A Phase 2 Trial of Carfilzomib for Metastatic Castration-Resistant Prostate Cancer Following Androgen Pathway Inhibitors

Study Protocol and Statistical Analysis Plan

NCT02047253

July 19, 2018

Guru Sonpavde, MD, Principal Investigator

University of Alabama at Birmingham

Birmingham, AL 35294

Comprehensive Cancer Center
University of Alabama at Birmingham (UAB)
Birmingham, Alabama

PROTOCOL: UAB 1336 and Outside Sites – A Phase 2 trial of Carfilzomib for metastatic castration-resistant prostate cancer following androgen pathway inhibitors

Coordinating Center: University of Alabama at Birmingham, Comprehensive Cancer Center
1802 Sixth Avenue South, NP 2515
Birmingham, AL 35294-3300

Principal Investigator: Guru Sonpavde, MD
UAB Comprehensive Cancer Center
1802 Sixth Avenue South, NP 2540B
Birmingham, AL 35294
Telephone: 205-975-3742
Fax: 205-934-9511
E-mail address: sonpavde@uab.edu

Co-Investigators: Graeme Bolger, MD
Mollie DeShazo, MD
Frederick Schnell, MD
Oliver Sartor, MD

Statistician:
Sejong Bae, PhD
Professor of Medicine
Co-Director-BBSF-Comprehensive Cancer Center
Deputy Director-CARDIA Coordinating Center
Department of Medicine,
Division of Preventive Medicine
University of Alabama at Birmingham
1717 11th Ave. South - Medical Towers Bldg., Rm 645
Birmingham, AL 35294-4410
205-975-5121 Phone
205-934-4262 Fax

Study Coordinator:
Lynn Merritt, RN

Supplied Agent: *Carfilzomib (IND #119209)*

Protocol Type / Version # / Version Date April 15, 2015

SYNOPSIS: A Phase 2 trial of Carfilzomib for metastatic castration-resistant prostate cancer following androgen pathway inhibitors

OBJECTIVES

Primary Objective
Clinical progression-free survival (PFS) at 6 months

Secondary Objectives

- PSA changes (response, PSA decline ≥30% within 3 months)
- CTC changes (unfavorable → favorable, >30% decline)
- Measurable disease response rate (RECIST)
- Pain responses (decline in present pain index ≥2, decrease in analgesics)
- Overall Survival
- Toxicities
- Association of outcomes with baseline whole blood 20S proteasome level

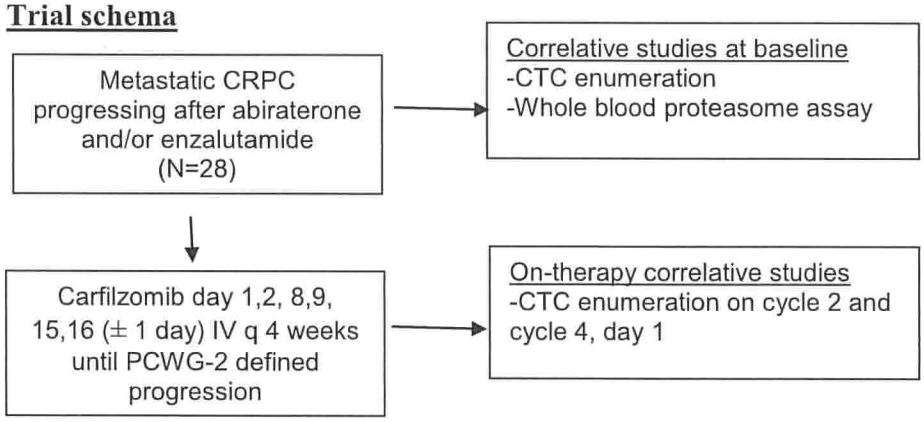
TRIAL DESIGN

This is a multi-center one-stage phase II trial conducted at UAB Comprehensive Cancer Center and outside sites, and managed by the CTNMO (Clinical Trial Network Monitoring Office) housed at the UAB Comprehensive Cancer Center. Clinical PFS as the primary end-point and the trial will enroll 28 patients. The eligible population includes men with metastatic castration-resistant prostate cancer (CRPC) who have received prior abiraterone and/or enzalutamide (prior chemotherapy is allowed). Carfilzomib is administered twice-weekly on consecutive days (± 1 day) (days 1, 2, 8, 9, 15, 16) as a 30 minute intravenous (IV) infusion for 3 weeks every 4 weeks (1 cycle) with dexamethasone and acetaminophen premedication as well as normal saline 250 ml over 30 minutes as pre-hydration. The dose of carfilzomib is 20 mg/m^2 on days 1 and 2 of cycle 1 and then escalated in succeeding weeks and cycles to 56 mg/m^2 for no dose limiting toxicities (DLTs) occur defined as any grade ≥3 non-hematologic toxicity or grade ≥4 neutropenia or thrombocytopenia lasting ≥7 days.

Acyclovir 400 mg orally twice daily is required during therapy, which may be discontinued ≥7 days after the last dose of carfilzomib. Therapy will continue until progression (as defined below) or severe toxicities. Patients removed from the trial for toxicities or other reasons will continue to be followed until progression or starting a new agent. Androgen deprivation therapy with LHRH analogue or antagonist and bone protecting agent (denosumab or zoledronic acid) will also continue. Comprehensive metabolic panel (CMP) evaluations are performed on day 1 every 4 weeks, complete blood cell (CBC) counts on days 1, 8 and 15 every cycle, and radiological evaluations are performed every 3 cycles or earlier if clinically indicated. Pain (PPI score, Appendix B) and analgesic intake (Appendix C) are recorded on day 1 of every cycle. Correlative studies include serial CTC enumeration (repeated on day 1 cycle 2 and day 1 cycle 4) and collection of whole blood is performed at baseline for 20S proteasome activity. Progression of disease will be defined clinically as the first occurrence of any of the following, and PSA progression alone will not constitute progression:

1) Two distinct new lesions on bone scan consistent with bone metastases in the best judgment of the investigator and confirmed by further new lesions on a subsequent scan ≥6 weeks later.
2) Progression in measurable disease as defined by RECIST criteria
3) Worsening of pain (increase in present pain index by ≥1 point, increased need for analgesics).
4) New bladder outlet or ureteral obstruction caused by cancer
5) New bone related events
   a. Pathologic fracture
   b. Spinal cord compression
   c. Need for palliative radiation, surgery, or kyphoplasty to any neoplastic bone lesion
6) Deterioration of performance status to ECOG level 3-4
7) Death

Trial schema



Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Histologically proven adenocarcinoma of the prostate
2. Metastatic disease
3. Progressive disease (PSA, radiologic, symptomatic) following abiraterone acetate and/or enzalutamide (prior sipuleucel-T and chemotherapy are allowed); PSA progression is defined as baseline increase followed by any PSA increase ≥1 week apart
4. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
5. Patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse if female partner of childbearing age.
6. An elevated PSA level of >2 ng/mL for patients progressing by PSA criteria is required (last confirmatory sample must be >2 ng/mL)
7. Currently on androgen ablation hormone therapy (an LHRH agonist/antagonist or orchiectomy) with testosterone level <50 ng/dL)
8. Has an ECOG Performance Status (PS) of 0-2 (Appendix A)
9. LVEF ≥ 40% on 2-D transthoracic echocardiogram (ECHO); Multigated Acquisition Scan (MUGA) is acceptable.
10. Is ≥19 years of age

11. Resolution of all acute toxic effects of prior chemotherapy or surgical procedures to NCI CTCAE Version 4.03 Grade <1, in the opinion of the Treating Physician (Appendix D)
12. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

Patients meeting any of the following exclusion criteria within 4 weeks (unless otherwise stated) of being enrolled are not to be enrolled in the study.

1. Patient has a platelet count of <100,000/mm^3, or absolute neutrophil count of <1500/mm^3 or Hemoglobin <8.0 gm/dL
2. Patient has a calculated or measured creatinine clearance of <30 mL/minute
3. Patient has total bilirubin >2 x ULN (upper limit of normal), or AST, ALT >3.5 X ULN
4. Patient has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.
5. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Before study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
6. Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
7. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
8. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the breast; c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
9. Known HIV, hepatitis B and hepatitis C infection
10. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization
11. Prior treatment with bortezomib
12. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
13. Has received prior radiation to >50% of the bone marrow
14. Has had significant bleeding/thrombosis in previous 4 weeks
15. Has received treatment with radiation therapy, surgery, chemotherapy, or an investigational agent within 4 weeks prior to registration, (6 weeks for radiation therapy, radionuclides, nitrosureas, or Mitomycin C) or who have not recovered from adverse events due to agents administered more than 4 weeks earlier
16. Has evidence of uncontrolled CNS involvement (previous radiation and off steroids is acceptable)
17. Patients may not be receiving any other investigational agents.
18. Has a serious uncontrolled intercurrent medical or psychiatric illness, including serious infection
19. Is unable to comply with study requirements
20. 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.

STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to administration of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	-28 days	-14 days (may serve as cycle 1 day 1 labs)	Day 1 (± 1 day) of every cycle (28 days)	Day 8 and 15 every cycle (± 1 day)	Day 1 Every 3 cycles	30 (± 7 days) post last treatment
ASSESSMENTS						
History and exam (H&P)	X		X			X[1]
ECOG performance status		X	X			X[1]
CBC with differential		X	X	X		X[1]
CMP		X	X			X[1]
PSA		X	X			X[1]
LDH		X				
Testosterone level		X				
Pain (PPI 0-5 scale)		X	X			X[1]
Analgesic intake (increased, decreased or stable)		X	X			X[1]
Echocardiogram	X		X[6,7]			
DISEASE ASSESSMENT						
CT chest , abdomen, pelvis	X				X	X[1]
Bone Scan	X				X	X[1]
TREATMENT						
Carfilzomib day 1,2, 8,9,15,16 (30 min IV infusion)			X[2]	X[2]		
Premedication (Dexamethasone, Acetaminophen)			X[3]	X[3]		
Pre-hydration (Normal saline 250-500 ml over 30 minutes)			X[4]	X[4]		
Acyclovir 400 mg PO bid			X[5]	X[5]		
LHRH analogue (if no prior orchiectomy)					X	
CORRELATIVE STUDIES						
CTC enumeration (3 time points)	X		X (cycle 2		X (cycle 4	

			only)		only)	
Whole Blood 20S proteasome assay	X					
FOLLOW-UP						
Disease progression and survival						X[1]

[1]Patients removed from trial for reasons other than progression will continue to be followed until progression or initiation of new therapy (whichever comes first); i.e. H&P, laboratory evaluation, pain, analgesic intake are performed every ~28 days and radiographic evaluation every ~90 days (+/-7 days)

[2]Dose is 20 mg/m^2 on days 1, 2 of cycle 1 and if no DLTs, escalate to 56 mg/m^2 for all remaining doses, Subjects with a Body Surface Area (BSA) > 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level) or 123 mg of carfilzomib (at the 56 mg/m^2 dose level).

