (16%)
- Nail Disorder (11%)
- Thrombocytopenia (8%)
- Febrile neutropenia (6%)
- Hypersensitivity reactions (6%)
- Myalgia (6%)
- Dysguesia (6%)
- Arthralgia (5%)

Rare (but may be serious) (less than 5% of patients):

- Hepatic dysfunction
- Renal dysfunction
- Gastrointestinal hemorrhage
- Severe hypotension
- Heart failure
- Arrhythmias (e.g., atrial fibrillation and flutter)
- Angina
- Pulmonary edema
- Hypertension
- Infusion site reaction
- Severe neutropenia with infection which can be fatal
- Severe hypersensitivity reaction which can be fatal
- Deep venous thrombosis
- Pulmonary embolism
- Alcohol intoxication. Docetaxel contains alcohol (ethanol) which may affect the central nervous system and cause you to feel intoxicated. This can impair your ability to drive or use machinery for 1-2 hours after infusion.
- Secondary malignancy

6.2 Dose Modifications for Toxicity

In general the criteria for the degree of resolution for adverse events is ≤ Grade 1 with the following exceptions where it is felt there are no safety concerns for retreatment in participants when the toxicity has resolved to ≤ Grade 2: anemia, fatigue, asthenia, lethargy, malaise, nail changes, or hyperglycemia in a participant with known diabetes mellitus.

6.2.1 Specific Dose Levels for Docetaxel and OGX-427 Modification

The tables below define the specific dose level modifications for docetaxel (Table 4) and OGX-427 (Table 5). Subsequent sections delineate when dose modifications should occur.

Table 4: Dose Level Modifications for Docetaxel

Dose Level	Docetaxel*
100%	75 mg/M^2
First dose reduction	60 mg/M^2
Second dose reduction*	45 mg/M^2

***Requirement for more than two dose reductions or a dose of less than 45 mg/M2 will lead to discontinuation from docetaxel treatment.**

Table 5: Dose Level Modifications for OGX-427

Dose Level	OGX-427
Weekly study dose	600 mg
First dose reduction	500 mg
Second dose reduction*	400 mg

***Requirement for a third dose reduction will lead to discontinuation from OGX-427 treatment.**

6.2.2 Dose Modifications for Infusion (Allergic/Hypersensitivity) Reactions

Infusion reactions (including fever, chills, diarrhea, rash, urticaria, erythema, pruritus, bronchospasm, hypotension, and anaphylaxis) can occur with the agents used in this protocol. For participants previously exposed, reactions to docetaxel can occur within minutes.

In the event of an infusion reaction, follow the Institutional Guidelines of each site and/or the recommendations shown in the tables below, based on the grade of the reaction.

To identify the grade of a reaction, refer to the list below adapted from the General Disorders and Administration Site Conditions section of the NCI CTCAE Version 4.0:

Grade 1: Mild transient 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 indicated for ≤ 24 hours).

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 other 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.

6.2.2.1 Dose Modifications for OGX-427 Infusion Reactions

During the Loading Dose Period, the dose of OGX-427 will be 600 mg. There will be no dose reductions of OGX-427 during the Loading Dose Period for infusion reactions. Grade 3 reactions have been uncommon. Should a grade 3 or 4 reaction occur during the loading dose period or at Cycle 1 Day 1, OGX-427 can be held until the AE is ≤ grade 1.

Should a participant manifest a grade 2 or greater AE during or subsequent to an infusion reaction of OGX-427 despite the above premedications, treatment with steroids is recommended. Should the need for steroid treatment occur on more than 1 occasion, the participant should receive prophylaxis with steroids throughout OGX-427 therapy prior to any dose modifications (see Section 5.13.1).

The tables below define the dose modifications for infusion reactions occurring during and following the Loading Dose Period.

Table 6: Dose Modifications for OGX-427 Infusion Reactions

Toxicity	Dose Modification
Grade 1 infusion reaction	Slow the rate of infusion of the OGX-427 until resolution of symptoms, then resume at the planned infusion rate.
Grade 2 or 3 infusion reaction	Stop the infusion. Give steroids (e.g., 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 after recovery of symptoms at a slower rate, and then increase incrementally toward the initial rate. If the reaction reoccurs, stop the infusion and do not administer the remaining volume. Should a grade 2 or 3 infusion reaction recur in the presence of steroid prophylaxis, reduce the OGX-427 by one dose level for all subsequent doses.
Grade 4 infusion reaction	Stop the infusion. Remove the participant from study treatment.

6.2.2.2 Dose Modifications for Docetaxel Infusion Reactions

All participants should be premedicated with corticosteroids in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Refer to institutional standards for recommendations on premedication prior to docetaxel chemotherapy.

Table 7: Dose Modifications for Docetaxel Infusion Reactions

	Dose Modification
Grade 1 infusion reaction	Interruption or intervention not indicated. Slow the rate of infusion of the drug until resolution of symptoms, then resume at the planned infusion rate.
Grade 2 infusion reaction	Interrupt the infusion. Follow institutional guidelines or give steroids (e.g., dexamethasone 8 mg IV), diphenhydramine 50 mg IV, and/or an H2 blocker (e.g. Ranitidine 50 mg IV) after consultation with the attendant physician. Resume after recovery of symptoms at a slower rate, and then increase incrementally toward the initial rate. If the reaction reoccurs, stop the infusion and do not administer the remaining volume.
Grade 3 or Grade 4 infusion reaction	Stop the infusion. Treat the participant as per grade 2 reaction above. Remove the participant from docetaxel therapy.

6.2.2.3 Docetaxel Dose Modifications for Hematology Toxicity

G-CSF and other growth factors (except oprelvekin) may be utilized at the discretion of the Investigator and should follow ASCO guidelines. The following table delineates how to modify or hold the dose of docetaxel based on the hematology results and clinical findings on Day 1 of each cycle.

NOTE: OGX-427 will not be held or modified for hematological toxicity.

Table 8: Dose Modification of Docetaxel Based on Hematologic Toxicity

Toxicity	Dose Modification
On Day 1 of a cycle: **ANC ≥1.5 x10^9 cells /L** and **platelet count ≥100 x 10^9/L**	100% of present docetaxel dose
On Day 1 of a cycle: **ANC <1.5 x10^9 cells /L** and/or **platelet count <100 x 10^9/L**	**Delay** Docetaxel. Continue to administer OGX-427. Repeat CBC weekly If ANC resolves to ≥1.5 x10^9 cells /L **and/or** platelet count ≥100 x 10^9/L, resume docetaxel at 100% of present dose If docetaxel is delayed for more than 1 week (but less than 4 weeks), resume docetaxel at one lower 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 If treatment is delayed for more than 4 weeks, the participant should be removed from further docetaxel chemotherapy (and proceed to maintenance therapy, if applicable)
Any time during the previous cycle for one of the following: **Grade 3 febrile neutropenia (defined as an ANC <1.0 x 10^9 cells/L and a single temperature >38.3°C or a sustained temperature of >38°C for more than an hour)** **Documented infection with grade 3 neutropenia (defined as an ANC <1.0 x 10^9 cells/L)** **Grade 4 neutropenia (defined as an ANC <0.5 x 10^9 cells/L lasting more than 5 days** **Grade 4 thrombocytopenia (platelet count <25 x 10^9/L) lasting for more than 5 days**	Delay treatment with docetaxel until improvement of symptoms and resolution of the ANC to ≥1.5 x10^9 cells /L and platelet count to ≥100 x 10^9/L. Weekly treatment with OGX-427 should continue. Decrease docetaxel by one dose level for all subsequent cycles. With recurrence of any of these toxicities, the participant should be removed from docetaxel chemotherapy (and proceed to maintenance therapy, if applicable).
Any time during the previous cycle for one of the following: **Grade 4 febrile neutropenia or infection with grade 4 neutropenia (both defined as septic shock)** **Thrombocytopenic hemorrhage (gross not occult bleeding) associated with a platelet count <50 x 10^9/L**	**Remove participant** from docetaxel chemotherapy (and proceed to maintenance therapy, if applicable).

6.2.2.4 Docetaxel Dose Modifications for Neurotoxicity

For grade 4 neurotoxicity (life threatening), the participant should be removed from study treatment.

For grade 3 neurotoxicity, docetaxel should be held until toxicity resolves to ≤ grade 1. Resume docetaxel at a dose reduction of one level.

6.2.2.5 Docetaxel Dose Modifications for Fluid Retention

There are no dose reductions for fluid retention. Participants should be treated with salt restrictions and diuretics. More aggressive therapy depends on the clinical situation. In severe situations, the Investigator, with the participant, should determine if it is in the participant's best interest to continue or discontinue study treatment.

6.2.2.6 Docetaxel Dose Modifications for Mucocutaneous Toxicity (Skin and Mucous Membranes)

For grade 4 mucocutaneous toxicity (life-threatening), the participant should be removed from study treatment.

For grade 3 mucocutaneous toxicity present on Day 1 of a cycle, docetaxel should be held until toxicity resolves to ≤ grade 1. Resume docetaxel at a dose reduction of one level.

If the grade 3 mucocutaneous toxicity does not resolve within 4 weeks, the participant should be removed from docetaxel treatment.

6.2.2.7 Docetaxel Dose Modifications for Diarrhea

In the case of grade 4 (life threatening) diarrhea, the participant should be removed from study chemotherapy treatment but may continue on OGX-427 as maintenance therapy (Arm A only). In the case of grade 3 diarrhea (≥ 7 stools per day over baseline; incontinence; need for IV fluids > 24 hours; or hospitalization), docetaxel should be held until resolution to ≤ grade 1 and the participant should receive prophylactic anti-diarrhea therapy in subsequent cycles.

If grade 3 diarrhea recurs despite maximal prophylactic treatment (e.g., loperamide, diphenoxylate hydrochloride with atropine, octreotide), the participant should be removed from docetaxel treatment.

6.2.3 Dose Modifications Specific for OGX-427 Toxicity

6.2.3.1 OGX-427 Dose Modifications for Renal Toxicity

Table 9: 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.

6.2.4 Dose Modifications for both Docetaxel and OGX-427

6.2.4.1 Docetaxel and OGX-427 Dose Modifications for Hepatic Toxicity

Modification on Day 1 of each cycle for both docetaxel and OGX-427 should be based on SGOT (AST), SGPT (ALT), and total bilirubin values. The dose adjustments are shown in the following table.

Table 10: Dose Modifications for Both Docetaxel and OGX-427 for Hepatic Toxicity

	Transaminase: SGOT (AST) and/or SGPT (ALT) levels			
	≤3.0 X ULN (Grade 1)	**>3.0 to 5.0 X ULN (Grade 2)**	**>5.0 to 20 X ULN (Grade 3)**	**>20 X ULN**
Total bilirubin ≤1.1 X ULN	100% of dose	**Hold** both docetaxel and OGX-427[1]. Resume when total bilirubin is ≤1.1 X ULN and SGOT (AST) and SGPT (ALT) are <3.0 X ULN. **Decrease** docetaxel[2] dose by 1 dose level. No change to OGX-427 dose.	**Hold** both docetaxel and OGX-427[1]. Resume when SGOT (AST) and SGPT (ALT) ≤3.0 X ULN, **Decrease** both the docetaxel[2] and OGX-427[3] dose by 1 dose level.	**Remove** from study therapy.
Total bilirubin >1.1 to ≤2.0 X ULN	**Hold** both docetaxel and OGX-427[1]. Resume when total bilirubin is ≤1.1 X ULN and SGOT (AST) and SGPT (ALT) are <3.0 X ULN **Decrease** docetaxel[2] dose by 1 dose level. No change to OGX-427 dose.	**Hold** both docetaxel and OGX-427[1]. Resume when total bilirubin is ≤1.1 X ULN and SGOT (AST) and SGPT (ALT) are ≤3.0 X ULN **Decrease** both the docetaxel[2] and OGX-427[3] dose by 1 dose level.	**Remove** from study therapy.	**Remove** from study therapy.
Bilirubin >2.0 X ULN			**Remove** from study therapy.	

[1] If no recovery after 4 weeks, participant will be removed from study treatment.
[2] Participants requiring a third dose reduction of docetaxel or a dose below 45 mg/M^2 will go off study treatment.
[3] Participants requiring a third dose reduction of OGX-427 will go off study treatment.

6.2.4.2 Docetaxel and OGX-427 Dose Modifications for Non-hematological Toxicities Not Covered Above

For all other clinically relevant grade 3 or non-life threatening grade 4 non-hematological toxicities not outlined above (excluding: alopecia, anemia, pain, cough, headache, insomnia, nail changes, changes in taste, and asymptomatic electrolyte values [e.g., hypokalemia, hypomagnesemia]), delay docetaxel therapy until the toxicity resolves to ≤ grade 1. Once the toxicity resolves to ≤ grade 1, resume docetaxel. If the toxicity was related to chemotherapy, resume docetaxel at a dose reduction of one level.. Weekly administration of OGX-427 should continue unless the toxicity is felt to be related to OGX-427. The dose of OGX-427 should be lowered by one dose level only if the toxicity is felt to be possibly related to OGX-427. If the toxicity does not resolve within 4 weeks, the participant should be removed from chemotherapy (and from OGX-427 if the toxicity if felt to be related to OGX-427). Otherwise the participant will continue on maintenance therapy, if applicable.