[3]Dexamethosone dose is 4 mg PO/IV with carfilzomib 20 mg/m^2 and 8 mg PO/IV with carfilzomib 56 mg/m^2, dexamethasone may be discontinued from cycle 2 day 1 if patient is tolerating carfilzomib therapy per investigator discretion and/or has adverse effects from dexamethasone, acetaminophen dose is 650 mg PO x 1

[4]Prehydration with 250-500 ml of normal saline is given during cycle 1 and may be discontinued from cycle 2 day1 per investigator discretion (post-hydration with 250-500 ml normal saline is optional per investigator discretion)

[5]Acyclovir to start on day 1 of cycle 1 and stop ≥7 days after last dose of carfilzomib

[6]Only if clinically indicated for patients who develop CHF on study

[7]Multigated Acquisition Scan (MUGA) is acceptable

STATISTICAL CONSIDERATIONS

Modest activity is considered clinically meaningful in this population with mCRPC that has received abiraterone acetate and/or enzalutamide (with prior chemotherapy and sipuleucel-T allowed). The null hypothesis for this trial is that the primary endpoint of 6-month PFS <10% is not clinically meaningful and the alternative hypothesis is that the true clinical PFS of interest is ≥30%. Since we will follow all subjects for at least 6 months or until progression or death, we do not expect any censoring. Thus 6 month PFS can be treated as a binomial random variable. With twenty five evaluable patients we will have 80% power for an exact binomial test at the one sided 0.05 significance level of the null hypothesis that the 6-month PFS rate is 10% if the actual rate is 30%. That null hypothesis will be rejected if 6 or more of the 25 subjects survive for 6 months progression free. Twenty-eight subjects will be accrued to allow for 10% inevaluable. The Kaplan-Meier method will be used to estimate PFS and OS rates over time with standard errors estimated using Greenwood's formula. Medians and their 95% confidence intervals will also be estimated. PSA response, PSA decline ≥30%, RECIST responses and regressions, pain response and CTC alterations will be analyzed as secondary endpoints. The association of baseline whole blood 20S proteasome level with PFS and other secondary endpoints will be examined using Cox regression to generate hypotheses for selecting suitable patients for further study.

TABLE OF CONTENTS

APPENDICES

1. BACKGROUND

1.1 Systemic therapy for metastatic castration-resistant prostate cancer

Approved agents

Docetaxel-based first-line chemotherapy extends survival for patients with metastatic castration resistant prostate cancer (CRPC). Although statistically significant, the median survival for patients with metastatic CRPC receiving docetaxel is approximately 19 months with a median progression free survival (PFS) of only 6 months, providing a modest 2.5 to 3 month survival extension.[1, 2] Following failure of docetaxel, cabazitaxel has demonstrated a modest improvement in median survival of ~2.5 months. [3] The androgen inhibitors, abiraterone and enzalutamide, both extend overall survival by 4-5 months in the post-docetaxel setting.[4, 5] Abiraterone is also effective in the chemo-naïve setting, with recent FDA approval in this setting.[6] Furthermore, an immunomodulating vaccine, sipuleucel-T has extended survival in patients with relatively asymptomatic disease. [7, 8] The alpha-emitting radiopharmaceutical, radium-223, reduced pain due to metastatic bone disease and extended median overall survival in a phase III trial and is now approved. Denosumab, a monoclonal antibody that targets RANK-ligand, provided an ~18% incremental benefit over zoledronic acid in the prevention of skeletal related events in men with bone metastases.[9]

Sequencing of novel agents

Optimal sequencing of all of the approved agents is unclear. Currently, abiraterone is approved for docetaxel-naïve patients with mCRPC, and the approval of enzalutamide for docetaxel-naïve patients is expected in the near future [10, 11]. Therefore, most patients are likely to prefer these oral and convenient drugs before receiving docetaxel chemotherapy for mCRPC.

The activity of docetaxel activity is partly attributable to interference with androgen receptor-signaling, a mechanism of action similar to abiraterone and enzalutamide, which may yield cross-resistance as demonstrated in preclinical studies [12]. Indeed, in one retrospective clinical study, 35 patients received docetaxel following abiraterone and demonstrated only modest activity [13]. Docetaxel resulted in a prostate-specific antigen (PSA) decline of ≥50% in only 9 patients (26%) and the median overall survival was only 12.5 months. All patients who failed to achieve PSA decline on abiraterone and were abiraterone-refractory were also docetaxel-refractory.

Cross resistance between abiraterone acetate and enzalutamide is also a concern. The PSA response rate (>50% decline) is lower for second-line treatment regardless of whether abiraterone acetate or enzalutamide has been given first (~30% response rate), and radiographic responses are rare. For example, in one large study of patients receiving enzalutamide after abiraterone, PSA response rate (22% vs. 26%; p=0.8), median time to radiologic/clinical progression (4.6 mo vs. 6.6 mo; p=0.6), and median OS (10.6 mo vs. 8.6 mo; p=0.2) did not differ significantly between docetaxel-treated and docetaxel-naive patients [14]. Enzalutamide also produces modest PSA responses and median survival of only 8.3 months in patients progressing following both chemotherapy and abiraterone [15]. In another report, treatment with either enzalutamide or docetaxel following prior abiraterone produced modest PSA responses

and median PFS of only ~4.5 months [16]. The activity of abiraterone acetate following enzalutamide and docetaxel also is modest [17, 18]. These data reveal that cross resistance between these agents is a significant concern and the relative benefits of sequencing docetaxel following abiraterone and/or enzalutamide, and of abiraterone→enzalutamide and enzalutamide →abiraterone vs. offering novel and promising agents on clinical trials warrants consideration.

Emerging agents

.[19] Despite these advances, the median survival in the first-line chemonaive setting of metastatic CRPC is ~20 months and in the post-docetaxel setting is 15-18 months. Given the modest incremental benefits conferred by these recently approved agents, novel and tolerable agents are necessary to make further gains. Multiple trials combining novel agents with first-line docetaxel based chemotherapy have not yielded improvements, e.g. bevacizumab, aflibercept, atrasentan, lenalidomide, DN101 and dasatinib. [20] A novel androgen synthesis inhibitor, TAK 100, is being investigated in pre-docetaxel and post-docetaxel settings. Immunotherapeutic agents undergoing phase III evaluation are ipilumimab and a poxvirus based agent, prostvac-tricom®.[21, 22] Recently, cabozantinib, an orally bioavailable tyrosine kinase inhibitor that targets MET and VEGF receptor 2 demonstrated a reduction of soft tissue lesions (72%) and improved PFS over placebo.[23] Agents with novel mechanisms of activity, e.g., custirsen (clusterin antisense oligonucleotide) and tasquinimod (immune modulatory and anti-angiogenic) are undergoing phase III assessment. [24, 25]

Intermediate endpoints to assess the activity of new agents

The choice of a primary endpoint in metastatic CRPC is difficult as this disease is characterized by a poor ability to measure response and PFS, the typical primary endpoints in phase II trials. Measurable lesions by RECIST are seldom observed, since the most common site of metastases is bone, a non-measurable site [26]. Although, a ≥30% or ≥50% PSA decline within 3 months and time to clinical progression may be useful surrogates for long-term outcomes with chemotherapeutic agents, its validity with biological agents is unknown [27-29]. Regression of measurable tumor was associated with survival in one study, but external validation is required and measurable tumors are found in the minority of patients. Prostate Cancer Working Group (PCWG)-2 guidelines recommend time to event primary endpoints rather than response endpoints[27]. Moreover, a an early switch in therapy within 3 months was discouraged due to the poor reliability of early changes in PSA and bone scans. Vaccines may potentially induce a transient rise in PSA as well as increases in size of measurable lesions by provoking an immune reaction in the normal and malignant prostate tissue. Guidelines have been recommended to standardize methodology used for the calculation and employment of PSA doubling time changes to provide a signal of activity in early trials [30].

Changes in CTCs (circulating tumor cells) appear promising as prognostic factors in the setting of chemotherapy and abiraterone, but require validation in the context of biologic agents [31, 32]. Moreover, it is unclear if unfavorable CTC alterations can be utilized to switch therapy. CTC is emerging as a highly important prognostic marker for metastatic CRPC and appears better than PSA. In one prospective trial, blood was drawn from CRPC patients with progressive disease starting a new line of chemotherapy before

treatment and monthly thereafter.[31] Patients were stratified into predetermined Favorable or Unfavorable groups (<5 and ≥5 CTC/7.5mL). Two hundred thirty-one of 276 enrolled patients (84%) demonstrated CTCs and were evaluable. Patients with Unfavorable pretreatment CTC (57%) had shorter OS (median OS, 11.5 versus 21.7 months; Cox hazard ratio, 3.3; $P < 0.0001$). Unfavorable post-treatment CTC counts also predicted shorter OS at 2 to 5, 6 to 8, 9 to 12, and 13 to 20 weeks (median OS, 6.7-9.5 versus 19.6-20.7 months; Cox hazard ratio, 3.6-6.5; $P < 0.0001$). CTC counts predicted OS better than PSA decrement algorithms at all time points; area under the receiver operator curve for CTC was 81% to 87% and 58% to 68% for 30% PSA reduction ($P = 0.0218$). Prognosis for patients with (a) Unfavorable baseline CTC who converted to Favorable CTC improved (6.8 to 21.3 months); (b) Favorable baseline CTC who converted to Unfavorable worsened (>26 to 9.3 months). These data led to Food and Drug Administration clearance of this assay for the evaluation of CRPC.

In another study, CTC count was assessed as a prognostic factor for survival in patients with progressive, metastatic, castration-resistant prostate cancer receiving first-line chemotherapy.[33, 34] The investigators identified patients with progressive metastatic castration-resistant prostate cancer starting first-line chemotherapy in the IMMC38 trial. CTCs were isolated by immunomagnetic capture from blood samples at baseline and after treatment. Baseline variables, including CTC count, PSA, LDH, and post-treatment variables (change in CTCs and PSA) were tested for association with survival with Cox proportional hazards models. Concordance probability estimates were used to gauge discriminatory strength of the informative factors in identifying patients at low-risk and high-risk of survival. Variables associated with high risk of death were high LDH (hazard ratio 6.44), high CTC (HR 1.58), high PSA (HR 1.26), low albumin (HR 0.10), and low hemoglobin (HR 0.72) at baseline. At 4 weeks, 8 weeks, and 12 weeks after treatment, changes in CTC number were strongly associated with risk, whereas changes in PSA were weakly or not associated ($P>0.04$). The most predictive factors for survival were LDH concentration and CTC counts. Thus, CTC number, analyzed as a continuous variable was useful to monitor disease status as an intermediate endpoint of survival in clinical trials. Prospective recording of CTCs as an intermediate endpoint in randomized clinical trials was felt to be warranted. Recently, the Phase III database of patients where abiraterone acetate was compared with placebo was investigated for prognostic factors. Baseline LDH and favorable CTC changes were independently significant. [32]

Therefore, overall survival is the only currently reliable endpoint for randomized phase III trials of in metastatic CRPC. Primary endpoints in phase II trials may need to be tailored based on mechanism of activity on agents. Generally, phase II trials evaluating new biologic agents are employing PFS based on clinical and radiographic endpoints in accordance with PCWG-2 guidelines, and not PSA-based changes. For example, the recent randomized phase II trial evaluating tasquinimod, a novel antiangiogenic and immune-modulating agent, employed these new guidelines and did not use PSA changes alone to make clinical decisions.[35]