For grade 4 life threatening toxicities, participants should be removed from study therapy.

6.2.5 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.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 OGX-427

7.1.1 Description

The OGX-427 drug substance is a synthetic oligonucleotide with phosphorothiolated internucleotide linkages commonly classified as 4-12-4 MOE gapmer oligonucleotide. The Sequence Code for OGX-427 is

5’-$\underline{\text{GGGA}}^{\text{Me}}\text{CG}^{\text{Me}}\text{CGG}^{\text{Me}}\text{CG}^{\text{Me}}\text{CT}^{\text{Me}}\text{CGG}\underline{^{\text{Me}}\text{U}^{\text{Me}}\text{CA}^{\text{Me}}\text{U}}$-3’

- The underlined nucleosides ($\underline{\text{G}}$, $\underline{\text{A}}$, $\underline{^{\text{Me}}\text{C}}$, and $\underline{^{\text{Me}}\text{U}}$) denote 2’-O-2-methoxyethyl (2’-MOE) modifications of the ribonucleosides guanosine, adenosine, 5-methylcytidine and 5-methyluridine.
- G, $^{\text{Me}}$C, and T represent the deoxyribonucleosides 2’-deoxyguanosine, 2’-deoxy-5-methylcytidine, and 2’-deoxythymidine.
- The internucleotide linkages are phosphorothioate diesters (sodium salts).

The molecular formula is $C_{224}H_{285}N_{79}Na_{19}O_{116}P_{19}S_{19.}$ The molecular weight is 7574.7 Da (Sodium salt form).

7.1.2 Form
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 as a clear, colorless to slightly yellow liquid in a USP Type I glass vial with a coated butyl rubber closure and aluminum seal with plastic flip-off button. Two different concentrations of OGX-427 will be provided during the trial: either 224 mg/vial (28 mg/mL in 8 mL) or 200 mg/vial (25 mg/mL in 8 mL). The dosage of OGX-427 administered will be the same regardless of concentration used. Additional details on dose preparation are provided in the Pharmacy Manual.

7.1.3 Storage and Stability
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 (D5W). 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.

7.1.4 Compatibility
OGX-427 will be reconstituted and administered separately. NOTE: Docetaxel should be administered immediately following the completion of the OGX-427 infusion. Ensure that IV tubing and Y sites are flushed thoroughly with normal saline between administration of OGX-427 and docetaxel.

7.1.5 Handling
OGX-427 is an investigational agent and is not known to be cytotoxic. No specific handling is required.

7.1.6 Availability
OGX-427 is an investigational agent and will be supplied free-of-charge from the drug sponsor, OncoGenex Technologies.

7.1.7 Preparation and Administration
OGX-427 vials require withdrawal and injection into an IV diluent solution D5W using aseptic technique. OGX-427 should be added to 250 mL D5W as close to the time of administration as possible. The dose will be administered using either a peripheral or central indwelling catheter intravenously as an infusion over approximately 2 hours per institutional standards.
One or more pharmacists (or qualified designees) will be responsible for all study treatment preparations (docetaxel and OGX-427).

Preparation and Administration of OGX-427 is further detailed for the Pharmacy in the Pharmacy Manual.

7.1.8 Ordering
Please refer to the SPM for detailed re-supply guidelines. For specific questions regarding re-supply, please contact OncoGenex Technologies Inc.

7.1.9 Accountability
The pharmacist(s) must confirm the quantity of OGX-427 received with each shipment as well as the maintenance of the cold chain during shipment. The Investigator or designee will maintain records to confirm that the product was stored at 2-8°C, product delivery to the trial site, product inventory at the site, the dose given to each participant and the return of unused vials to the Funder (or where otherwise mandated, the destruction of unused vials). The sponsor-investigator's monitoring staff will verify the trial site's product accountability documentation.

7.1.10 Destruction and Return
At the end of the study, unused supplies of OGX-427 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form (See SPM for forms and guidelines).

7.2 Docetaxel (Taxotere®)
Please refer to the FDA approved package for comprehensive mixing instructions and adverse drug reaction information.

7.2.1 Description
Taxotere® is a semisynthetic analog of paclitaxel using a precursor extracted from the needles of the European yew tree. Taxotere®'s high affinity for binding to microtubules enhances tubular polymerization, leading to inhibition of mitosis and cell division. Taxotere® is a cell-cycle specific agent with activity in the mitotic phase. Taxotere® is a member of the taxoid family. The molecular weight is 861.94 Da.

7.2.2 Form
Taxotere® is formulated in polysorbate 80 and commercially available.

7.2.3 Storage and Stability
Taxotere® vials should be stored between 2-25ºC. Unopened vials require protection from light. Allow to stand at room temperature for 5 minutes before reconstitution. Taxotere® is reconstituted with the provided diluent to give a concentration of 10 mg/mL. Use only glass, polypropylene or polyolefin plastic IV bags. It is then further diluted in an appropriate volume of D5W or normal saline to a final concentration of 0.3 to 0.94 mg/mL. Taxotere® final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Taxotere® final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

7.2.4 Incompatibilities
Intravenous bags and administration sets containing DEHP (di-[2ethylexyl] phthalate).

7.2.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.2.6 Availability
Taxotere® is commercially available from sanofi-aventis U.S. LLC.

7.2.7 Preparation and Administration
Please follow package insert for specific instructions.

1-vial Taxotere® (docetaxel) Injection Concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.
2. Aseptically withdraw the required amount of TAXOTERE injection concentrate (20 mg docetaxel/ mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.
   If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

The Taxotere® dilution for infusion should be administered intravenously over approximately 1-hour per institutional standards, under ambient room temperature (below 25°C) and lighting conditions.

1-vial Taxotere® Injection Concentrate is a sterile, non-pyrogenic, pale yellow to brownish-yellow solution at 20 mg/mL concentration. Each mL of 1-vial Taxotere® contains 20 mg docetaxel (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution.[1]

Taxotere® is supplied in a single use clear glass vial with a red flip-off cap for the 80-mg vial and a green cap for the 20-mg vial. Each vial is provided in a blister pack in a single carton.[1] Contact of the Taxotere concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. To minimize participant exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Taxotere® dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.[1]

Please note the following important information about Taxotere® preparation:

- **DO NOT use the 2-vial formulation (injection concentrate and diluent) with the 1-vial formulation**
- Each vial is a single-dose vial and should not be used for multiple doses
- Opened vials may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 4 hours
- If vials are refrigerated, allow the appropriate number of Taxotere®vials to stand at room temperature for approximately 5 minutes before use
- Taxotere® should be visually inspected prior to use. Solutions containing any precipitate or particulate matter must not be used
- Fully prepared infusion solution should be used within 4 hours (including the 1 hour IV administration)
-

[1]Taxotere® Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC; September 2011.

7.2.8 Side Effects

Cardiac: arrhythmias, pericardial effusions.

Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, anemia.

Metabolic: hypoglycemia, hypernatremia.

Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.

Neurologic: reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.

Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).

Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.

Hepatic: increased transaminase, alkaline phosphatase, and bilirubin, hepatic failure, hepatic drug reaction.

Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions.

Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites, fever, flu-like symptoms.

7.2.9 Ordering
Taxotere® is commercially available and will not be provided.

8. CORRELATIVE/SPECIAL STUDIES
HCRN will provide kits and shipping supplies for tissue and serum collected for assays evaluating Hsp27 and other biomarker proteins. University of Miami will provide kits and shipping supplies for peripheral blood collected for CTC assays.

8.1 Blood Collection for Assays Evaluating Hsp27
Blood for serum assays for evaluating Hsp27 will be collected (at screening, prior to the first loading dose (Arm A only), pre-dose Day 1 of each cycle, every 3 weeks during maintenance (Arm A only) and at the End of Treatment visit), processed at the local site, and shipped to a central laboratory for analysis. Refer to the SPM for collection, processing, labeling and central lab shipping instructions. Baseline and changes in Hsp27 protein levels will be explored in relation to participant outcomes as a possible prognostic and predictive biomarker for OGX-427 biologic activity. The purpose of assessing changes in other proteins (e.g., other Hsp family members and their client proteins) is to evaluate their usefulness as biomarkers that may have prognostic or predictive factors in urothelial cancer.

8.2 Archived Tissue for Associations Between Tumor Hsp27 and Clinical Outcomes
Where available, archived FFPE primary and metastatic tumor tissue will be obtained from registered study participants Refer to the SPM for collection, processing, labeling and central lab shipping instructions. Associations between primary tumor Hsp27 IHC staining intensity and clinical outcomes will be performed. Analysis of additional biomarkers of interest may also be performed based on tumor tissue availability. All analyses will be hypothesis generating. As such, no formal sample size calculations have been performed for this portion of the correlative analyses.

We are requesting patient consent to store samples from archival tumor in our already established repository for possible future IRB approved research to determine if somatic mutations are associated with treatment outcome.

8.3 Blood Collection for CTC Assays
Peripheral blood for circulating tumor cell (CTC) analysis will be collected at Screening and pre-dose on Day 1 of Cycles 2, 3 and 5. If sample is missed at Screening, it should be collected pre-dose at loading dose 1 for Arm A and pre-dose Day 1 Cycle 1 for Arm B. Refer to the SPM for collection, processing, labeling and central lab shipping instructions.

8.4 Blood Collection for Other Relevant Proteins
Blood for other relevant proteins will be collected prior to first loading dose (Arm A only), pre-dose on Day 1 of Cycle 1 (Arm B only), pre-dose on Day 1 of Cycles 3 and 5. Refer to the SPM for collection, processing, labeling and central lab shipping instructions.

9. STUDY CALENDAR (Footnotes on next pages)

		Arm A Only: OGX-427 Loading Dose Period				Treatment Period: Docetaxel with or without OGX-427 (± 1 working day)						Arm A Only: OGX-427 Maintenance Period[4]					
	Screening Period (28 + 3 days)[1]	Three Loading Doses[3] (at least every other day)				Cycle 1			Cycles 2-10			Until disease progression			End of Treatment Visit	Disease Progression Follow-up Period[5]	Survival[6]
Procedure	**Screening Visit**	**RANDOMIZATION[2]**	**Dose 1**	**Dose 2**	**Dose 3**	**DAY 0**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**q wk**	**q 3 wks**	**q 6/12 wks**	**30 (±7) days following withdrawal from study treatment**	**Every 6 weeks (±7 days)**	**Every 3 months (±7) days**
Informed Consent	X																	
Disease History[7], Demographics, Concurrent Illnesses, Medical History	X		X[8]				X[8]											
Physical Exam[9], Weight[10], BSA[11]	X[9]						X			X				X[11]		X[11]	X[10, 11]	
Height	X																	
Vitas signs[12]	X						X			X				X		X		
ECOG	X						X			X				X		X	X	
Hematology[13] Chemistry[14]	X		X[15]				X[16]	X[13]	X[13]	X				X		X		
Serum pregnancy (for WOCBP)	X																	
Serum Hsp27[17]	X		X				X			X				X		X		
Serum for Other Protein analysis[18]			X[18]				X[18]			X[18]								
Blood for CTC capture/analysis[19]	X[19]		X[19]				X[19]			X[19]								
Radiographic Evaluations[20]	X									X[20]					X[20]	X[20]	X[20]	
Record Disease Sites	X																	
Study Drug Pre-Medication[21]			X	X	X		X	X	X	X[21]			X[21]					
OGX-427 Administration (Arm A only)[3]			X	X	X		X	X	X	X	X	X	X					
Docetaxel Administration (Both Arms)							X			X								
Adverse Events[22]			X	X	X		X	X[22]	X[22]	X	X[22]	X[22]	X			X		
Concomitant Medications[23]	X		X	X	X		X	X	X	X	X	X	X			X[23]		
Survival Status																		X
Subsequent Therapy																		X
Archived Tumor Samples[24]							X											

Study Calendar Footnotes:

[1]Screening evaluations will be completed within a 28-day period + 3 days (i.e. from the first screening evaluation to randomization) unless otherwise specified.

[2]Participants will be randomly assigned with equal probability to one of two arms: Arm A: docetaxel plus OGX-427; Arm B: docetaxel alone. Participants must receive their first dose of Study Drug within 5 days of randomization.

[3]For participants in Arm A, three separate administrations of OGX-427 (600 mg OGX-427) will be given IV over 2 hours per institutional standards. The 3 loading doses must be administered with at least one "non-treatment" day between each dose. To allow for holidays and clinical availability, a maximum of 9 days is allowed to complete the Loading Dose period. There must also be a minimum of 1 and maximum of 7 days between the 3rd loading dose and Cycle 1, Day 1. During Cycles 1-10, OGX-427 will be administered at a dosage of 600 mg given IV over 2 hours per institutional standards on Days 1, 8, and 15 of each cycle. Arm A participants who have completed all 10 cycles of docetaxel, or have received at least 2 cycles of docetaxel with weekly OGX-427, and have discontinued study treatment without documented disease progression and not due to toxicity related to OGX-427 may continue to receive OGX-427 at the 600 mg dosage as maintenance until disease progression or unacceptable toxicity.