1.2 Proteasome activity as a therapeutic target in metastatic CRPC

Proteasome inhibitors are promising agents for the therapy of prostate cancer.[36] The ubiquitin-proteasome pathway plays an essential role in the proteolysis of most intracellular proteins in eukaryotic cells. The 26S proteasome degrades damaged, oxidized and misfolded proteins, as well as regulatory proteins that govern the cell cycle, transcription factor activation, apoptosis and cell trafficking.[37] The degradation of key regulatory proteins is required to progress through the mitotic cell cycle. In addition, the activation of nuclear factor-kappa B (NF-κβ), a key transcription factor, is dependent on proteasome-mediated degradation of the inhibitory protein IκB. NF-κβ induces expression of cell adhesion molecules, pro-survival proteins and growth factors. NF-κβ is required to maintain the viability of the cell in response to environmental stress or cytotoxic agents. Bortezomib inhibits the degradation of IκB, leading to down-regulation of NF-κβ related factors of cancer progression and chemotherapy resistance. In preclinical studies, single agent bortezomib at concentrations of 7 to 500 nmol/L induced growth arrest and apoptosis *in vitro* and *in vivo* against androgen-dependent (LNCaP) and androgen-independent (PC-3 and DU-145) prostate cancer cell lines.[37-40] *In vitro* and *in vivo* studies of prostate cancer suggest that bortezomib activity is enhanced when given with docetaxel.[41, 42]

In a phase I trial of bortezomib in androgen-independent prostate cancer, 24 patients were treated: two had > 50% PSA decline, 25% had stable PSA and 11% had partial responses seen in measurable disease.[43] Dose-dependent inhibition of whole-blood proteasome activity was observed. In a follow-up phase two trial, 30 men with progressive castration-resistant disease were treated with bortezomib. [44] The primary end point was no evidence of disease progression at 12 weeks, defined as no increase in PSA and no radiographic progression. Only one of 24 evaluable patients achieved this end point; however, this is an un-validated endpoint and this was a small-sized trial not powered to make definitive conclusions. Other phase II trials have suggested that bortezomib either as monotherapy or in combination with androgen blockade or systemic therapy may have benefit. [42, 45] Bortezomib has been combined with weekly docetaxel or mitoxantrone in nonrandomized phase II trials and feasibility has been demonstrated in men with metastatic CRPC, although it is difficult to make conclusions regarding activity in the absence of a randomized trial and owing to the suboptimal weekly chemotherapy templates employed in these trials[42, 46, 47]. One phase II trial evaluated 4 weeks of bortezomib preceding radical prostatectomy and demonstrated single agent biologic activity (cytoplasmic entrapment of NF-κB) in the early localized high-risk hormone naïve stage [48].

Potential predictive biomarkers for the activity of proteasome inhibition

A biomarker predictive for the clinical activity of proteasome inhibitors has not been clinically validated. Multiple potential biomarkers have been investigated including tumor NF-κB as a surrogate for the activity of proteasomes and whole blood 20S proteasome activity. CTC profiling for biomarkers is plagued by lack of high CTC yield in most patients and the expense of CTC molecular profiling. Baseline whole blood 20S proteasome activity is affordable and yields measurable levels of activity in most patients and may be associated with clinical efficacy.[49, 50]

1.3 Carfilzomib

Preclinical studies

Carfilzomib is a novel second-generation epoxyketone-based irreversible proteasome inhibitor, and is structurally distinct from bortezomib.[51-54] In pre-clinical studies, carfilzomib (formerly PR-171) demonstrated irreversible binding to the proteasome and minimal off-target inhibition of other proteases. [55] In vitro experiments with continuous (72-hour) exposure to carfilzomib demonstrate potent pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture including bortezomib-resistant tumor cell lines. Incubation of tumor cell lines with carfilzomib for as little as 1 hour (mimicking intermittent IV administration) leads to rapid inhibition of proteasome activity; followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death.

Administration of carfilzomib to animals resulted in the dose-dependent inhibition of the chymotrypsin-like proteasome activity in all tissues examined with the exception of the brain. It was well tolerated when administered for either two of five consecutive days of doses resulting in > 80% proteasome inhibition in blood and most tissues. In human tumor xenograft models, carfilzomib mediated a dose and schedule dependent anti-tumor response. The antitumor efficacy of PR-171 delivered on two consecutive days was stronger than that of bortezomib. Please refer to the current Investigator's Brochure for further details and extensive information.

Phase I Clinical studies

In clinical studies carfilzomib has demonstrated substantial antitumor activity in hematologic malignancies while exhibiting a well-tolerated side-effect profile. Grade III or IV neuropathy was minimally reported, suggesting a possible advantage over bortezomib. With single agent carfilzomib, dose-limiting toxicity was hematologic, i.e. thrombocytopenia and neutropenia. Fatigue, nausea and diarrhea were also observed, but neurotoxicity was minimal. Across all studies peripheral neuropathy was seen in 14% of all patients, and only 1.3% experienced grade 3 neurotoxicity. Additional safety measures based on information from ongoing clinical carfilzomib studies. Steps were instituted in later studies, including tumor lysis syndrome (TLS) prophylaxis using dexamethasone (4 mg orally [PO]) prior to each dose of carfilzomib in Cycle 1, and as needed in subsequent cycles, to mitigate possible adverse events (AEs) temporally associated with dosing. These AEs may include events similar to cytokine release and are notable for fever, chills, dyspnea, and rigors occurring most commonly in the evening following the first or second infusion during the first cycle of therapy or the first escalation cycle of therapy. The regimen of carfilzomib of 20/27 mg/m2 on a once daily over 2-10 mins x2 dosing schedule, in concert with dexamethasone and tumor lysis prophylaxis, appeared to permit safe dosing during the first cycle, as well as dose-escalation in subsequent cycles for possible greater efficacy.

An ongoing, open-label, multicenter, Phase 1b/2 study (PX-171-007) is being conducted to evaluate the safety and efficacy of carfilzomib in adults with advanced solid tumors and myeloma. Based on review of the safety and tolerability of carfilzomib, solid tumor patients received higher doses of 30-minute infusions of carfilzomib monotherapy.

Prolonging the infusion to 30 mins was shown to yield a lower Cmax, which was associated with lower toxicities and preservation of efficacy. The highest carfilzomib dose administered to solid tumor patients by a slower 30-minute infusion at the time of the data cutoff date was 20/70 mg/m^2. The majority of early study drug discontinuations were due to PD (25, 53.2%). Thirteen (27.7%) patients discontinued treatment early due to 1 or more AE, and 6 (12.8%) patients discontinued treatment early for other reasons. The "other" reasons for discontinuation included no clinical benefit (3 patients), magnetic resonance imaging (MRI) showing metastases to brain (PD; 1 patient), went on to a different study (1 patient), and persistent severe pain from osseous metastases along with decrease in performance. Of the 47 solid tumor or lymphoma patients, 34 (72.3%) reported at least one Grade 3 or higher AE. The most common Grade 3 or higher AE reported was anemia in 7 (14.9%) patients, followed by disease progression (6 patients; 12.8%). Sixteen (34.0%) patients reported Grade 3 or higher AEs that were considered related to study drug; the most common related Grade 3 or higher AEs were anemia in 5 (10.6%) patients, followed by fatigue in 4 (8.5%) patients. Seven (14.9%) patients experienced AEs with an outcome of death within 30 days of their last dose of study drug: 5 of the deaths were attributed to disease progression, 1 was attributed to hepatic failure (unrelated), and 1 to pneumonitis (possibly related). SAEs were reported by 26 (55.3%) patients; the only SAE reported in greater than 3 patients was disease progression (reported in 6 patients; 12.8%). In multiple myeloma patients receiving 30-minute infusions of carfilzomib monotherapy, the MTD was determined to be 56 mg/m2

Moreover, safety has been demonstrated in those with significant renal dysfunction.[56] Carfilzomib is rapidly systemically cleared extra-hepatically by peptidase cleavage and epoxide hydrolysis with a short half life of < 1 hour and renal clearance is not a significant pathway for elimination. Hence dose adjustments appear unnecessary in those with renal dysfunction. Pharmacokinetic studies showed excellent peripheral tissue distribution. None of the metabolites inhibit the activity of the 20S proteasome. However, despite the rapid clearance of carfilzomib from the blood compartment, prolonged potent proteasome inhibition is observed. The pharmacodynamic (PD) half-life of carfilzomib is $\geq$ 24 hours in humans. In clinical studies, carfilzomib doses of 15 to 36 mg/m^2 lead to an average of 77% to 86% proteasome inhibition in whole blood and PBMCs at 1 hour after dosing. CYP450 mediated metabolism plays a minor role suggesting that CYP450 inhibitors are unlikely to interact with carfilzomib. Although inhibition of CYP3A system by carfilzomib was noted, the pharmacokinetics of midazolam was not affected. Thus, the rapid clearance and unique metabolism may limit toxicities and drug interactions. Please refer to the current KYPROLIS Investigator's Brochure for further details and extensive information.

Phase II studies

In patients with relapsed or refractory multiple myeloma, twice weekly consecutive day single agent carfilzomib 20mg/m^2 IV over 2-10 mins for three weeks every 28 days, escalating to 27mg/m^2 the second cycle was associated with a 58% overall response and benefit rate in bortezomib-naïve patients and a 26% benefit rate in bortezomib and immunomodulatory drug refractory patients.[57] These data led to the FDA approval of carfilzomib for refractory multiple myeloma. The combination of carfilzomib,

lenalidomide and dexamethasone (CRd) was highly active in newly diagnosed patients with myeloma, with all patients attaining at least very good partial response (VGPR).[58] In this trial, carfilzomib was administered as 20, 27, or 36mg/m^2 on days 1, 2, 8, 9, 15, 16 and 1, 2, 15, 16 after cycle 8. Please refer to the current KYPROLIS Investigator's Brochure for further details and extensive information.

Ongoing phase III studies

A phase III trial (PX-171-006) is comparing CRd with Rd (lenalidomide, dexamethasone) as first-line therapy for myeloma. Study 2011-003 is a Phase 3 multicenter, open-label, randomized trial comparing carfilzomib plus dexamethasone (Cd) or bortezomib (Velcade) plus dexamethasone (Vd) in patients with multiple myeloma whose disease has relapsed after at least 1, but not more than 3 prior therapeutic regimens. The key objectives of the trial are to support the approval of a higher dose / longer infusion of carfilzomib (20/56 mg/m2 over 30 minutes), and to show superiority over Velcade in relapsed patients. Please refer to the current KYPROLIS Investigator's Brochure for further details and extensive information.