[4]Participants in Arm A who have completed all 10 cycles of docetaxel, or who have received at least 2 cycles of docetaxel with weekly OGX-427 infusions and have discontinued study treatment without documented disease progression and not due to toxicity related to OGX-427 should continue weekly OGX-427 infusions as maintenance until disease progression or unacceptable toxicity.

[5]Off Treatment Follow-up Period: evaluations should continue every 6 weeks (± 7 days) until disease progression.

[6]Participants who have documented disease progression will be followed every 3 months (± 7 days) for documentation of anticancer therapy, secondary malignancies, and survival status. Survival follow-up can be accomplished by routine clinic visits, telephone contact with the participant, or through the primary practitioner or caregiver.

[7]Disease history, including histological diagnosis of urothelial carcinoma and documentation of mixed histology as required, date of initial diagnosis, TNM stage at diagnosis and prior administration of all cancer therapy for bladder cancer including intravesicular, neo-adjuvant or adjuvant therapy, surgery, hormonal therapy, radiation, chemotherapy, biologics, and experimental agents.

[8]Update concurrent illnesses prior to first loading dose for Arm A. Update concurrent illnesses prior to first dose Cycle 1 Day 1 for Arm B.

[9] Perform complete physical examination at Screening (including tumor measurements of palpable disease, if appropriate). A limited PE examination related to signs, symptoms and concurrent illnesses is appropriate during the study.

[10]Weight is not required during the Off Treatment Follow-up Period.

[11]BSA is not needed for Maintenance, End of Treatment Visit, and during the Off Treatment Follow-up Period.

[12]Vital signs including BP, heart rate and temperature should be documented with each physical exam (PE). Vital signs should also be documented with any signs or symptoms during or immediately after an infusion. Vital signs are not required during the Off Treatment Follow-up Period.

[13]Hematology (WBC, absolute neutrophils, absolute lymphocytes, platelet count and hemoglobin) to be performed in local laboratory at screening, prior to the first loading dose (Arm A only) (need not repeat if completed within 14 days of the first loading dose), within 48 hours prior to Day 1 (both Arms) of each cycle (need not repeat if within 3 days of Cycle 1 Day 1), every three weeks (±2 days) during maintenance therapy (Arm A only), and at the End of Treatment Visit (both arms). Within 48 hours to study visit on Cycle 1 Days 8 and 15, collect 5 mL blood for additional hematology assessments, to include: WBC, hemoglobin, absolute neutrophils and lymphocytes and platelet count (both arms).

[14]Chemistry (sodium, potassium, chloride, CO2, calcium, phosphorus, serum creatinine, BUN, SGOT [AST], SGPT [ALT], alkaline phosphatase, total bilirubin, LDH, albumin, and uric acid) to be performed at the local laboratory at screening, prior to the first loading dose (Arm A only) (need not repeat if completed within 14 days of the first loading dose), within 48 hours prior to Day 1 of each cycle (need not repeat if within 3 days of Cycle 1 Day 1), every three weeks (± 2 days) during maintenance therapy (Arm A only) and at the End of Treatment Visit.

[15]Not required if performed within 14 days of the first loading dose.

[16]Not required if performed within 3 days of the first dose of Cycle 1 Day 1.

[17]Serum for measurement of Hsp27 will be collected and shipped to a Central Laboratory where analysis will be performed. Blood should be drawn at screening, prior to the first loading dose (Arm A only), on pre-dose Day 1 of each cycle, every three weeks during maintenance therapy (Arm A only), and at the End of Treatment Visit (See SPM for collection processing and shipping instructions)

[18].Serum for other protein analysis will be collected at prior to first loading dose (Arm A only), pre-dose day 1 cycle 1 (Arm B only), pre-dose day 1 cycle 3 and 5. (See SPM for collection processing and shipping instructions)

[19]Blood for circulating tumor cell (CTC) capture and analysis will be collected and shipped to University of Miami (UM). Blood should be drawn at screening and pre-dose on Day 1 of Cycles 2, 3 and 5. (See SPM for collection processing and shipping instructions). If blood for CTC is missed at Screening, collect pre-dose at loading dose 1 for Arm A and pre-dose Day 1 Cycle 1 for Arm B.

[20]Obtain chest/abdomen/pelvic CT scans (CT preferred, but MRI acceptable especially for participants with increased risk of contrast related nephropathy or other contraindications) plus bone scan, and any other imaging studies, as appropriate, for disease assessment including palpable disease measured during the physical examination. (A brain scan is not mandated by the study unless the participant has signs or symptoms of CNS disease). Preferably, the baseline and subsequent imaging will be by the same type of

procedure (e.g. CT vs. MRI scan) whenever possible. Participants with any type of scan performed as standard of care prior to consent for this study within 28 days of study enrollment that is available at the same facility where subsequent scans will be performed will NOT be required to have repeat scan unless they have developed new signs or symptoms of disease. CT scans should be performed per RECIST Criteria v1.1. CT of chest/abdomen/pelvis (CT preferred, but MRI acceptable especially for participants with increased risk of contrast related nephropathy or other contraindications) will be performed at baseline, every 6 weeks until disease progression, and with any sign or symptom of new or worsening disease. A bone scan is required at baseline and, if positive, every 6 weeks during the first 4 cycles of treatment (i.e., at the end of Cycles 2 and 4) every 12 weeks thereafter until disease progression (i.e., at the end of Cycle 8, at End of Treatment, and during maintenance with OGX-427 [Arm A only]), and with any sign or symptom of new or worsening bone disease or increase in alkaline phosphatase felt to be of bone origin. If new clinical signs or symptoms of disease progression have developed, repeat imaging as clinically indicated, preferably using the same modality as baseline, when appropriate. There is a 5 day window for scans prior to Day 1 of each cycle while patients are on treatment. There is a 7 day window for scans at EOT, disease progression/follow-up and survival.

[21]Participants should be pre-medicated at 30-90 minutes prior to each of the three loading doses and Cycle 1, Day 1, 8 and 15 with an antihistamine, H2 antagonist and if needed corticosteroid. If the participant has not manifested signs or symptoms of an infusion reaction during the loading doses and Cycle 1, participant may be treated in subsequent cycles without some or all of the premedications. Should Grade 2 or greater reactions occur, the participant should resume premedications, including dexamethasone, prior to Study Drug for the duration of treatment. See Section 5.13.1 for details.

[22]Adverse events to be graded using NCI CTCAE 4.0. The adverse event reporting period begins from the initiation of the first dose of Study Drug until 30 days after the last dose of Study Drug. All SAEs and Grade 3 or higher AEs that are ongoing at the end of study treatment need to be followed until each event resolves or is assessed as chronic. Beginning Cycle 2, (for Arm B only) contact participant by telephone to assess for any change in the participant's status that might warrant a clinic visit for further assessment. Document the phone call.

[23]Concomitant Medications should be documented from the screening visit until 30 days after the last dose of Study Drug. After 30 days following the last dose of Study Drug record only concomitant medications associated with SAEs and Grade 3 or higher adverse events that have not resolved.

[24] Where available, archived FFPE primary and metastatic tumor tissue will be collected from registered participants and shipped to HCRN. Analysis for associations between primary tumor Hsp27 IHC staining intensity and clinical outcomes will be performed. Analysis of additional biomarkers of interest may also be performed based on tumor tissue availability. (See SPM for collection processing and shipping instructions)

10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable and/or non-measurable disease will be assessed by RECIST v1.1. For the purposes of this study, participants should be reevaluated every 6 weeks.

10.1 Antitumor Effect on Measurable and Non-measurable Disease (RECIST v1.1)

For the purposes of this study, participants should be re-evaluated for response every 6 weeks. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).[38] Changes in the diameter (unidimensional measurement) of the tumor lesions are based on the RECIST v1.1 criteria as described below for both measurable and non-measurable disease.

10.1.1 Measurable Disease (Target Lesions)

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. All measurements should be taken and recorded in millimeters.

Lesions in previously irradiated areas should not be selected as target lesions, unless there has been demonstrated progression in the lesion.

CT scans with contrast (unless contraindicated i.e. especially for participants 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, whenever possible.

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 which 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 progression. Multiple target lesions should be reported consistently on the eCRFs in the same lesion order (i.e., with the same number) and with the same location descriptor on each subsequent examination.

10.1.2 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 small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) or measurable lesions in excess of 2 per organ or 5 in total. Measurements of these lesions are not required, but each lesion must be recorded as "present", "absent", or "new" at the time of each tumor evaluation. Multiple non-target lesions should be reported consistently on the eCRFs in the same lesion order (i.e., with the same number) and with the same location descriptor on each subsequent examination.

10.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up whenever possible. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.3 Response Criteria

All participants must have measurable disease defined as at least one target lesion that has not been irradiated and can be accurately measured in at least one dimension by RECIST v1.1 criteria.

10.3.1 Complete Response (CR)

Complete disappearance of all measurable and non-measurable disease with no new lesions. Any pathological lymph node (target or non-target) must have a reduction in short axis to < 10 mm). All markers of disease must have normalized. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When determining a CR, it is recommended that such lesions be investigated by fine needle aspirate or biopsy whenever possible.

10.3.2 Partial Response (PR)

A decrease from baseline of ≥30% of the diameter(s) of all target measurable lesions with no unequivocal progression of non-measurable lesions and no new lesions.

10.3.3 Stable Disease (SD)

Does not qualify for CR, PR, or progression.

10.3.4 Progression of Disease (PD)

One or more of the following 3 criteria must occur for documentation of disease progression:

1. Appearance of any new lesion or site of disease. (Lesions in areas not previously imaged will be considered new).
2. A 20% increase in the sum of the diameter(s) of target measurable lesions over either the smallest sum observed or over baseline if no decrease during therapy has occurred. The sum must also demonstrate an absolute increase of at least 5 mm.
3. **Unequivocal** progression of non-target lesions alone.

Note: Disease progression based solely on “non-target” lesions alone is **exceptional** and must be made in the context of the entire clinical picture. 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. In addition, the following will **not** constitute unequivocal progression:

- Worsening (increased in intensity or size of a lesion) of pre-existing lesions on bone scan only, with no new documented lesions.
- Appearance or worsening of pleural effusions, unless cytologically proven to be malignant in origin.

10.3.5 Not Evaluable (NE)

When no imaging/measurement is performed at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless PD is otherwise determined. Prior to any new anticancer therapy, every attempt should be made to perform an imaging evaluation.

10.3.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of measurement criteria. Overall response rate will be defined as achieving complete or partial response [CR+PR] and disease control rate will be defined as achieving stable disease (SD) or better [CR+PR+SD].

For Participants with Measurable Disease (i.e., Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (i.e., Non-Target Lesions)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	NonCR/non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

10.3.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from randomization until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.3.8 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from randomization to time of objective disease progression or death from any cause, whichever occurs first. In the absence of objective disease progression, PFS will be censored at the date of last disease evaluation without progression, unless death occurs within a short period of time (6 weeks, corresponding to the interval between disease evaluations) following the date last known progression-free, in which case the death will be counted as a PFS event.

10.3.9 Response Review

No central review of the radiology assessments is planned.

10.4 Other Response Parameters

10.4.1 Overall Survival

Overall survival (OS) is defined as the duration of time from randomization until death due to any cause, or censored at the date last known alive.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

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. Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- hospital admission solely for administration of study drug or chemotherapy

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific eCRF forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Adverse events (AEs) will be recorded from first dose of study drug and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to HCRN and/or others as described below.

11.4 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study within one business day of discovery of the event. This includes events both related and unrelated to the investigational product.

The completed SAE Report Form (see Study Procedure Manual) must be faxed to HCRN <u>within 1 working day of discovery</u> of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

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

Follow-up information will be faxed to HCRN, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the participant continued or withdrew from study participation.

11.5 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a participant is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported **within one working day of discovery of the event**. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be faxed to HCRN **within one working day of discovery of the event**.

11.6 HCRN Requirements for Reporting SAEs

HCRN will report any SAE to OncoGenex **<u>within one working day</u>** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

HCRN will fax the SAE form to OncoGenex and will provide follow-up information as reasonably requested.

11.7 Reporting to the Institutional Review Board (IRB)

The Principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB.

11.8 Reporting to the Food and Drug Administration (FDA)

HCRN has been designated to manage the Investigator held IND on behalf of Noah Hahn, MD, Sponsor Investigator and will be responsible for all communication with the FDA. HCRN will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

According to CFR 312.32, unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA by fax or phone as soon as possible but in no event later than 7 calendar days after initial receipt of the information. The fax should be sent to the FDA project manager assigned to the IND (301) 796-9845. A comprehensive written report will be submitted as an amendment to the IND within an additional 8 days (15 calendar days total).

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as an amendment to the IND as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events may be reported to the FDA using Form FDA 3500A or narrative format. Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.9 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving OGX-427 (outside SAEs) received from outside sources will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

11.10 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the sponsor-investigator or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participating investigators should report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify HCRN and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Independent Data Safety Monitor (DSM)

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, there will be a scheduled DSM safety review after the first 20 participants have been enrolled (approximately 10 per treatment arm) and treated for at least one cycle as a precaution to assess the frequency of ≥ Grade 3 adverse events and serious adverse events in this participant population. Further safety reviews will be conducted according to the schedule outlined in Section 12.3.