1.4 Rationale for studying carfilzomib in metastatic castration resistant prostate cancer

Carfilzomib is a more potent and irreversible proteasome inhibitor without significant neurotoxicity compared to bortezomib. We propose a non-randomized proof-of-concept phase II trial to evaluate carfilzomib for men with metastatic progressive CRPC following prior abiraterone acetate and/or enzalutamide. Given the suboptimal activity of a second-line androgen inhibitor or switch to docetaxel chemotherapy after the initial androgen inhibitor, it is not considered necessary to require exposure to both enzalutamide and abiraterone and doceaxel chemotherapy before offering a promising novel agent. Given the feasibility of doses up to 56 mg/m^2 in advanced solid tumors, following the starting dose of 20mg/m^2 during the first week of cycle 1 (days 1, 2), intra-patient dose escalation can be justified in succeeding weeks and cycles to 56 mg/m^2 if no dose-limiting toxicities occur. The dose escalation will enhance the delivery a dose tailored to each patient based on tolerability. A clinically defined PFS may be justified as the primary endpoint as recommended by PCWG-2 guidelines and since PSA and objective response are problematic endpoints.[27] Supportive evidence for carfilzomib clinical efficacy can be derived from PSA declines, pain responses, measurable tumor progression, CTC declines and overall survival.[27, 31, 49]

2. OBJECTIVES

2.1 Primary Objective

Clinical progression-free survival (PFS) at 6 months

2.2 Secondary Objectives

- PSA changes (response, PSA decline ≥30% within 3 months)
- CTC changes (unfavorable → favorable, >30% decline)
- Measurable disease response rate (RECIST)
- Pain responses (decline in present pain index ≥2, decrease in analgesics)
- Overall Survival

- Toxicities
- Association of outcomes with baseline whole blood 20S proteasome level

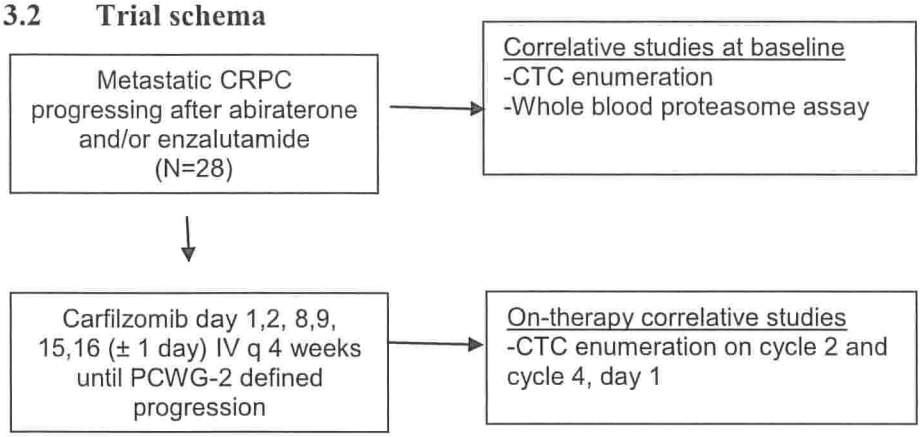
3. OVERALL TRIAL DESIGN

3.1 Design

This is a 2-center one-stage phase II trial conducted at UAB Comprehensive Cancer Center and outside sites, and managed by the CTNMO (Clinical Trial Network Monitoring Office) housed at the UAB Comprehensive Cancer Center. Clinical PFS as the primary end-point and the trial will enroll 28 patients. The eligible population includes men with metastatic CRPC who have received prior abiraterone and/or enzalutamide (prior chemotherapy and sipuleucel-T are allowed). Carfilzomib is administered twice-weekly on consecutive days (± 1 day) (days 1, 2, 8, 9, 15, 16) as a 30 minute intravenous (IV) infusion for 3 weeks every 4 weeks (1 cycle) with dexamethasone and acetaminophen premedication as well as normal saline 250 ml over 30 mins as pre-hydration. The dose of carfilzomib is 20 mg/m^2 on days 1 and 2 of cycle 1 and then escalated in succeeding weeks and cycles to 56 mg/m^2 for no dose limiting toxicities (DLTs) occur. DLTs are defined as any grade ≥3 non-hematologic toxicity or grade ≥4 neutropenia or thrombocytopenia lasting ≥7 days. Acyclovir 400 mg orally twice daily is required during therapy, which may be discontinued ≥7 days after the last dose of carfilzomib. Therapy will continue until progression (as defined below) or severe toxicities. Patients removed from the trial for toxicities or other reasons will continue to be followed until progression or starting a new agent. Androgen deprivation therapy with LHRH analogue or antagonist and bone protecting agent (denosumab or zoledronic acid) will also continue. Comprehensive metabolic panel (CMP) evaluations are performed on day 1 every 4 weeks, complete blood cell (CBC) counts on days 1, 8 and 15 every cycle, and radiological evaluations are performed every 3 cycles or earlier if clinically indicated. Pain (PPI score, Appendix B) and analgesic intake (Appendix C) are recorded on day 1 of every cycle. Correlative studies include serial CTC enumeration (repeated on day 1 cycle 2, then q 3 cycles) and collection of whole blood is performed at baseline for 20S proteasome activity. Progression of disease will be defined clinically as the first occurrence of any of the following, and PSA progression alone will not constitute progression:

1. Two distinct new lesions on bone scan consistent with bone metastases in the best judgment of the investigator and confirmed by further new lesions on a subsequent scan ≥6 weeks later.
2. Progression in measurable disease as defined by RECIST 1.1 criteria
3. Worsening of pain (increase in present pain index by ≥1 point, increased need for analgesics).
4. New bladder outlet or ureteral obstruction caused by cancer
5. New bone related events
   a) Pathologic fracture
   b) Spinal cord compression
   c) Need for palliative radiation, surgery, or kyphoplasty to any neoplastic bone lesion
6. Deterioration of performance status to ECOG level 3-4

3.2 Trial schema



4. PATIENT SELECTION

4.1 Eligibility Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Histologically proven adenocarcinoma of the prostate
2. Metastatic disease
3. Progressive disease (PSA, radiologic, symptomatic) following abiraterone acetate and/or enzalutamide (prior chemotherapy and sipuleucel-T is allowed); PSA progression is defined as baseline increase followed by any PSA increase ≥1 week apart
4. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
5. Patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse if female partner of childbearing age.
6. An elevated PSA level of >2 ng/mL for patients progressing by PSA criteria is required (last confirmatory sample must be >2 ng/mL)
7. Currently on androgen ablation hormone therapy (an LHRH agonist/antagonist or orchiectomy) with testosterone level <50 ng/dL)
8. Has an ECOG Performance Status (PS) of 0-2 (Appendix A)
9. LVEF ≥ 40% on 2-D transthoracic echocardiogram (ECHO); Multigated Acquisition Scan (MUGA) is acceptable.
10. Is ≥19 years of age
11. Resolution of all acute toxic effects of prior chemotherapy or surgical procedures to NCI CTCAE Version 4.03 Grade <1, in the opinion of the Treating Physician (Appendix D)
12. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria within 4 weeks (unless otherwise stated) of being enrolled are not to be enrolled in the study.

1. Patient has a platelet count of $<100,000/mm^3$, or absolute neutrophil count of $<1500/mm^3$ or Hemoglobin <8.0 gm/dL
2. Patient has a calculated or measured creatinine clearance of <30 mL/minute
3. Patient has total bilirubin >2 x ULN (upper limit of normal), or AST, ALT >3.5 X ULN
4. Patient has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.
5. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Before study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
6. Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
7. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
8. Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the breast; c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
9. Known HIV, hepatitis B and hepatitis C infection
10. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization
11. Prior treatment with bortezomib
12. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
13. Has received prior radiation to >50% of the bone marrow
14. Has had significant bleeding/thrombosis in previous 4 weeks
15. Has received treatment with radiation therapy, surgery, chemotherapy, or an investigational agent within 4 weeks prior to registration, (6 weeks for radiation therapy, radionuclides, nitrosureas, or Mitomycin C) or who have not recovered from adverse events due to agents administered more than 4 weeks earlier
16. Has evidence of uncontrolled CNS involvement (previous radiation and off steroids is acceptable)
17. Patients may not be receiving any other investigational agents.
18. Has a serious uncontrolled intercurrent medical or psychiatric illness, including serious infection
19. Is unable to comply with study requirements
20. 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.

5. SUBJECT ENROLLMENT AND REGISTRATION PROCEDURES

General Guidelines

Eligible patients will be entered on study centrally at the Kirklin Clinic, UAB Hospitals and outside sites by the Study Coordinator (to be designated by Elizabeth Busby Director of Oncology Clinical Trials, CSU, UAB). All sites should call the Study Coordinator to verify agent availability. Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Registration Process

The Clinical Trials Network (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at CTNMO sites to achieve timely study subject enrollment and to provide subjects at CTNMO sites with access to CCC investigator-initiated studies. The CTNMO site maintains an accurate screening log for each study and forwards this to the CTNMO Coordinating Center Manager on a monthly basis. Once a study subject has been screened and deemed eligible for study entry by the CTNMO site, a study-specific study subject eligibility checklist, a copy of the dated and signed consent form, and corresponding source documentation are faxed to the CTNMO Coordinating Center Manager for eligibility verification. Subsequently, a study-specific number is assigned to the study subject and sent to the CTNMO site. Finally, a Patient Registration Form is completed and faxed by the CTNMO site to the CTNMO Coordinating Center Manager. Queries regarding data accuracy are forwarded from the CTNMO Coordinating Center Manager to the CTNMO site for clarification or correction. Once queries are addressed by the CTNMO site, any corrected data forms or copies of corrected source documentation are faxed to the CTNMO Coordinating Center Manager.

6. TREATMENT PLAN

6.1 Carfilzomib administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Carfilzomib is administered twice-weekly as a 30 minute intravenous (IV) infusion on 2 consecutive-days for 3 of every 4 weeks (1 cycle) with premedication, i.e. on days 1, 2, 8, 9, 15, 16 (± 1 day) every cycle. The dose is 20 mg/m^2 on days 1 and 2 of cycle 1 and then escalated in succeeding weeks and cycles to 56 mg/m^2 if no dose limiting toxicities (DLTs) occur. DLTs are defined as any grade ≥ 3 non-hematologic toxicity, or grade ≥ 4 neutropenia or thrombocytopenia lasting ≥ 7 days.

- Carfilzomib for injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration. The dose will be

calculated using the subject's actual body surface area (BSA) at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.

- IV hydration will be given immediately prior to carfilzomib. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload
- If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.
- The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic under observation for at least 1 hour following each dose of carfilzomib in Cycle 1 and following the dose on Cycle 2 Day 1. During these observation times, post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) may be given based on investigator discretion. Subjects should be monitored periodically during this period for evidence of fluid overload.

Premedication administered ~30 minutes before each carfilzomib infusion is ondansetron (or equivalent) IV/PO, dexamethasone (4 mg IV/PO with carfilzomib 20 mg/m^2 and 8 mg IV/PO with 56 mg/m^2) and acetaminophen 650 mg orally (to prevent infusion reactions). Dexamethasone may be discontinued from the second cycle if the patient is tolerating carfilzomib (per investigator discretion). Normal saline (NS) 250 ml IV is administered as pre-hydration over 30 minutes. After the first cycle, pre-hydration may be discontinued at the discretion of the investigator. Carfilzomib for injection is provided as a sterile, frozen liquid formulation containing 2 mg/mL of drug.

6.2 General Concomitant Medication and Supportive Care Guidelines

Carfilzomib is rapidly metabolized extra-hepatically by peptidase cleavage and epoxide hydrolysis with a short half-life of < 1 hour. Hence the potential for interactions with other drugs is minimal. However, because there is a marginal potential for interaction of carfilzomib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Other agents known to be metabolized by the CYP3A system should also be captured since there is a possibility of interaction with carfilzomib. No carfilzomib dose adjustments or withholding of ongoing concurrent medications is suggested.

6.3 Duration of Therapy

Therapy will continue until progression (as defined below) or severe toxicities. Acyclovir will continue from day 1 of cycle 1 until ≥7 days after the last dose of carfilzomib. Androgen deprivation therapy with LHRH analogue or antagonist and bone protecting agent (denosumab or zoledronic acid) will also continue. If the bone protective agent has not already been initiated ≥4 weeks before trial registration, initiation of a bone protection agent is not allowed. CMP evaluations are performed on day 1 every 4 weeks,

CBC on days 1, 8 and 15 every cycle, and radiological evaluations are performed every 3 cycles or earlier if clinically indicated. Correlative studies include serial CTC enumeration (repeated on day 1 cycle 2, then q 3 cycles) and collection of whole blood is performed at baseline for 20S proteasome activity and other potential future correlative studies.

Progression of disease will be defined clinically as the first occurrence of any of the following and PSA progression alone will not constitute progression.

1) Two distinct new lesions on bone scan consistent with bone metastases in the best judgment of the investigator and confirmed by further new lesions on a subsequent scan ≥6 weeks later.
2) Progression in measurable disease as defined by RECIST criteria
3) Worsening of pain in the judgment of the investigator.
4) New bladder outlet or ureteral obstruction caused by cancer
5) New bone related events
   a. Pathologic fracture
   b. Spinal cord compression
   c. Need for palliative radiation, surgery, or kyphoplasty to any neoplastic bone lesion
6) Deterioration of performance status to ECOG level 3-4
7) Death

Therapy is also discontinued for other non-progression events below:

1) Intercurrent illness that prevents further administration of treatment
2) Unacceptable adverse event(s)
3) Patient decides to withdraw from the study
4) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.4 Duration of Follow Up

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, and subsequent progression or initiation of new therapy (whichever comes first).

6.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 6.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

7. DOSING DELAYS/DOSE MODIFICATIONS/SAFETY CONSIDERATIONS

According to design of drug administration, patients not experiencing DLTs in the first week of the first cycle with 20 mg/m^2 (defined as any grade ≥3 non-hematologic toxicity (except grade ≥2 neurotoxicity), or grade ≥4 neutropenia or thrombocytopenia lasting ≥7 days) will undergo dose escalation from the second week to 56 mg/m^2. Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the

previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (Appendix D).

Carfilzomib is to be restarted at the same schedule the patient was on before therapy was held, and the dose must be reduced for toxicities as follows:

- If the patient was receiving 56 mg/m^2, reduce the dose to 45 mg/m^2.
- If the patient was receiving 45 mg/m^2, reduce the dose to 36 mg/m^2.
- If the patient was receiving 36 mg/m^2, reduce the dose to 20 mg/m^2.
- If the patient was receiving 20 mg/m^2, reduce the dose to 15 mg/m^2.

Dose reductions for Hematologic Toxicities

Study drug will be withheld from subjects with:

- Grade 4 lymphopenia persisting for > 14 days, if lymphopenia was not pre-existing
- Grade 4 thrombocytopenia with active bleeding
- Grade 4 anemia and thrombocytopenia requires the carfilzomib dose to be withheld. Subjects should receive supportive measures in accordance with institutional guidelines.

The following table outlines the dose reduction guidelines for carfilzomib for thrombocytopenia and neutropenia:

Thrombocytopenia	
	Recommended Action
When Platelets:	Carfilzomib
Fall to $< 30 \times 10^9$/L	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9$/L	Resume at full dose
Subsequently drop to $< 30 \times 10^9$/L	Interrupt carfilzomib, follow CBC weekly
Return to $\geq 30 \times 10^9$/L	Resume at 1 dose decrement

Neutropenia	
	Recommended Action
When ANC	Carfilzomib
Falls to $< 0.5 \times 10^9$/L	Interrupt carfilzomib
	add filgrastim per ASCO guidelines if Gr ≥ 3 with fever, follow CBC weekly
Returns to $> 1.0 \times 10^9$/L (if neutropenia was the only toxicity noted)	Resume at full dose

Returns to > 1.0×10^9/L (if other toxicity noted)	Resume at 1 dose decrement
Subsequently drops to < 0.5×10^9/L	Interrupt carfilzomib
Returns to > 1.0×10^9/L	Resume at 1 dose decrement

Dose Reductions for Non-Hematologic Toxicities

Study drug should be held for ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline. After resolution of the event to ≤ Grade 1 or return to baseline, if the adverse event was not treatment-related, subsequent treatment with carfilzomib may resume at full dose. If the event was treatment-related, subsequent treatment with carfilzomib will resume at one level dose reduction. If toxicity continues or recurs, further carfilzomib dose reduction may be permitted at the discretion of the investigator. If toxicity continues to recur after dose reduction to 15 mg/m^2, the subject should be removed from study. If there is no resolution of toxicity after 3 weeks of withholding treatment, the subject will be withdrawn from the study.

Dose adjustment guidelines for non-hematologic toxicities are summarized as follows:

Symptom	**Recommended Action**
	Carfilzomib
Allergic reaction/hypersensitivity	
Grade 2 – 3	Hold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue
Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection Grade 3 or 4	Hold carfilzomib until systemic treatment for infection complete. If no neutropenia, restart at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex of any grade	Hold carfilzomib until lesions are dry. Reinstitute at full dose
Gr 2 treatment emergent neuropathy with pain	Continue to dose. If neuropathy persists for more than two weeks hold carfilzomib until resolved to ≤ Gr 2 without pain. Then restart at 1 dose decrement

Grade ≥3 neuropathy	Discontinue
Renal Dysfunction	
CrCl <30 mL/min	Hold until CrCl ≥ 30 mL/minute; restart at 1 dose decrement
Congestive heart failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the subject may be withdrawn from the study. If no resolution after 2 weeks, the subject will be withdrawn from the study.
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement.

Increased Creatinine or Decreased CrCl

Study drug should be held for CrCl < 30 mL/min. A phase I study of Carfilzomib in patients with relapsed and refractory multiple myeloma and varying degrees of renal insufficiency was reported at the 2009 American Society of Hematology meeting. At the time of this preliminary analysis, 22 patients had been treated on the trial. Ten patients had creatinine clearance ≥80 mL/min; 9 had creatinine clearance 50-79 mL/min; 9 patients had creatinine clearance 30-49 mL/min; 9 patients had creatinine clearance < 30 mL/min and 2 patients were on chronic dialysis. Adverse events in these patient groups were similar regardless of degree of renal dysfunction and included anemia, fatigue, and diarrhea as the most common adverse events observed.

Renal Dysfunction	Recommended Action
Normal to mild (CrCl ≥30 mL/min)	Full dose
Severe (CrCl ≤ 30 mL/min)	Severe CrC1 < 30 mL/min/Hold carfilzomib until CrCl ≥ 30 mL/min; restart at one level dose reduction

Infections

Subjects with active or suspected infections should have treatment withheld until infection has resolved and anti-infective treatment has been completed. After the infection has resolved and anti-infective treatment has been completed, treatment may continue at the original dose. If there is no resolution of toxicity after 3 weeks, the subject will be withdrawn from the study.

Congestive Heart Failure (CHF)

Any subject with symptoms of CHF or any other suspected acute cardiac event, whether or not drug related, must have the dose held until resolution. After the event has resolved or returned to baseline, treatment may continue at a reduced dose, with the approval of the Onyx Medical Monitor, or the subject may be withdrawn from the study. If there is no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.

Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the above guidelines. Carfilzomib does not need to be held in the following cases:

- Grade 3 nausea, vomiting or diarrhea (unless persisting > 3 days with adequate treatment of anti-emetics or anti-diarrheals)
- Grade 3 fatigue (unless persisting for >14 days)
- Alopecia
- ≥ Grade 3 hyperglycemia attributed to dexamethasone

Missed Doses

Missed doses will not be replaced during a cycle. If a subject misses more than 2 doses of any cycle for reasons other than toxicity, the subject will be discontinued.

Changes in Body Surface Area (BSA)

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%. Subjects with a Body Surface Area (BSA) > 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level) or 123 mg of carfilzomib (at the 56 mg/m^2 dose level).

Safety Considerations

Based upon the experience in the Phase 1 and 2 clinical studies with carfilzomib, the following observations are noted:

- A "first dose effect" has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.
- Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.
- Dexamethasone 4 mg PO/IV will be administered prior to all carfilzomib doses during the 1st cycle and prior to all carfilzomib doses during the first dose-escalation (56 mg/m^2) cycle. If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (4 mg PO/IV) should be re-started and administered prior to subsequent doses.
- Acyclovir or similar should be given to all subjects unless contraindicated.

- CrCl changes are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation as outlined.
- Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been completed.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts ≤ 25,000/mm3, carfilzomib dosing must be held. If platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions / Adjustments rules outlined in this protocol.
- Subjects should have anemia corrected in accordance with the Institutional guidelines.
- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of anti-emetics or anti-diarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

Concomitant Medications

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before Day 1 through the end of the subject's study participation. Any change in concomitant medications must be recorded.

Required Concomitant Medications

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential. Dexamethasone 4 mg PO/IV will be administered prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose-escalation cycle. If treatment-related fever, rigors, chills, and/or dyspnea are observed post any dose of carfilzomib after dexamethasone has been discontinued, dexamethasone (4 mg PO/IV) should be re-started and administered prior to subsequent doses. Subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis.

Optional and Allowed Concomitant Medications

Allopurinol (in subjects at risk for tumor lysis) is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycles.

Subjects may receive RBC or platelet transfusions if clinically indicated in accordance with institutional guidelines. Subjects who require repeated platelet transfusion support

should be discussed with the Lead Principal Investigator. Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive anti-emetics and anti-diarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used in accordance with ASCO guidelines if neutropenia occurs but should not be given prophylactically. Antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone (or trimethroprim/ sulfamethoxazole if fluoroquinoles are contraindicated) is per physician discretion.

Subjects may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed. Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines. Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

Excluded Concomitant Medications

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed. Other investigative agents (e.g., antibiotics or anti-emetics) should not be used during the study.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to administration of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	-28 days	-14 days (may serve as cycle 1 day 1 labs)	Day 1 (± 1 day) of every cycle (28 days)	Day 8 and 15 every cycle (± 1 day)	Day 1 Every 3 cycles	30 (± 7 days) post last treatment
ASSESSMENTS						
History and exam (H&P)	X		X			X[1]
ECOG performance status		X	X			X[1]
CBC with differential		X	X	X		X[1]
CMP		X	X			X[1]
PSA		X	X			X[1]
LDH		X				
Testosterone level		X				
Pain (PPI 0-5 scale)		X	X			X[1]
Analgesic intake (increased, decreased or stable)		X	X			X[1]
Echocardiogram	X		X[6,7]			
DISEASE ASSESSMENT						

CT chest , abdomen, pelvis	X				X	X[1]
Bone Scan	X				X	X[1]
TREATMENT						
Carfilzomib day 1,2, 8,9,15,16 (30 min IV infusion)			X[2]	X[2]		
Premedication (Dexamethasone, Acetaminophen)			X[3]	X[3]		
Pre-hydration (Normal saline 250-500 ml over 30 minutes)			X[4]	X[4]		
Acyclovir 400 mg PO bid			X[5]	X[5]		
LHRH analogue (if no prior orchiectomy)					X	
CORRELATIVE STUDIES						
CTC enumeration (3 time points)	X		X (cycle 2 only)		X (cycle 4 only)	
Whole Blood 20S proteasome assay	X					
FOLLOW-UP						
Disease progression and survival						X[1]

[1]Patients removed from trial for reasons other than progression will continue to be followed until progression or initiation of new therapy (whichever comes first); i.e. H&P, laboratory evaluation, pain, analgesic intake are performed every ~28 days and radiographic evaluation every ~90 days (+/-7 days); [2]Dose is 20 mg/m^2 on days 1, 2 of cycle 1 and if no DLTs, escalate to 56 mg/m^2 for all remaining doses, Subjects with a Body Surface Area (BSA) > 2.2 m^2 will receive a capped dose of 44 mg of carfilzomib (at the 20 mg/m^2 dose level) or 123 mg of carfilzomib (at the 56 mg/m^2 dose level); [3]Dexamethosone dose is 4 mg PO/IV with carfilzomib 20 mg/m^2 and 8 mg PO/IV with carfilzomib 56 mg/m^2, dexamethasone may be discontinued from cycle 2 day 1 if patient is tolerating carfilzomib therapy per investigator discretion and/or has adverse effects from dexamethasone, acetaminophen dose is 650 mg PO x 1; [4]Prehydration with 250-500 ml of normal saline is given during cycle 1 and may be discontinued from cycle 2 day1 per investigator discretion (post-hydration with 250-500 ml normal saline is optional per investigator discretion); [5]Acyclovir to start on day 1 of cycle 1 and stop ≥7 days after last dose of carfilzomib; [6]Only if clinically indicated for patients who develop CHF on study; [7]Multigated Acquisition Scan (MUGA) is acceptable

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Serious Adverse Events (SAEs) are reported by the site Lead Investigator within 24 hours to the Clinical Trial Network Monitoring Office (CTNMO) Coordinating Center Manager

by email (pamdixon@uab.edu) or by fax (205) 975-9875. The 24 hour paging number for the CTNMO Coordinating Center Manager is (205) 934-3411, beeper #5904. The CTNMO Manager is then responsible for reporting SAEs to the UAB IRB and protocol P.I. in accordance with study-specific requirements. SAEs occurring at CTNMO sites are reported to the UAB IRB as "non-UAB" events.

A Serious Adverse Event (SAE) is an AE that 1) results in patient hospitalization or prolongation of hospitalization; 2) results in persistent or significant disability or incapacity; 3) results in death; 4) is a cancer or congenital abnormality or 5) results in the development of drug dependence or abuse. An AE must be considered an SAE when the nature or severity of the event is not consistent with the current Investigator's Brochure. CTNMO site SAEs must be reported by the CTNMO site Lead Investigator to the CTNMO Coordinating Center Manager by email or by fax. It is also the responsibility of the CTNMO site Lead Investigator to report SAEs to the CTNMO site IRB and to submit copies of that report to the CTNMO Coordinating Center Manager. It is the CTNMO Coordinating Center Manager's responsibility to report the SAE to the appropriate regulatory agency and / or industry sponsor. This submission of IND Safety Reports will be cross referenced according to local regulations to Onyx Investigational Compound Number (IND) at the time of submission.

Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03.
- "Expectedness": AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are bold and italicized in the CAEPR.
- Attribution of the AE:
  - 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.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Expedited Adverse Event Reporting

Expedited AE reporting for this study must use the reporting procedures briefly outlined in the table below.

Expedited Reporting Guidelines – Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Un-expected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:

24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported.
- Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Expedited Reporting by Investigator to Onyx

The Investigator must inform Onyx in writing by e-mail or Fax at the contact information listed below of all Expedited Safety Reports submitted to the relevant health authorities (HA). **These notifications should be performed in parallel to the HA submissions [e.g., within 7 calendar days for any fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) and within 15 calendar days for all other SUSARs}, but in no case any later than 1 business day from the submission date. This must be documented on a FDA 3500a MEDWATCH or CIOMS I form. All other SAEs will be sent to Onyx within 30 days of the event on a FDA 3500a MEDWATCH, CIOMS I, or local SAE form. All forms must be completed and provided to Onyx in English.**

The initial report must be as complete as possible, at a minimum including the SAE term(s), patient identifier, date of awareness of the event, an investigator assessment of the causal relationship between the event and the Onyx product(s), and name of the investigator. Information not available at the time of the initial report (e.g., an end date for the SAE or laboratory values received after the report) must be documented on a follow-up form, and submitted to Onyx in the same timelines as outlined above. The Onyx protocol number (IST-CAR-612) and the institutional protocol number should be included on all SAE reports to Onyx.

All other SAE's will be sent to Onyx on a biannual basis in the form of a line listing in English. The line listing must include the following information; patient initials, date of birth, sex, SAE onset date, SAE stop date, event name (term), outcome, date of first dose of study drug(s), date of last dose of study drug(s) prior to the event, action taken with study drug(s) the Investigator's assessment of causality (relationship to carfilzomib), and the Investigator's assessment of expectedness to carfilzomib. The sponsor reserves the right to review the CRFs or source documents in response to any inquires by regulatory agencies that the sponsor may receive.

Onyx Drug Safety and Pharmacovigilance Contact Information:

Drug Safety Reporting Email: AdverseEvents@onyx.com
Drug Safety Reporting Fax +1 650-266-0501 (toll fax) or 1 800-783-7954 (US toll-free fax)

Pregnancy Reporting by Investigator-sponsor to Onyx

If a subject or partner of a subject becomes pregnant during treatment with an Onyx product(s) or up to 30 days following the last dose of an Onyx product(s), the Investigator-sponsor will notify Onyx within 24 hours of learning of the pregnancy. The investigator will complete a local Pregnancy Monitoring Form and report the information regarding the pregnancy, outcome, and status of the newborn, to Onyx via the contact information above as appropriate.

If the subject becomes pregnant while taking an Onyx product(s), the drug will be immediately discontinued. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided). Pregnancies will be followed through the outcome of the pregnancy. Newborns should be followed for a minimum of 12 weeks.

Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. AEs reported must also be reported in routine study data submissions. Safety will be monitored throughout the study by physical examinations, review of adverse events (AEs), and laboratory studies. The frequency of safety monitoring procedures is outlined in Section 7. Criteria that will be used throughout the study for dose interruption, reduction, and discontinuation of chemotherapeutic agents are specified in Section 7. The frequency of efficacy monitoring and procedures are outlined in Sections 8.

Data and Safety Monitoring Plan

Subjects treated at UAB will be monitored by the UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP). Adverse reactions observed during treatment will be closely monitored by the Clinical Trials Monitoring Committee (CTMC) on a weekly basis. The CTMC is responsible for data and safety monitoring of the trial and adherence to the DSMP. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to the DSMP. Reports from the CTMC are reviewed monthly by the QAC.

Protocol Management and Oversight of Participating Outside Sites

Dr. Guru Sonpavde functions as the sponsor of the trial at UAB and at the outside sites. The outside sites will utilize their respective IRB of record. The Principal Investigator at the outside sites will be responsible for ensuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper data entry. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data

10. STATISTICAL CONSIDERATIONS

Study Design/Endpoints

This is a 2-center one-stage non-randomized phase II trial conducted at UAB Comprehensive Cancer Center and outside sites. Clinical PFS as the primary end-point and the trial will enroll 28 patients. The eligible population includes men with metastatic CRPC who have received prior abiraterone and/or enzalutamide (prior chemotherapy and sipuleucel-T are allowed). Therapy will continue until progression (as defined below) or severe toxicities. Patients removed for reasons other than progression will continue to be followed until progression or initiation of another agent. Correlative studies include serial CTC enumeration (day 1 of cycles 1, 2 and cycle 4) and collection of whole blood is performed at baseline for 20S proteasome activity. Progression of disease will be defined clinically as the first occurrence of any of the following, and PSA progression alone will not constitute progression:

1) Two distinct new lesions on bone scan consistent with bone metastases in the best judgment of the investigator and confirmed by further new lesions on a subsequent scan $\geq$6 weeks later.
2) Progression in measurable disease as defined by RECIST criteria
3) Worsening of pain in the judgment of the investigator.
4) New bladder outlet or ureteral obstruction caused by cancer

5) New bone related events
a. Pathologic fracture
b. Spinal cord compression
c. Need for palliative radiation, surgery, or kyphoplasty to any neoplastic bone lesion
6) Deterioration of performance status to ECOG level 3-4
7) Death

Modest activity is considered clinically meaningful in this relatively heavily pretreated population with metastatic CRPC that has received abiraterone acetate and/or enzalutamide (prior chemotherapy and sipuleucel-T are allowed). The null hypothesis for this trial is that the primary endpoint of 6-month PFS <10% is not clinically meaningful and the alternative hypothesis is that the true clinical PFS of interest is ≥30%. Since we will follow all subjects for at least 6 months or until progression or death, we will not have censoring and 6 months PFS can be treated as a binomial random variable. With twenty five evaluable patients we will have 80% power for an exact binomial test at the one sided 0.05 significance level of the null hypothesis that the 6-month PFS rate is 10% if the actual rate is 30%. That null hypothesis will be rejected if 6 or more of the 25 subjects survive for 6 months progression free. Twenty-eight subjects will be accrued to allow for 10% inevaluable patients.

Sample Size/Accrual Rate
A total of 28 patients will be enrolled for this trial. Accrual period will be 6 to 12 months.

Analysis of Secondary Endpoints
The Kaplan-Meier method will be used to estimate PFS and OS rates over time with standard errors estimated using Greenwood's formula. Medians and their 95% confidence intervals will also be estimated. PSA response, PSA decline ≥30% within 3 months, RECIST responses and regressions, pain response and CTC alterations will be analyzed as secondary endpoints. CTC changes will include changes from unfavorable (≤5/7.5ml) to favorable, and declines by >30%. Pain response is defined as decline in present pain index ≥2 points and/or decrease in analgesics. Linear regression with PSA as the dependent variable and time as the dependent variable will be performed and used to estimate PSA DT. The association of baseline whole blood 20S proteasome level with PFS and other secondary endpoints will be examined using Cox regression to generate hypotheses for selecting suitable patients for further study.

Reporting and Exclusions
All patients will be evaluable for toxicity from the time of their first treatment with carfilzomib. CTCAE v 4.03 will be utilized to grade toxicities (Appendix). All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown"

status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals should also be provided.

11. MEASUREMENT OF EFFECT

Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every 12 weeks and earlier if clinically required. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[26]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

All patients will be evaluable for toxicity from the time of their first treatment with Carfilzomib. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. Lymph nodes are considered measurable if the sort axis diameter is $\geq$15 mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Bone disease: According to PCWG-2 guidelines, 2 distinct new lesions on bone scan consistent with bone metastases in the best judgment of the investigator and confirmed by further new lesions on a subsequent scan ≥6 weeks later is defined as bone scan progression.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease
All measurements should be taken and recorded in metric notation using a ruler or calipers. 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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI should be performed with cuts of 10 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. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

The utilization of endoscopy techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated

equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient 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.

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.

Response Criteria for the evaluation of Target Lesions
Complete Response (CR): Disappearance of all target lesions
Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
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: Patients 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.

Duration of 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 recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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 the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Pain response and progression

Patients with a PPI score of at least 2, or need for analgesics, or both at baseline are assessed for the pain response. A pain response is defined as a two-point reduction in the PPI score from baseline without an increase in the analgesic use or as a reduction in analgesic use without an increase in the PPI score. Pain progression is defined as an increase in the PPI score of at least one point from the nadir, an increase in analgesic use, or a requirement for palliative radiotherapy.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever comes first.

12. CORRELATIVE STUDIES

Circulating Tumor Cell (CTC) enumeration will be used as a secondary marker for efficacy of response to the treatment. Baseline CTC will be obtained prior to initiation of therapy and day 1 of cycles 2 and 4. Baseline whole blood 20S proteasome activity will also be determined.

CTC enumeration

The CELLSEARCH® System led to the first standardized, FDA-cleared semi-automated system that detects and enumerates CTCs of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) from a 7.5-mL blood sample with high sensitivity and specificity. The CELLSEARCH® System uses unique immunomagnetic and fluorescence imaging technology to provide rapid and reproducible analysis of CTCs with a simple 3-step process: sample collection, sample preparation, and sample analysis. System components include:

- Proprietary CellSave Preservative sample tubes
- CELLSEARCH® CTC Test and Control kits
- Automated CELLTRACKS® AUTOPREP® System
- CELLTRACKS ANALYZER II®

CellSave Preservative tubes provide an optimized cell preservative that stabilizes CTCs for up to 96 hours at room temperature, which allows shipment of samples to remote locations for analysis and improves the reproducibility and reliability of CTC analysis. CTCs are fragile and tend to degrade within a few hours when collected in standard evacuated blood collection tubes.

Once the blood sample is collected for UAB patients, the tube will be delivered to UAB main laboratory to be sent out to Quest Diagnostics for CTC enumeration. For outside sites, the tube will be sent directly to Quest Diagnostics for CTC enumeration.

Whole Blood 20S Proteosome Activity

This analysis will be conducted at the UAB PK/PD Shared Facility directed by Dr Edward Acosta. Blood should be stored at -70C or lower until shipment. The sample is shipped on dry ice to the UAB PK/PD Shared Facility. Ship the samples to Attention: Daniel Ross; University of Alabama at Birmingham School of Medicine; 1670 University Boulevard; Volker Hall; Lab 175; Birmingham, AL 35294-0019. A 1.0 mL whole blood sample should be collected in a green-top (heparin) tube. The tube should be gently inverted several times, and then placed directly into the freezer at -70 or 80°. Samples can be batched and stored at -70 or 80°C, then shipped on dry ice. Ten (10) µL of whole blood will be added to 300µL of cold lysis buffer (5 mmol/L EDTA), mixed, and incubated on ice for 15 to 20 minutes. Samples will be centrifuged at 6,600 x g, 4°C, for 20 minutes. The resulting supernatant (200 µL) will be added to 200 µL of buffer [40 mmol/L HEPES (pH 8.0), 1 mml/L EDTA, and 20% glycerol], mixed, and assayed

immediately or stored at -80°C. For 20S β5 proteasome assay, lysates prepared from whole blood will be thawed at room temperature and diluted 1:5 with proteasome assay buffer [20 mmol/L HEPES, 0.5 mmol/L EDTA (pH 7.4)]. Five microliters of lysate will be added to wells of a 96-well plate followed by 100 µL of proteasome assay buffer at 37°C containing 40 µmol/L Suc-LLVY-AMC and 12 nmol/L recombinant human PA28α. The progress curves will be monitored in a plate reader for 1 h at 37°C. The slopes of the progress curves will be converted to substrate turnover by use of an AMC calibration standard. 20S β1 and β2 proteasome assays can be done identically to the β5 proteasome assay except the substrates Z-LLE-AMC and Z-VLR-AMC would be used respectively.

13. PHARMACEUTICAL INFORMATION

Carfilzomib Description

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

Formulation

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

Availability

Carfilzomib is provided to UAB Cancer Center under a Collaborative Agreement with Onyx.

Agent Ordering

Carfilzomib may be requested from Onyx by the Principal Investigator (or their authorized designee) at each participating institution. The responsible investigator at each participating institution must be registered through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, carfilzomib should be ordered under the name of one lead investigator at that institution.

Storage

Lyophilized Carfilzomib for Injection must be stored at 2–8°C under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel.

Accountability

Onyx, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record. Drug accountability records must be readily available for inspection by representatives of Onyx and by regulatory authorities. Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Onyx and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

14. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements). The CTNMO Coordinating Center Manager also ensures that the following are accomplished:

- Develop and implement plans for monitoring and auditing CTNMO site studies
- Provide initial protocol and consent documents to CTNMO sites
- Coordinate CTNMO site initiation visits / teleconferences
- Receive and evaluate documents from CTNMO sites and determine the need for further evaluation
- Submit required regulatory documentation to the UAB IRB
- Generate study-specific queries and develop resolutions
- Perform monitoring visits at CTNMO sites
- Provide for needed fiscal management including development of CTNMO site budgets and sub-contracts
- Provide for distribution of study-specific funds to CTNMO sites.

Data Reporting

Data collection and submission is the responsibility of the site Lead Investigator. Data collection forms are provided by the CTNMO Coordinating Center Manager. Each CTNMO site maintains a study-specific research data file (research chart) for study subjects enrolled into a study. The research chart includes completed CRFs and copies of all source documentation. Completed CRFs are reviewed, signed and dated by CTNMO site Lead Investigator. Any deviations from the study protocol are documented in the study subject's medical record and research chart. Missing data is documented in the research chart. Copies of the completed CRFs, other study-related documents, and source documents are faxed to the CTNMO Coordinating Center Manager on a monthly basis.

Multicenter guidelines and study monitoring

This protocol will adhere to the policies and requirements of Multicenter trial Guidelines. Each study subject is discussed at the CTNMO site's weekly Clinical Trials Monitoring

Committee meeting by the CTNMO site research nurses and Lead Investigator and is, in turn, presented at the next weekly CCC Clinical Trials Monitoring Committee meeting by the CTNMO Coordinating Center Manager. All questions and concerns regarding the conduct of a study at a CTNMO site are directed to the site Lead Investigator who consults with the CTNMO Director and / or the CTNMO Coordinating Center Manager when necessary. The P.I. (assisted by the CTNMO Coordinating Center Manager) is the primary contact for study-specific questions such as dose modifications, toxicities, and supportive care. The CTNMO Coordinating Center Manager is the primary contact for issues regarding patient registration, regulatory documents, completion of CRFs, data collection, and data submission.

Comprehensive monitoring of all CTNMO site studies (100% of patients) is conducted "off-site" at the CTNMO Coordinating Center using the CRFs and supporting source documents that are transmitted from the CTNMO site on a monthly basis. Following each monitoring exercise, queries and/or requests for additional documentation are generated by the CTNMO Coordinating Center Manager generally within 2 weeks of receipt of the CTNMO site documents. Subsequently, the CTNMO site reviews and responds to queries and implements the necessary corrective action(s). Within two weeks, the CTNMO site submits query responses and, if appropriate, a written summary of corrective actions to the CTNMO Coordinating Center Manager. When necessary, the CTNMO Coordinating Center Manager conducts "on-site" monitoring visits to provide staff education and to assist in implementing corrective action at the CTNMO site.

Informed Consent

Patients will receive a written and IRB approved current informed consent form. Patients will be provided with information regarding the trial and alternatives available for therapy. The risks and potential benefits will be provided.

Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Onyx with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved. The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Onyx as follows:

Onyx Inc., Regulatory Department
249 East Grand Ave,
South San Francisco, CA 94080

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected. Onyx will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study. Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee and Onyx with a summary of the trial's outcome.

Subject Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician. The Investigator/Institution will permit direct access to source data and documents by Onyx, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

15. REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-12, 2004
2. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-20, 2004
3. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147-54, 2010
4. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011
5. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187-97, 2012
6. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-48
7. Higano CS, Schellhammer PF, Small EJ, et al: Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer 115:3670-9, 2009
8. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. The New England journal of medicine 363:411-22, 2010
9. Fizazi K, Carducci M, Smith M, et al: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 377:813-22, 2011
10. Nilsson S, Strang P, Aksnes AK, et al: A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 48:678-86, 2012
11. Kelly WK, Halabi S, Carducci M, et al: Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol 30:1534-40, 2012
12. Thompson RH, Allison JP, Kwon ED: Anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) immunotherapy for the treatment of prostate cancer. Urol Oncol 24:442-7, 2006
13. Kantoff PW, Schuetz TJ, Blumenstein BA, et al: Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol 28:1099-105, 2010
14. Smith DC, Smith MR, Sweeney C, et al: Cabozantinib in Patients With Advanced Prostate Cancer: Results of a Phase II Randomized Discontinuation Trial. J Clin Oncol 31:412-9, 2013
15. Chi KN, Hotte SJ, Yu EY, et al: Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 28:4247-54, 2010

16. Pili R, Haggman M, Stadler WM, et al: Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J Clin Oncol 29:4022-8, 2011
17. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009
18. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-59, 2008
19. Armstrong AJ, Garrett-Mayer E, Ou Yang YC, et al: Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. J Clin Oncol 25:3965-70, 2007
20. Petrylak DP, Ankerst DP, Jiang CS, et al: Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst 98:516-21, 2006
21. Arlen PM, Bianco F, Dahut WL, et al: Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. The Journal of urology 179:2181-5; discussion 2185-6, 2008
22. de Bono JS, Scher HI, Montgomery RB, et al: Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 14:6302-9, 2008
23. Scher H, Heller G, Molina A, Kheoh T, Attard G, Moreira J, Sandhu S, Parker C, Logothetis C, McCormack R, Fizazi K, Anand A, Danila D, Fleisher M, Olmos D, Haqq C, De Bono J.: Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): Planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. J Clin Oncol 29: 2011 (suppl; abstr LBA4517^), 2011
24. Shaffer DR, Leversha MA, Danila DC, et al: Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. Clin Cancer Res 13:2023-9, 2007
25. Scher HI, Jia X, de Bono JS, et al: Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol 10:233-9, 2009
26. Pili R, Haggman M, Stadler WM, et al: Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J Clin Oncol 29:4022-8
27. Papandreou CN, Logothetis CJ: Bortezomib as a potential treatment for prostate cancer. Cancer Res 64:5036-43, 2004
28. Adams J, Palombella VJ, Sausville EA, et al: Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 59:2615-22, 1999
29. Frankel A, Man S, Elliott P, et al: Lack of multicellular drug resistance observed in human ovarian and prostate carcinoma treated with the proteasome inhibitor PS-341. Clin Cancer Res 6:3719-28, 2000

30. Ikezoe T, Yang Y, Saito T, et al: Proteasome inhibitor PS-341 down-regulates prostate-specific antigen (PSA) and induces growth arrest and apoptosis of androgen-dependent human prostate cancer LNCaP cells. Cancer Sci 95:271-5, 2004
31. Williams S, Pettaway C, Song R, et al: Differential effects of the proteasome inhibitor bortezomib on apoptosis and angiogenesis in human prostate tumor xenografts. Mol Cancer Ther 2:835-43, 2003
32. Nawrocki ST, Sweeney-Gotsch B, Takamori R, et al: The proteasome inhibitor bortezomib enhances the activity of docetaxel in orthotopic human pancreatic tumor xenografts. Mol Cancer Ther 3:59-70, 2004
33. Dreicer R, Petrylak D, Agus D, et al: Phase I/II study of bortezomib plus docetaxel in patients with advanced androgen-independent prostate cancer. Clin Cancer Res 13:1208-15, 2007
34. Papandreou CN, Daliani DD, Nix D, et al: Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol 22:2108-21, 2004
35. Morris MJ, Kelly WK, Slovin S, et al: A phase II trial of bortezomib and prednisone for castration resistant metastatic prostate cancer. J Urol 178:2378-83; discussion 2383-4, 2007
36. Kraft AS, Garrett-Mayer E, Wahlquist AE, et al: Combination therapy of recurrent prostate cancer with the proteasome inhibitor bortezomib plus hormone blockade. Cancer Biol Ther 12:119-24, 2011
37. Hainsworth JD, Spigel DR, Barton J, et al: Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 113:765-71, 2008
38. Siefker-Radtke AO PV, Mathew P, et al: Preliminary evidence of efficacy and tolerance for weekly intravenous bortezomib plus mitoxantrone in patients with advanced androgen-independent prostate cancer (AIPCa). J Clin Oncol 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 4567
39. Ayala G, Yan J, Li R, et al: Bortezomib-mediated inhibition of steroid receptor coactivator-3 degradation leads to activated Akt. Clin Cancer Res 14:7511-8, 2008
40. Attard G, Swennenhuis JF, Olmos D, et al: Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer research 69:2912-8, 2009
41. Lightcap ES, McCormack TA, Pien CS, et al: Proteasome inhibition measurements: clinical application. Clin Chem 46:673-83, 2000
42. Kuhn DJ, Chen Q, Voorhees PM, et al: Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood 110:3281-90, 2007
43. Khan ML, Stewart AK: Carfilzomib: a novel second-generation proteasome inhibitor. Future Oncol 7:607-12, 2011

44. O'Connor OA, Stewart AK, Vallone M, et al: A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res 15:7085-91, 2009
45. Ruschak AM, Slassi M, Kay LE, et al: Novel proteasome inhibitors to overcome bortezomib resistance. J Natl Cancer Inst 103:1007-17, 2011
46. Demo SD, Kirk CJ, Aujay MA, et al: Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res 67:6383-91, 2007
47. Badros AZ, Vij R, Martin T, et al: Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia
48. Vij R, Wang M, Kaufman JL, et al: An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood 119:5661-70, 2012
49. Jakubowiak AJ, Dytfeld D, Griffith KA, et al: A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 120:1801-9, 2012
50. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. The New England journal of medicine. 2013 Jan 10: **368**:138-48
51. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. The New England journal of medicine. 2014 Jun 1:
52. van Soest RJ, van Royen ME, de Morree ES, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. European journal of cancer. 2013 Dec: **49**:3821-30
53. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Nov: **23**:2943-7
54. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer Patients. European urology. 2014 Jul 10:
55. Brasso K, Thomsen FB, Schrader AJ, et al. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. European urology. 2014 Aug 6:
56. Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. The Prostate. 2014 Sep: **74**:1278-85
57. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013 Jul: **24**:1802-7

58. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013 Jul: **24**:1807-12
59. Papandreou CN, Daliani DD, Nix D, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol. 2004 Jun 1: **22**:2108-21

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: PPI Patient Diary

Baseline	Day - 7	Day - 6	Day - 5	Day - 4	Day - 3	Day - 2	Day - 1

Complete a minimum of 7 days preceding Cycle 1, Day 1 dosing

Cycle #	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Cycle #	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14

Cycle #	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21

(choose only 1 score each day; do not report a range)

0 – no pain;
1 – mild;
2 – discomforting
3 – distressing
4 – horrible
5 – excruciating

Appendix C: Analgesic intake

	In the last 3 weeks, your use of pain meds has: (check one)*
Cycle 1 Day 1*	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 2 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 3 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 4 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 5 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 6 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 7 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 8 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 9 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 10 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 11 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
Cycle 12 Day 1	☐ Increased ☐ Decreased ☐ Remained the same
End of	☐ Increased

trial therapy	☐ Decreased ☐ Remained the same
Follow-up	☐ Increased ☐ Decreased ☐ Remained the same

* For cycle 1 day 1, note analgesic intake over prior 1 week; for other time points, note for prior 3 weeks (or entire cycle if longer than 3 weeks)

APPENDIX D: NCI-CTCAE VERSION 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v4.03

Publish Date: June 14, 2010
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[1] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7: **351**:1502-12

[2] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004 Oct 7: **351**:1513-20

[3] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct: **376**:1147-54

[4] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26: **364**:1995-2005

[5] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27: **367**:1187-97

[6] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. Jan 10: **368**:138-48

[7] Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009 Aug 15: **115**:3670-9

[8] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. The New England journal of medicine. 2010 Jul 29: **363**:411-22

[9] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011 Mar 5: **377**:813-22

[10] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. The New England journal of medicine. 2013 Jan 10: **368**:138-48

[11] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. The New England journal of medicine. 2014 Jun 1:

[12] van Soest RJ, van Royen ME, de Morree ES, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. European journal of cancer. 2013 Dec: **49**:3821-30

[13] Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Nov: **23**:2943-7

[14] Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer Patients. European urology. 2014 Jul 10:

[15] Brasso K, Thomsen FB, Schrader AJ, et al. Enzalutamide Antitumour Activity Against

Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. European urology. 2014 Aug 6:
[16] Suzman DL, Luber B, Schweizer MT, Nadal R, Antonarakis ES. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. The Prostate. 2014 Sep: **74**:1278-85
[17] Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013 Jul: **24**:1802-7
[18] Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013 Jul: **24**:1807-12
[19] Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer. 2012 Mar: **48**:678-86
[20] Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol. 2012 May 1: **30**:1534-40
[21] Thompson RH, Allison JP, Kwon ED. Anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) immunotherapy for the treatment of prostate cancer. Urol Oncol. 2006 Sep-Oct: **24**:442-7
[22] Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010 Mar 1: **28**:1099-105
[23] Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in Patients With Advanced Prostate Cancer: Results of a Phase II Randomized Discontinuation Trial. J Clin Oncol. 2013 Feb 1: **31**:412-9
[24] Chi KN, Hotte SJ, Yu EY, et al. Randomized phase II study of docetaxel and prednisone with or without OGX-011 in patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2010 Sep 20: **28**:4247-54
[25] Pili R, Haggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J Clin Oncol. 2011 Oct 20: **29**:4022-8
[26] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan: **45**:228-47
[27] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008 Mar 1: **26**:1148-59
[28] Armstrong AJ, Garrett-Mayer E, Ou Yang YC, et al. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. J Clin Oncol. 2007 Sep 1: **25**:3965-70
[29] Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst. 2006 Apr 19: **98**:516-21
[30] Arlen PM, Bianco F, Dahut WL, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. The Journal of urology. 2008 Jun:

179:2181-5; discussion 5-6
[31] de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res. 2008 Oct 1: **14**:6302-9
[32] Scher H HG, Molina A, Kheoh T, Attard G, Moreira J, Sandhu S, Parker C, Logothetis C, McCormack R, Fizazi K, Anand A, Danila D, Fleisher M, Olmos D, Haqq C, De Bono J. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): Planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. J Clin Oncol 29: 2011 (suppl; abstr LBA4517^). 2011:
[33] Shaffer DR, Leversha MA, Danila DC, et al. Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. Clin Cancer Res. 2007 Apr 1: **13**:2023-9
[34] Scher HI, Jia X, de Bono JS, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol. 2009 Mar: **10**:233-9
[35] Pili R, Haggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. J Clin Oncol. Oct 20: **29**:4022-8
[36] Papandreou CN, Logothetis CJ. Bortezomib as a potential treatment for prostate cancer. Cancer Res. 2004 Aug 1: **64**:5036-43
[37] Adams J, Palombella VJ, Sausville EA, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res. 1999 Jun 1: **59**:2615-22
[38] Frankel A, Man S, Elliott P, Adams J, Kerbel RS. Lack of multicellular drug resistance observed in human ovarian and prostate carcinoma treated with the proteasome inhibitor PS-341. Clin Cancer Res. 2000 Sep: **6**:3719-28
[39] Ikezoe T, Yang Y, Saito T, Koeffler HP, Taguchi H. Proteasome inhibitor PS-341 down-regulates prostate-specific antigen (PSA) and induces growth arrest and apoptosis of androgen-dependent human prostate cancer LNCaP cells. Cancer Sci. 2004 Mar: **95**:271-5
[40] Williams S, Pettaway C, Song R, Papandreou C, Logothetis C, McConkey DJ. Differential effects of the proteasome inhibitor bortezomib on apoptosis and angiogenesis in human prostate tumor xenografts. Mol Cancer Ther. 2003 Sep: **2**:835-43
[41] Nawrocki ST, Sweeney-Gotsch B, Takamori R, McConkey DJ. The proteasome inhibitor bortezomib enhances the activity of docetaxel in orthotopic human pancreatic tumor xenografts. Mol Cancer Ther. 2004 Jan: **3**:59-70
[42] Dreicer R, Petrylak D, Agus D, Webb I, Roth B. Phase I/II study of bortezomib plus docetaxel in patients with advanced androgen-independent prostate cancer. Clin Cancer Res. 2007 Feb 15: **13**:1208-15
[43] Papandreou CN, Daliani DD, Nix D, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol. 2004 Jun 1: **22**:2108-21
[44] Morris MJ, Kelly WK, Slovin S, et al. A phase II trial of bortezomib and prednisone for castration resistant metastatic prostate cancer. J Urol. 2007 Dec: **178**:2378-83; discussion 83-4
[45] Kraft AS, Garrett-Mayer E, Wahlquist AE, et al. Combination therapy of recurrent prostate cancer with the proteasome inhibitor bortezomib plus hormone blockade. Cancer Biol Ther. 2011 Jul 15: **12**:119-24

[46] Hainsworth JD, Spigel DR, Barton J, et al. Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer. 2008 Aug 15: **113**:765-71
[47] Siefker-Radtke AO PV, Mathew P, et al. Preliminary evidence of efficacy and tolerance for weekly intravenous bortezomib plus mitoxantrone in patients with advanced androgen-independent prostate cancer (AIPCa). J Clin Oncol 2005 ASCO Annual Meeting Proceedings Vol 23, No 16S, Part I of II (June 1 Supplement), 2005: 4567.
[48] Ayala G, Yan J, Li R, et al. Bortezomib-mediated inhibition of steroid receptor coactivator-3 degradation leads to activated Akt. Clin Cancer Res. 2008 Nov 15: **14**:7511-8
[49] Attard G, Swennenhuis JF, Olmos D, et al. Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer research. 2009 Apr 1: **69**:2912-8
[50] Lightcap ES, McCormack TA, Pien CS, Chau V, Adams J, Elliott PJ. Proteasome inhibition measurements: clinical application. Clin Chem. 2000 May: **46**:673-83
[51] Kuhn DJ, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007 Nov 1: **110**:3281-90
[52] Khan ML, Stewart AK. Carfilzomib: a novel second-generation proteasome inhibitor. Future Oncol. 2011 May: 7:607-12
[53] O'Connor OA, Stewart AK, Vallone M, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009 Nov 15: **15**:7085-91
[54] Ruschak AM, Slassi M, Kay LE, Schimmer AD. Novel proteasome inhibitors to overcome bortezomib resistance. J Natl Cancer Inst. 2011 Jul 6: **103**:1007-17
[55] Demo SD, Kirk CJ, Aujay MA, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007 Jul 1: **67**:6383-91
[56] Badros AZ, Vij R, Martin T, et al. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia. Jan 31:
[57] Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012 Jun 14: **119**:5661-70
[58] Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012 Aug 30: **120**:1801-9