The DSM will be an oncologist experienced in the treatment of cancer patients with chemotherapy regimens. The primary responsibility of the DSM will be overall safety for participants on the protocol. The DSM will monitor the safety of individual participants during the entire adverse event reporting period (i.e., from the first administration of Study Drug through 30 days after completion of the final cycle of chemotherapy treatment or maintenance, whichever comes last). The DSM will:

a. Review all SAEs reported to the HCRN. The HCRN will provide the DSM with a copy of any unexpected Study Drug-related SAE Report Form within 15 business days of receipt by the HCRN. The Medical Monitor will also provide the DSM with copies of all expedited SAE reports submitted to regulatory agencies.
b. Perform periodic reviews of all safety data for individual participants. This will be accomplished by review of individual participant data listings provided by an independent, unblinded statistician. These listings will 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, prior cancer therapies, Study Drug administration, vital signs during infusion, clinical laboratory data (serum chemistry, hematology, coagulation, urine dipstick), reported adverse events and concomitant medications.
c. Perform continued monitoring of Grade 3 and higher adverse events and SAEs on an ongoing basis for all participants.

12.2 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 guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies. The trial site may also be subject to quality assurance audit by OncoGenex or its designee as well as inspection by appropriate regulatory agencies.
It is important for the investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

12.3 Data and Safety Monitoring Board

The Dana-Farber/Harvard Cancer Center (DF/HCC) Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this trial. The board is chaired by a medical oncologist from outside of DF/HCC (See Section 12.1.1 regarding the DSM) and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed with the Sponsor Investigator, Co-PIs, statistician, and study team members. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the trial.
The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided by HCRN and study Statistician to the DSMB may include: participant accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.4 Data/Safety Monitoring and Reporting Guidelines

HCRN will compile data summary reports for this trial and submit these reports monthly to the Sponsor Investigator. HCRN will submit data summary reports twice-yearly to the DF/HCC Data and Safety Monitoring Board (DSMB) for review.

13. DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included participant. The trial statistical analysis will be coordinated and performed by the study Statistician at Dana-Farber Cancer Institute. The completed dataset is the property of the Sponsor Investigator and/or Institution and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission of the Sponsor Investigator and/or Institution. The Sponsor Investigator, Institution, and Hoosier Cancer Research Network shall each grant OncoGenex and its representatives reasonable access to study data and HCRN, at OncoGenex's expense, shall provide to OncoGenex and its representatives SAS data sets containing all observations, results and conclusions related to or resulting from the study at the completion of the study.

Sponsor Investigator and Institution grant to OncoGenex a license, with the right to grant sublicenses, to use the study data for its business purposes and to study sites for their own internal research and educational purposes.

13.2 Record Retention

To enable evaluations and/or audits from Health Authorities, HCRN, or the Sponsor Investigator, the Participating Investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

14. REGULATORY CONSIDERATIONS

14.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Study procedures will not be changed without the mutual agreement of the Sponsor Investigator, HCRN, and OncoGenex.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by HCRN and must be approved by each IRB, OncoGenex, and if applicable, also the local regulatory authority. Local requirements must be followed. Protocol amendments must also be submitted to the FDA.

If a protocol amendment requires a change to the Written Informed Consent Form, then each IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The Participating Investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

All decisions of the IRB concerning the conduct of the study must be made in writing. OncoGenex's willingness to supply OGX-427 is predicated upon the review of the protocol. HCRN agrees to provide written notice to OncoGenex of any modifications to the protocol or informed consent.

14.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

14.3 Ethics and Good Clinical Practice (GCP)

14.3.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the HCRN office before he or she can enroll any participant into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. OncoGenex will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

14.3.2 Ethical Conduct of the Study

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Local institutional research policies and procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries to the eCRF include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

15. STATISTICAL CONSIDERATIONS

Statistical analysis for this study will be the responsibility of the Dana-Farber Cancer Institute (DFCI) Dept. of Biostatistics and Computational Biology.

15.1 Study Design/Primary Objectives

This is a randomized, open-label trial to evaluate whether suppression of Hsp27 production using OGX-427, a second-generation antisense oligonucleotide (ASO), in combination with docetaxel can prolong OS time compared to docetaxel alone in participants with metastatic or inoperable, locally-advanced urothelial carcinoma (UC) that are relapsed after, or refractory to a platinum-containing regimen. Participants will be randomized with 1:1 allocation to receive docetaxel +/- OGX-427 using permuted blocks methods within strata.[39] Overall survival is defined in Section 10.4.

Based on the docetaxel plus vandetanib vs. docetaxel trial[33] in a similar patient population, the median OS on the docetaxel control arm is expected to be 6 months (hazard rate of 0.1155). This study is designed to have adequate power to detect a 33% reduction in the OS hazard rate (to 0.0770) on the docetaxel + OGX-427 arm corresponding to a hazard ratio (docetaxel + OGX-427/ docetaxel) = 0.667. If OS follows an exponential distribution, then this difference corresponds approximately to a 50% improvement in median OS (to 9 months on the docetaxel + OGX-427 arm). The null hypothesis is no difference in treatment effect. The primary analysis is a superiority test of OS, performed at one-sided 0.10 significance level using a stratified logrank test.[40] There will be 90% power to detect this OS difference assuming 200 participants are enrolled over 31 months with 8 months of additional follow-up (39 months/3.25 years total duration). Full information under the alternative hypothesis will occur at 162 deaths.

The Kaplan-Meier (KM) method will be used to estimate OS distributions by treatment arm.[41] A stratified Cox proportional hazards (PH) regression model will estimate the OS treatment hazard ratio and 80% 2-sided confidence intervals in unadjusted and adjusted models.[42] Exploratory subgroup analyses will investigate heterogeneity of treatment effects according to subgroups defined by the stratification factors, estimating hazard ratios within subgroups and testing for treatment-by-subgroup interaction in Cox PH regression models.

The study will also be monitored for futility with one interim analysis, planned prior to completion of accrual at approximately 50% information (approximately 81 deaths). Routine study procedures will continue during the interim analysis. The decision for early rejection of the experimental therapy will be guided by a hazard ratio boundary using the spending function methodology of Lan and DeMets with O'Brien-Fleming parameter to adjust the boundary for the actual interim analysis time. If conducted precisely at 50% information, the cut-off hazard ratio is 1.052 corresponding to a z-scale value of -0.227. If the hazard ratio estimate lies above 1.052, the study may be stopped early. Under the null hypothesis, the boundary crossing probability is 0.41. The futility rule with a beta spent of 0.020 at the one interim analysis is incorporated in the power calculation for efficacy and has negligible impact on sample size.

Sample size and interim monitoring considerations used East version 5.2 (Cytel Inc.).

15.2 Sample Size/Accrual Rate

To enroll 200 participants, accrual duration is expected to be 31 months (2.6 years) with a segmented accrual rate target to account for slower accrual while institutions activate the trial: 4 participants per month in the first 6 months and 7 participants per month for the remainder of the accrual period. Thus in years 1, 2 and 3 the accrual goals are 66, 84 and 50 participants, respectively. Accrual expectations use as reference the multi-institution (n=17 institutions) vandetanib docetaxel trial, which achieved an overall accrual rate of 4 participants per month, but the accrual rate in the last year was 7 participants per month.

15.3 Stratification Factors

As specified in Section 5.6, randomization will be stratified in order to minimize between-arm imbalance using two stratification factors: time from prior systemic chemotherapy (<3 versus ≥3 months); and number of Bellmunt[37] prognostic factors prior to randomization (0 versus 1-3 factors).

Evaluation of primary and secondary endpoints incorporates methods for stratified analyses.

15.4 Analysis of Secondary Objectives

Safety and tolerability of OGX-427 in combination with docetaxel will be compared to that of docetaxel alone. Each reported adverse event will be summarized as the highest grade experienced. Adverse events will be summarized according to grade, overall and by treatment arm, as number and percentage of participants. Specific adverse events (to be pre-specified in the Statistical Analysis Plan) will be compared between groups using Fisher's exact tests.

Overall response rate and disease control rate (defined in Section 10.3.6) will be summarized as number and percentage of participants by treatment arm with two-sided 80% CI and compared using Fisher's exact tests. With 100 participants per treatment arm and assuming 10% overall response rate in the docetaxel control arm, there is 80% power to detect an improvement to 22% in the experimental docetaxel + OGX-427 arm (Fisher's exact test, one-sided α=0.10).

The distributions of duration of response (Section 10.3.7) and PFS (Section 10.3.8) will be estimated using KM method by treatment arm, with median and two-sided 80% CI of the distribution summarized. PFS will be compared between treatment arms using a stratified

logrank test. With 100 participants per group and assuming 1.5 month (6 week) median PFS in the docetaxel control arm, there is over 90% power to detect an improvement to 3 month (12 week) median PFS in the experimental docetaxel + OGX-427 arm (logrank test, one-sided α=0. 10; 71 required PFS events).

Serum levels of Hsp27 (or other proteins) will be summarized descriptively over time as median and inter-quartile ranges at baseline and each treatment cycle, separately by treatment arm. The percentage changes in serum levels from baseline over time will also be summarized, as well as the maximum percentage of serum level decline from baseline over 2 cycles and over all cycles of treatment.

Serum Hsp27 levels at baseline will be explored as a possible prognostic or predictive marker. It is hypothesized that participants with higher baseline Hsp27 level will have better OS when treated with docetaxel+OGX-427 vs. docetaxel alone relative to participants with lower Hsp27 levels. Since no clinically meaningful cutoff point has been previously established, serum Hsp27 (or other protein) levels will be categorized at quartiles or median for assessing the associations with OS. The distribution of OS according to Hsp27 level will be estimated using KM method, overall and by treatment arm. A stratified Cox PH regression model will be used to assess the association of Hsp27 with OS, to estimate treatment hazard ratios by Hsp27 subgroup, and to test the treatment-by-Hsp27 interaction. To investigate the association of percentage changes in serum Hsp27 level with OS, a landmark analysis approach (with a landmark set after cycle 2, i.e., 6 weeks, when the first imaging takes place) will be used. The serum Hsp27 measurements during the first 2 cycles on study therapy will be used to calculate the maximum percentage of decline from baseline. Among participants who are alive after cycle 2, the association of maximum decline in serum Hsp27 levels with OS (re-defined from the landmark point) will be investigated as described above.

CTC enumeration and expression of Hsp27 and other relevant proteins will be measured by immunoflourescence and levels of telomerase will be analyzed by quantitative PCR at Screening, day 1 cycle 2, day 1 cycle 3 and day 1 cycle 5. The associations of CTC number, telomerase activity and CTC expression of Hsp27 at Screening with OS will be evaluated, similarly as described above for serum Hsp27 levels. The changes of CTC number, telomerase activity and expression of Hsp27 from Screening to day 1 cycle 2 will be summarized descriptively, and their association with OS will be evaluated using a landmark analysis. CTC measurements and telomerase activity also will be summarized according to patient disease status at time of day 1 cycle 3 and day 1 cycle 5 when radiographic evaluation are done.

Hsp27 protein is highly expressed in bladder tumor tissue, with one cohort[20] of 42 samples reporting 9.5%, 7%, 28.5%, 55% of samples having 0, 1-50%, 51-80% and >80% Hsp27 immunostaining, respectively. Tumor expression of Hsp27 will be summarized descriptively as median and inter-quartile ranges. Since no clinically meaningful cutoff point has been previously established, Hsp27 expression will be categorized at quartiles or median, and the association with OS investigated as described above for serum levels.

In consideration of power for correlative studies, we assume 80% of participants have samples assayed (160 participants; 130 deaths). Assuming Hsp27 is dichotomized at the median, there is

80% power to detect a hazard ratio of 0.69 (one-sided α=0.10). To test treatment-by-Hsp27 interaction, assuming the overall treatment hazard ratio is 0.67 and the Hsp27 hazard ratio is 0.69, then there is 75% power to detect an interaction ratio of 0.5 (e.g., high Hsp27 treatment HR=0.44 vs. low Hsp27 HR=0.88) (one-sided α=0.10).

15.5 Reporting and Exclusions

15.5.1 Evaluation of toxicity

Randomized participants who received at least one dose of the trial treatment will be included in the safety and tolerability analyses

15.5.2 Evaluation of efficacy

All randomized participants will be in the analysis of efficacy endpoints and analyzed according to randomized treatment assignment, based on the intention-to-treat (ITT) principle.

16. PUBLICATION PLAN

HCRN assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov prior to participant enrollment. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

The first publication relating to the study will reflect the overall results of the study at all sites. The first publication will be the responsibility of the Sponsor Investigator, Co-PIs and study Statistician. In the event there is no multi-center publication within 12 months after the study data lock, or unless otherwise notified earlier by OncoGenex, Sponsor Investigator and the study sites shall have the right to publish the results from the study.

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18. APPENDICES

Appendix A: Guidelines to Evaluate the Response to Treatment in Solid Tumors (RECIST v1.1)

This information is available on line at: http://imaging.cancer.gov/clinicaltrials/imaging.

Appendix B: ECOG Performance Status **ECOG Performance Status**	
Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead