**Study Title: Phase II Study of Carfilzomib in Patients with Refractory Renal Cell Carcinoma**

**Institution Name: University of Texas MD Anderson Cancer Center**

**Principal Investigator Information:**
Name: Eric Jonasch, M.D.
Address: 1155 Pressler Street, Unit 1374
Phone No: (713) 792-2830
Fax No: (713) 745-1625
Email Address: ejonasch@mdanderson.org

**Co-Investigators:** Nizar Tannir, M.D.

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| °C | degrees Centigrade |
| °F | degrees Fahrenheit |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time (also PTT) |
| ASaT | All Subjects as Treated |
| AST | aspartate aminotransferase |
| bid | twice daily |
| BSA | body surface area |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CHF | congestive heart failure |
| CR | complete response |
| CrCl | Creatinine Clearance |
| CRF | case report form(s) |
| CRO | clinical research organization |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | curriculum vitae |
| dL | deciliter |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| DVT | deep venous thrombosis |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FAS | Full Analysis Set |
| FCBP | Females of childbearing potential |
| FDA | Food and Drug Administration |
| FISH | fluorescent in situ hybridization |
| FLC | free light chain |
| G-CSF | granulocyte colony stimulating factor |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GM-CSF | granulocyte macrophage colony stimulating factor |

| | |
|---|---|
| h | hour(s) |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug (Application) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IV | intravenous |
| kg | kilogram(s) |
| LDH | lactate dehydrogenase |
| mg | milligram(s) |
| min | minute(s) |
| mIU | Milli International Units |
| mL | milliliter(s) |
| MM | multiple myeloma |
| $mm^2$ | millimeter(s) squared |
| $mm^3$ | millimeter cubed |
| MR | minimal response |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NHL | non-Hodgkin's lymphoma |
| ORR | overall response rate |
| PBMC | peripheral blood mononuclear cells |
| PD | progressive disease |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PO | per os (oral) |
| PR | partial response |
| PSA | prostate-specific antigen |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| QDx5 | daily dosing for five days |
| QIU | Qualified Investigator Undertaking Form |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| sCR | stringent complete response |

| | |
|---|---|
| SD | stable disease |
| SEER | Surveillance, Epidemiology, and End Results |
| SPEP | serum protein electrophoresis |
| $STD_{10}$ | severely toxic dose in 10% of animals |
| TLS | Tumor lysis syndrome |
| TTP | time to tumor progression |
| ULN | upper limit of the normal range |
| UPEP | urine protein electrophoresis |
| VGPR | very good partial response |
| WBC | white blood count |

# 1 INTRODUCTION

## 1.1 DISEASE SPECIFIC BACKGROUND

Cancers of the kidney and renal pelvis are diagnosed in nearly 60,000 individuals in the USA every year, and approximately 13,000 will die annually.[1] Renal cell carcinoma (RCC) comprises the majority of these diagnoses, and clear cell renal cell carcinoma (ccRCC) is the most common histological subtype.

Renal cell carcinoma has seen the approval of a significant number of agents in the past seven years, with a strong emphasis on VEGF and VEGF receptor targeting agents,[2-5] as well as mammalian target of rapamycin (mTOR) blocking agents.[6,7] Although these agents have clearly provided prolonged progression free survival (PFS) relative to placebo or to cytokine therapy, and have as a group increased OS of patients with advanced RCC, they possess several shortcomings. The first is that these agents are rarely curative. Additionally, VEGF ligand and receptor inhibitors do not target the tumor cell, and mTOR inhibitors appear to exert cytostatic, and not cytotoxic effects. There is clearly room in the RCC therapeutic space to explore new mechanisms of action for treatment of this disease.

## 1.2 PROTEASOME BACKGROUND

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity. [8]

## 1.3 CARFILZOMIB BACKGROUND

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®).[8] In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib.[9-11]

### *1.3.1 CARFILZOMIB TOXICOLOGY STUDIES*

In the initial Good Laboratory Practice (GLP)-compliant toxicity studies done by the drug maker, Onyx, carfilzomib was administered to rats and monkeys as two complete two-week cycles of QDx5 for five days with nine days rest[12]. Administration to rats at 12 mg/m$^2$, the severely toxic dose in 10% of animals ($STD_{10}$), caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomib. Daily

administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The dose-limiting toxicities (DLTs) of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In 6-month rat and 9-month chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the active anti-tumor regimen being used in ongoing Phase II studies in myeloma and solid tumors[12]. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity, including neuropathology, observed, even at high doses. This is in stark contrast to that observed with bortezomib. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to related to Cmax effects. Of note, neutropenia was not observed; rather, transient neutrophilia was seen following acute dosing. Renal, cardiovascular and gastrointestinal toxicities were similar to those observed with bortezomib. Finally, cyclical thrombocytopenia, likely due to inhibition of platelet budding from megakaryocytes, was similar to that seen with bortezomib. Proteasome inhibition in the blood in excess of 90% was achievable at well-tolerated doses, which contrasts with the ~70% proteasome inhibition achieveable with bortezomib at its maximum tolerated dose (MTD). In summary, these animal toxicity studies support the tolerability of carfilzomib in clinical studies, even on intensive dosing schedules and at doses achieving proteasome inhibition in excess of what can be achieve with bortezomib at its MTD on a less intensive schedule.

### *1.3.2 CARFILZOMIB PRECLINICAL ANTITUMOR ACTIVITY*

Based upon the results of *in vitro* and *in vivo* studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti-tumor activity relative to bortezomib. Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture[1,6]. Incubation of hematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines[1,6].

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level. Bortezomib at its MTD has no activity in this xenograft model using the standard Day 1, Day 4 schedule.[13]

### *1.3.3 PHASE 1 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY*

A Phase 1 clinical trial, PX-171-002, testing carfilzomib in subjects with relapsed/refractory hematologic malignancies, is being completed. During the dose escalation portion of the trial, 36 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

No dose limiting toxicities (DLTs) were observed in the initial seven cohorts (doses ranged from 1.2 to 15 mg/m$^2$) of three subjects each. At the 20 mg/m$^2$ dose level, one of eight patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m$^2$ dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m$^2$ dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were rechallenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M-protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels although some increases in LDH and other markers of tumor lysis were noted. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies and have essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects.

Hematologic toxicities were primarily mild or moderate. The thrombocytopenia reported with carfilzomib is cyclical and similar to that reported with bortezomib. The cause and kinetics of the thrombocytopenia following treatment are different from those of standard cytotoxic agents. To maximize the likely benefit of carfilzomib, subjects with thrombocytopenia should be supported as clinically indicated rather than having treatment reduced due to thrombocytopenia.

Of the 36 evaluable patients enrolled in PX-171-002, 20 had MM.[14] Four MM patients achieved a partial response (PR), one of two at the 15 mg/m$^2$ dose, one of six at the 20 mg/m$^2$ dose, and two of five at the 27 mg/m$^2$ dose. The responses have been rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m$^2$ wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or

immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. These results led to the initiation of two Phase 2 studies. A dose escalation study was also performed, PX-171-007, which is described in more detail in section 1.4.

### *1.3.4 PHASE 2 EXPERIENCE WITH CARFILZOMIB AS A MONOTHERAPY*

Two Phase 2 clinical studies are ongoing with carfilzomib in MM patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM.[15] In both studies, patients were dosed with 20 mg/m$^2$ on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. Since these guidelines were implemented, no further cases of TLS have been reported including in >350 additional patients with relapsed or refractory MM treated in ongoing Phase II studies. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of treatment-emergent peripheral neuropathy, 2.2% Grade 3/4, was observed in PX-171-003-A0 despite the fact that 78% of patients had Grade 1/2 neuropathy upon study entry.[15]

The response rate in PX-171-003-A0 was 18% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time to progression on the PX-171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months).[15]

A "stepped up" dosing schedule, referred to as 20/27 mg/m$^2$, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of carfilzomib. Patients receive 20 mg/m$^2$ for the first cycle and 27 mg/m$^2$ thereafter. The study completed enrollment of 266 patients by the end of 2009 and may form the basis for an accelerated approval NDA filing by the end of 2010. To date, this dosing schedule has been well tolerated.[14] An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed and rates of BUN and creatinine elevation dropped sharply, with Grade 3/4 renal impairment dropping to 2.2% in A1( from 15% in A0), most likely due to hydration and very low dose dexamethasone. The other most common adverse events were similar to the A0 portion of the study. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 15% Grade 1/2 and one (0.7%) Grade 3/4 event reported to date on PX-171-003-A1.[15] In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow allowing superior normal marrow reconstitution. Rates of thrombocytopenia and neutropenia were

similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date.[15]

In PX-171-004, a first cohort of patients received 20 mg/m$^2$. The subset of patients (N=54) that had not seen bortezomib had an ORR of 46% (2% CR, 9% VGPR and 35% PR), while the bortezomib treated patients (N=33) had an ORR of 18% (3% CR, 3% VGPR and 12% PR).[13,16] The median TTP was 7.6 and 5.3 months in these two groups, respectively. Thus, carfilzomib can induce very high levels of response in patients who have not previously been treated with bortezomib and, even in bortezomib-treated patients, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability and no cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

The protocol was amended to allow patients to increase to 27 mg/m$^2$ in Cycle 2 or later based on tolerability, similar to that used in PX-171-003 – A1.

Further information about the Phase 2 studies is presented in the Investigator's Brochure.

### *1.3.5 EXPERIENCE WITH CARFILZOMIB IN COMBINATION WITH LENOLIDOMIDE AND DEXAMETHASONE*

PX-171-006 is an ongoing Phase 1b study in patients with relapsed, multiple myeloma in which carfilzomib is administered in combination with lenalidomide (Revlimid®) and dexamethasone. "Low-dose" dexamethasone 40 mg/day is given on Days 1, 8, 15, and 22 in all cases. Carfilzomib is administered IV on Days 1, 2, 7, 8, 15, and 16; lenalidomide is administered PO on Days 1 through 21.

Enrollment has closed in this study, and no MTD was reached. The maximum per protocol doses of carfilzomib (27mg/m$^2$) with lenalidomide 25mg and low dose dexamethasone are being used. After 8 patients tolerated these doses well, an additional 44 patients were enrolled in an "expansion" cohort at this level, and this regimen is being taken into Phase III in study PX-171-009.[17]

To date, 40 patients were treated in cohorts 1-6 and 44 in the cohort 6 expansion. 27/32 patients in cohorts 1–5 are evaluable for safety and 29/32 for response. Patients were heavily pre-treated; 72% received prior BTZ and 87.5% received prior LEN or thalidomide (Thal). 47% of patients were refractory to their last therapy (typically lenalidomide + high dose dexamethasone; > 84% of patients had a history of neuropathy with 67% BTZ- or Thal-related. No treatment emergent fatigue, neuropathy, or thrombotic events ≥ Grade (G) 3 were observed. Hematological AEs ≥G3 (thrombocytopenia [n=6], anemia [n=4], and neutropenia [n=6]) were reversible. 4 patients had drug-related SAEs as follows: transient G3 sinus bradycardia, G3 upper respiratory tract infection, febrile neutropenia, and G3 diarrhea + G3 urinary infection. ORR and CBR for the 29 evaluable patients are 59% and 72%, respectively. Response data is shown in the table below. Initial responses improved with continued therapy, (up to 18 cycles). Median duration of response has not been reached

(median follow-up 5.2 months). No dose-limiting toxicities or deaths attributed to study treatment have been observed. Several patients have completed the study (in the lower dose cohorts) after 18 cycles and are continuing in an extension study. Updated efficacy data are presented in the following table:

| | CRd: Cohorts 1–5 (CFZ: 15 to 20 mg/m$^2$; LEN: 10 to 25 mg) | | |
|---|---|---|---|
| **Response** | **Relapsed (n=16)** | **Refractory (n=13)** | **Overall (n=29)** |
| ≥ CR/nCR | 5 (31) | 1 (8) | 6 (21) |
| ≥ VGPR | 7 (44) | 4 (31) | 11 (38) |
| ≥ PR | 9 (56) | 8 (62) | 17 (59) |
| ≥ MR | 11 (67) | 10 (77) | 21 (72) |

Together, these results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in combination are active and well tolerated and that there are no significant overlapping toxicities (in the dose ranges tested). Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with carfilzomib, even up to 27mg/m$^2$, suggesting that carfilzomib will combine well with other anti-cancer agents.

## 1.4 DOSE RATIONALE

Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m$^2$. Maximum proteasome inhibition was seen at doses 11 mg/m$^2$ and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half life of < 60 minutes at the 20 mg/m$^2$ dose. Large, single arm studies of the 27 mg/m$^2$ dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

By the end of 2009, 269 patients with relapsed and refractory multiple myeloma have been enrolled in the PX-171-003-A1 study. The goal of dose escalating to 27 mg/m$^2$ beginning with Cycle 2 is to improve ORR, DOR, and TTP.

In multiple preclinical studies, the tolerability of carfilzomib in rats has been shown to be significantly higher when administered as a 30 min infusion as compared to a rapid IV bolus. Toxicities observed with IV bolus injection of carfilzomib *above the MTD* at a dose of 48 mg/m$^2$ include evidence of prerenal azotemia (transient increases in BUN > creatinine) as well as lethargy, piloerection, dyspnea, and gastrointestinal bleeding. Notably, death occurred in ~50% of animals at 48 mg/m$^2$ when carfilzomib was given as a bolus. Administration of the same dose (48 mg/m$^2$) as a 30 min continuous infusion was well tolerated, with no changes in BUN and creatinine and substantially reduced signs of lethargy, piloerection, or dyspnea. Moreover, all animals in the infusion treatment groups survived. The only toxicity observed following infusion of carfilzomib for 30 min was gastrointestinal

bleeding. The reduced toxicity seen with dosing by infusion may reflect the reduced $C_{max}$ of carfilzomib vs that with bolus dosing. Inhibition of the pharmacological target of carfilzomib (the chymotrypsin-like activity of the proteasome) was equivalent in the bolus and infusion treatment groups.

In the clinic, the MTD of carfilzomib has not been reached in the multiple myeloma (MM) setting, particularly when administered as a 30' infusion. 27mg/m$^2$ of carfilzomib (bolus administration over 2-10') is well tolerated in MM patients overall and can be tolerated for >12 cycles in late stage MM patients with substantial comorbidities.

A phase 1 dose escalation study (PX-171-007) of single agent carfilzomib administered is ongoing and as of 10 July 2009, over 65 patients with solid tumors had started treatment in the initial Phase 2 portion of the study at 36 mg/m$^2$ (bolus administration over 2-10'). A review of the tolerability of 36 mg/m$^2$ carfilzomib in these patients indicates that this regimen was very well tolerated with only one DLT (fatigue) and an overall adverse event profile similar to that seen with the 27mg/m$^2$ carfilzomib experience with bolus dosing (see IB for details). Three patients completed > 12 cycles of therapy at 36 mg/m$^2$ with no evidence of cumulative toxicity. There were no significant DLTs observed; the majority of discontinuations on the study were due to progressive disease. Because of the long-term tolerability carfilzomib, the Phase 1b portion of this study was reopened, and a separate arm for multiple myeloma was added.

In the PX-171-007 trial, patients were treated with carfilzomib given as a 30-minute infusion in order to potentially minimize Cmax-related infusion events. Patients ≥18 years of age, ECOG performance status 0–2 with relapsed and/or refractory MM after ≥2 prior treatment regimens were eligible for the study. In each 28-day cycle, carfilzomib was given as a 30-min intravenous (IV) infusion on days (D) 1, 2, 8, 9, 15, and 16. C1D1 and 2 doses were 20 mg/m$^2$, followed by cohort escalation to 36, 45, 56, or 70 mg/m$^2$ (stepped-up dosing). Prior to infusion of carfilzomib, dexamethasone (4 mg for ≤45 mg/m$^2$, 8 mg for >45 mg/m2) was given as premedication to mitigate potential infusion-related reactions. The MTD was defined as the highest dose at which ≤33% of patients experienced treatment-related dose-limiting toxicity (DLT) during the first cycle or, when appropriate, the maximum planned dose, with doses ranging from 36 mg/m$^2$ to 70 mg/m$^2$. No DLTs were seen in the initial 20/36 mg/m$^2$, 20/45 mg/m$^2$, or 20/56 mg/m$^2$ dose cohorts. Reversible DLTs were recorded in 2 patients in the 20/70mg/m$^2$ cohort; both patients were successfully rechallenged and continued on treatment at reduced doses. The MTD was determined as 56 mg/m$^2$ and this cohort was expanded to a total of 24 patients. At 20/56 mg/m$^2$, 38% of patients have started at least 7 cycles of treatment and 79% did not require dose reductions due to an AE. A total of 28 patients were evaluable for efficacy. 20 patients were evaluable in the 20/56 mg/m$^2$ cohort. Four patients from this cohort withdrew, 3 due to early-onset toxicity (including hypertension, neutropenia, and thrombocytopenia) that prevented escalation to 56 mg/m$^2$. One patient withdrew consent. ORR for the expanded 20/56 mg/m$^2$ cohort was 60%. Median duration of response for the 20/56 mg/m$^2$ cohort was 8 months and median TTP as well as PFS was 7 months. The most common ≥G3 AEs in the 20/56 mg/m$^2$ cohort were thrombocytopenia (38%), anemia (21%), and hypertension (13%). The majority of the AEs

in this cohort were G1–2 in severity. There was 1 report of peripheral neuropathy (G1) in the 20/56 mg/m$^2$ cohort.

In addition to the above observations, a phase I study of carfilzomib in patients with relapsed and refractory multiple myeloma was reported in abstract form at the 2009 American Society of Hematology meeting which demonstrated that carfilzomib can be safely administered to patients with substantial renal impairment (CrCl < 30, including patients on dialysis) without dose adjustment. These data indicate that carfilzomib does not exacerbate underlying renal dysfunction, and confirm the "pre-renal" etiology of the BUN/creatinine elevations observed with IV bolus carfilzomib.[18]

## 1.5 STUDY RATIONALE

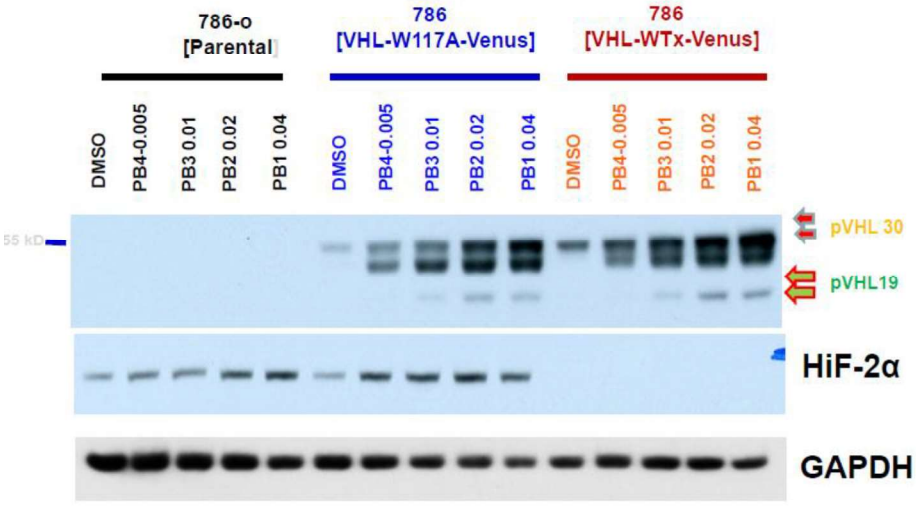
A von Hippel Lindau (VHL) mutation or functional inactivation occurs in the large majority of cases of ccRCC, which results in the dysregulation of a number of key cellular functions, including control over proangiogenic signaling. As a result, ccRCC secrete vascular endothelial growth factor (VEGF) as well as other proangiogenic factors, and histological evaluation of the tumor demonstrates a high degree of vascularity. VHL also regulates the cilia centrosome cycle via the primary cilium, and has been shown to bind to p53. Strategies to manage the consequences of VHL inactivation will ideally remediate all of these pathways. This is a very difficult to do, as each of the VHL functions are quite separate and would require specific therapeutic interventions.

Approximately one third of VHL disruption occurs via missense mutations, which generate full-length, but destabilized protein in the cell. Evaluation of the functional status of some of the most common mutations provides evidence that residual functionality is preserved. These findings raise the possibility that by stabilizing point-mutated pVHL in the cell, either functionality can be restored, thereby providing a differentiation effect on the tumor cell, or will result in aggregation of mutated VHL resulting in tumor-cell specific toxicity.

One potential approach to achieve this goal is to inhibit the proteasome. Preliminary data show that MG132 and bortezomib are capable of upregulating point-mutated pVHL in 786-0 RCC cell lines.

A phase II study evaluating bortezomib was published in 2004. In this treatment refractory patient group, four out of 37 patients showed prolonged progression free survival (PFS). A high throughput screen and candidate compound assessment revealed that agents with proteasome inhibition properties were able to stabilize point-mutated VHL. [19,20] Further analysis of bortezomib function in parental 786-0 RCC cell and in, W117A, VHL WT and R167Q VHL infected 786-0 cells showed that VHL levels were increased with bortezomib dosages that were not lethal to cells, and raised HIF2a levels either very little (in case of parental and W117A cells) or not at all [wt VHL and VHL R167Q (not shown)]. Xenograft experiments are currently being performed to further explore the mutational subtypes most likely to benefit from carfilzomib and bortezomib treatment.

**Figure 1: 786 cells treated with bortezomib for 24h in DMEM**




A paper by Kondagunta et al [21] assessed the efficacy and toxicity of bortezomib in patients with metastatic RCC. Thirty-seven patients with metastatic RCC were treated with bortezomib. The first 25 patients enrolled onto the trial were treated with a dose of 1.5 mg/m2. The dose was decreased to 1.3 mg/m2 for the subsequent 12 patients, because more than 50% of the patients treated at the higher dose required dose reductions. Bortezomib was given by intravenous administration on a twice-weekly schedule for 2 weeks followed by 1 week without treatment until progression or unacceptable toxicity occurred. Twenty-three patients (62%) previously had undergone nephrectomy, and 19 patients (51%) had previously been treated with cytokine therapy. Of the 37 assessable patients, the best response was a partial response in four patients (11%; 95% CI, 3% to 25%) and stable disease in 14 patients (38%; 95% CI, 23% to 55%). The four patients with partial response experienced response durations of 8, 8+, 15+, and 20+ months. Grade 2 or 3 sensory neuropathy was present in 10 patients (53%) overall. One patient in the 1.5 mg/m2 group had grade 3 sensory neuropathy; no grade 3 sensory neuropathy was seen in the 1.3 mg/m2 group. Although a relatively low response rate was seen in this study, approximately ten percent demonstrated a striking and prolonged benefit from bortezomib therapy. It is possible that this response is linked to the VHL genotype. Unfortunately, no samples were retrievable from these patients for hypothesis testing (R. Motzer, personal communication).

The molecular characteristics of this subgroup are not known. These findings raise the hypothesis that treatment of advanced RCC patients with a well-tolerated proteasome inhibitor will specifically benefit patients whose tumors carry specific molecular characteristics. Our preliminary data suggest that point-mutated VHL in the tumor may be a marker of patient benefit.

To test this hypothesis, we will perform a phase II study on patients with metastatic ccRCC refractory to at least one conventional agent. Because this is a hypothesis generating study, inclusion criteria will be open to all patients with clear cell histology. We will collect tumor tissue on these patients and determine whether mutational type is associated with clinical benefit.

# 2 OBJECTIVES

## 2.1 PRIMARY OBJECTIVE

1. To assess progression free survival (PFS) of carfilzomib therapy in patients refractory or intolerant to at least one prior systemic therapy.

## 2.2 SECONDARY OBJECTIVES

1. To assess overall response rate (ORR)

2. To assess overall survival (OS)

3. To assess safety of carfilzomib treatment in patients with metastatic RCC

4. To assess PFS and ORR as a function of VHL mutation subtype

# 3 EXPERIMENTAL PLAN

## 3.1 STUDY DESIGN

This is a single arm, single-center, non-randomized study of Carfilzomib in Patients with Refractory Renal Cell Carcinoma. Up to 40 patients will be enrolled over two years. Patients will receive carfilzomib at a dose of 20 mg/m$^2$ over 30 minutes via IV infusion on Days 1 and 2 and a dose of 56 mg/m$^2$ over 30 minutes via IV infusion on Days 8, 9, 15, and 16 of each 4 week cycle. Week 4 of each cycle will be a rest week; the patient will not receive any treatment with the study drug. Days 1, 8, 15 and the start of the rest week may occur within +/- 4 days; Days 2, 9, 16 and the start of the next cycle will be adjusted accordingly, per physician approval. Patients will be restaged every 8 weeks and will continue on therapy until meeting a reason for removal as discussed in section 5.5.

# 4 SUBJECT SELECTION

## 4.1 INCLUSION CRITERIA

1. Biopsy proven clear cell kidney cancer with metastatic disease. Progressive disease or intolerance to at least one but not more than three (3) prior systemic therapy(ies)
2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for

non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

3. Age ≥ 18 years
4. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
5. Adequate hepatic function, with serum ALT and AST ≤ 3.0 times the upper limit of normal and serum direct and total bilirubin ≤ 1.5 times the upper limit of normal
6. Absolute neutrophil count (ANC) ≥ $1.0 \times 10^9$/L; patients with an ECOG performance status of 2 at study entry must have an ANC ≥ $1.5 \times 10^9$/L
7. Hemoglobin ≥ 8 g/dL (80 g/L) within 14 days prior to beginning study treatment (subjects may be receiving red blood cell [RBC] transfusions in accordance with institutional guidelines); Patients with an ECOG performance status of 2 at study entry must have a hemoglobin ≥ 9 g/dL (transfusion assistance acceptable)
8. Platelet count ≥ $50 \times 10^9$/L; Patients with an ECOG performance status of 2 at study entry must have a platelet count ≥ $100 \times 10^9$/L
9. Creatinine clearance (CrCl) ≥ 30 mL/minute, either measured or calculated using a standard formula (eg, Cockcroft and Gault)
10. Written informed consent in accordance with federal, local, and institutional guidelines.
11. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception during the study and for a period of 6 weeks after you stop receiving the study drug
12. Male subjects must agree to practice contraception during the study and for a period of 6 weeks after you stop receiving the study drug

## 4.2 EXCLUSION CRITERIA

1. Brain metastases not controlled with surgery, whole brain radiotherapy, or with sterotactic radiosurgery
2. Systemic therapy within two weeks of treatment initiation
3. Pregnant or lactating females
4. Major surgery within 21 days prior to beginning study treatment
5. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to beginning study treatment
6. Known human immunodeficiency virus infection
7. Active hepatitis B or C infection

8. Unstable angina or myocardial infarction within 4 months prior to beginning study treatment , NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
9. Uncontrolled hypertension (defined by BP consistently > 150/100) or uncontrolled diabetes (defined by HbA1c > 8.5) within 14 days prior to beginning study treatment
10. Nonhematologic malignancy within the past 2 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) 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
11. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to beginning study treatment
12. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
13. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
14. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to beginning study treatment
15. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

# 5 SUBJECT ENROLLMENT

## 5.1 SCREENING

Within four weeks prior to starting study treatment:

- Radiological studies shall include a chest X-ray, and CT scans of the chest and abdomen for the baseline tumor measurement, an MRI of the brain, and a bone scan. Appropriate additional studies should be obtained to fully define the extent and severity of existing or suspected malignant disease.

- A MRI of the spine should be obtained, if there is suspicion of evolving cord or nerve root compression. Spinal cord or nerve root compression syndromes should be managed before trial entry.

- A skeletal survey and a CT scan of the pelvis will be ordered as clinically indicated at the discretion of the treating physician.

Within two weeks prior to starting study treatment:

- All patients must undergo a complete history and physical examination, including vital signs, ECOG performance status, recent weight loss, height, and current weight.

- Concurrent non-malignant disease and medical therapy must be documented. On-study forms must be filled out completely.

- All prior anti-cancer treatment must be recorded in proper detail. Any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Toxicity Criteria v4.0.

- Patient's MSKCC prognostic criteria will be recorded. (Appendix 1).

- Laboratory studies shall include CBC w/differential, platelet count, chemistry panel (total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, glucose), amylase, lipase, and urinalysis (pH, specific gravity, ketones, RBC, WBC, bilirubin, and protein). T4, TSH will be obtained, fasting glucose will be obtained. Serum pregnancy test in female patients of childbearing potential will also be included and must be negative within 24 hours of beginning study treatment on this study. Minimally elevated levels will be repeated to determine pregnancy vs. tumor marker.

Optional studies with patient consent**:**

- Nephrectomy or metastasectomy blocks or 20 unstained slides, 4 micron thickness on positively charged slides, will be acquired to test for VHL mutation status in tumor, as well as copy number analysis. Banked/archived samples at MD Anderson or from an outside institution are acceptable. A random blood sample will be drawn prior to first dose for a) plasma and serum analysis of cytokines and angiogenesis factors b) circulating monocytic cells.

## 5.2 EVALUATION DURING TREATMENT

On-study evaluations will consist of the following study activities every **four weeks +/- four days**:

- History and physical exam by physician, or mid-level provider at each scheduled visit
- Vital signs (including weight) and ECOG performance status
- Record concomitant medications.
- Monitor for adverse events.
- Serum chemistry including total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, and fasting glucose at each scheduled visit. Note: Patient must fast for 8 hours prior to glucose testing.
- Hematology, including CBC with differential and platelet counts
- Amylase and lipase will be repeated at each scheduled visit as clinically indicated

Optional studies with patient consent **every four weeks +/- four day**:

- Blood will be drawn for a) plasma and serum analysis of cytokines and angiogenesis factors and b) circulating monocytic cells.

*Note: Cycle 1 Day 1 blood testing will not be done if screening labs were done in the previous 7 days.*

On study evaluations will also consist of the following study activities **every week during week 1, 2 and 3 of each cycle**:

- Vital signs (including weight)
- Serum chemistry including alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, and glucose
- Hematology including CBC with differential and platelet counts

In addition to the above, the following will be performed **every eight weeks+/- 7 days**:

- Repeat radiologic studies (CT, MRI, Chest x-ray and bone scan as indicated) to evaluate disease progression or response (in accordance with restaging of disease).

Studies to confirm a complete response or document progressive disease will be performed as needed.

- Serum pregnancy test in female patients of childbearing potential

## 5.3 END OF TREATMENT

The following study activities will be completed within 30 days of treatment discontinuation for any reason:

- Physical exam
- Vital Signs including weight
- Radiologic assessment and assessment of response
- Serum chemistry including total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, and glucose
- Hematology to include: CBC with differential and platelet count
- Record for concomitant medications
- Monitor for adverse events and followed until resolution

Optional studies with patient consent:

- Blood will be drawn for a) plasma and serum analysis of cytokines and angiogenesis factors b) circulating monocytic cells

## 5.4 SURVIVAL UPDATES

Survival updates will take place at 6 month (+/- 1 month) intervals from the off treatment date. This will consist of a phone call, e-mail or medical record review.

## 5.5 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression

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

# 6 TREATMENT PROCEDURES

## 6.1 DRUG PREPARATION AND ADMINISTRATION.

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 BSA at baseline. Subjects with a BSA > 2.2 $m^2$ will receive a dose based upon a 2.2 $m^2$ BSA. Dose adjustments do not need to be made for weight gains/losses of ≤ 20%.

DOSE LEVELS:

| Dose level | Carfilzomib Dose |
|---|---|
| 0 | 20 mg/$m^2$ IV over 30 minutes on days 1 and 2 and 56 mg/$m^2$ IV over 30 minutes on days 8, 9, 15 and 16 of each cycle |
| -1 | 20 mg/$m^2$ IV over 30 minutes on days 1 and 2 and 45 mg/$m^2$ IV over 30 minutes on days 8, 9, 15 and 16 of each cycle |
| -2 | 20 mg/$m^2$ IV over 30 minutes on days 1 and 2 and 36 mg/$m^2$ IV over 30 minutes on days 8, 9, 15 and 16 of each cycle |

**IV hydration** will be given immediately prior to carfilzomib during Cycle 1. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) at Cycle 2 Day 1, then the recommended IV hydration should be given additionally before each dose in Cycle 2. The goal of the hydration program is to maintain robust urine output (eg, ≥ 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.

Carfilzomib will be given as an IV infusion over approximately 30 minutes. More rapid infusion must not be performed. 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. During these observation times, **post dose IV hydration** (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) will be given. Subjects should be monitored periodically during this period for evidence of fluid overload.

## 6.2 DEFINITION OF DOSE-LIMITING TOXICITY

Subjects will be evaluated for toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.0.
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

The following events will be considered dose limiting toxicities for purposes of applying early stopping rules described in Section 8.

Non-hematologic:

- ≥ Grade 2 neuropathy with pain
- ≥ Any Grade 3 toxicity (excluding nausea, vomiting, diarrhea)
- ≥ Grade 3 nausea, vomiting, or diarrhea despite maximal antiemetic/antidiarrheal therapy
- ≥ Grade 4 fatigue lasting for ≥ 7 days
- Any non-hematologic toxicity requiring a dose reduction within Cycle 1
- Inability to receive Day 1 dose of Cycle 2 due to drug related toxicity persisting from Cycle 1 or drug related toxicity newly encountered on Day 1 of Cycle 2.

Hematologic:

- Grade 4 neutropenia (ANC < 0.5 x $10^9$/L) lasting for ≥ 7 days
- Febrile neutropenia (ANC < 1.0 x $10^9$/L with a fever ≥ 38.3ºC)
- Grade 4 thrombocytopenia (platelets < 25.0 x $10^9$/L) lasting ≥ 7 days despite dose delay
- Grade 3-4 thrombocytopenia associated with bleeding
- Any hematologic toxicity requiring a dose reduction within Cycle 1
- Inability to receive Day 1 dose of Cycle 2 due to drug related toxicity persisting from Cycle 1 or drug related toxicity newly encountered on Day 1 of Cycle 2.

## 6.3 DOSE REDUCTIONS/ADJUSTMENTS

The dose of carfilzomib should be held and/or reduced according to the following guidelines:

### *6.3.1 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 (without active bleeding) do not require the carfilzomib dose to be withheld. However, subjects should receive supportive measures in accordance with institutional guidelines. *For patients with Grade 4 thrombocytopenia without evidence of bleeding, study drug dosing may occur at the discretion of the investigator.*

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

**Thrombocytopenia**

| | **Recommended Action** |
|---|---|
| **When Platelets:** | **Carfilzomib** |
| Fall to < 25,000/mm$^3$ | Interrupt carfilzomib, follow CBC weekly |
| Return to ≥ 25,000/mm$^3$ | Resume at full dose |
| Subsequently drop to < 25,000/mm$^3$ | Interrupt carfilzomib, follow CBC weekly |
| Return to ≥ 25,000/mm$^3$ | Resume at 1 dose decrement |

**Neutropenia**

| | **Recommended Action** |
|---|---|
| **When ANC** | **Carfilzomib** |
| Falls to < $0.5 \times 10^9$/L | Interrupt carfilzomib<br>add filgrastim if Gr 3 with fever or Gr 4, follow CBC weekly |
| Returns to > $1.0 \times 10^9$/L (if neutropenia was the only toxicity noted) | Resume at full dose |
| Returns to > $1.0 \times 10^9$/L (if other toxicity noted) | Resume at 1 dose decrement |
| Subsequently drops to < $0.5 \times 10^9$/L | Interrupt carfilzomib |
| Returns to > $1.0 \times 10^9$/L | Resume at full dose |

.

### *6.3.2 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, a 2nd carfilzomib dose reduction may be permitted the discretion of the investigator. No more than two dose reductions will be permitted in an individual subject on study. If toxicity continues or recurs after two dose reductions, the subject should be removed from study.

If the subject tolerates the reduced dose for two cycles, subject may be dose escalated to the dose prior to reduction

If there is no resolution of toxicity after 2 weeks of withholding treatment (up to 3 weeks for infection 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 or Grade 3 neuropathy | 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 4 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**

A phase I study of Carfilzomib in patients with relapsed and refractory multiple myeloma and varying degrees of renal insufficiaency has been initiated and preliminary results were 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 creatine clearance 50-79 mL/min; 9 patients had creatinine clearance 30-49 mL/min; 9 patients had creatine 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.

**Dose Adjustment Guideline for Renal Dysfunction**

| Renal Dysfunction | Recommended Action |
|---|---|
| Normal to mild (CrCl >50 mL/min) | Full dose |
| Moderate (CrCl 31–50 mL/min) | Full dose |
| Severe (CrCl ≤ 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

### *6.3.3 MISSED DOSES*

Missed doses will not be replaced during a cycle. If a subject misses more than 2 doses within 1 cycle without notifying the research nurse, for reasons other than toxicity, the subject will be discontinued.

### *6.3.4 DOSING MODIFICATIONS*

Dose modifications and delays different from those stated in the protocol, for management of toxicities, will be permitted at the discretion of the Investigator.

## 6.4 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 (56mg/$m^2$) 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, per physician preference, 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 weekly. Carfilzomib must be held for subjects with a CrCl $\leq$ 30 mL/min at any time during study participation as outlined in Section 6.3.2
- 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 $\leq$ 25,000/$mm^3$, 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 Section 6.3.1.
- 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 antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

### *6.4.1 GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF TUMOR LYSIS SYNDROME (TLS)*

TLS, which may be associated with multiorgan failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with carfilzomib. This is unlikely to be an issue for patients with RCC.

#### 6.4.1.1 Hydration and Fluid Monitoring

1. Intravenous Fluids

   250–500 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before *and* after each carfilzomib dose during Cycle 1. If lactate dehydrogenase (LDH) or uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for Cycle 2. 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.

   In subjects considered to be still at risk for TLS at completion of Cycle 1, hydration should be continued into Cycle 2, if clinically indicated. Patients in whom this program of oral and IV fluid hydration is contraindicated, e.g., due to pre-existing pulmonary, cardiac, or renal impairment, will not be eligible to participate in the clinical trial.

#### 6.4.1.2 Laboratory Monitoring

Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

#### 6.4.1.3 Clinical Monitoring

Inform subjects of signs and symptoms that may be indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output. Advise subjects to report such symptoms immediately and seek medical attention.

#### 6.4.1.4 Management of Tumor Lysis Syndrome

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.
All cases of TLS must be reported to Onyx as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

## 6.5 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.

### *6.5.1 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. 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.

All subjects must receive prophylaxis with hydration (see Section 6.1).

### *6.5.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS*

Allopurinol (in subjects at risk for TLS due to high tumor burden) 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 Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator.

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 antiemetics and antidiarrheals as necessary, but these should not be administered unless

indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

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.

### *6.5.3 EXCLUDED CONCOMITANT MEDICATIONS*

Concurrent therapy with an approved or investigative anticancer therapeutic is not allowed. Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

## 7 SAFETY AND ADVERSE EVENT REPORTING

## 7.1 REPORTING REQUIREMENTS

### *7.1.1 ADVERSE DRUG REACTION REPORTING*

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Adverse events for this protocol will be documented and entered into the Department of Genitourinary Medical Oncology Oracle database (GURU) and used as the case report form according the Recommended Adverse event Recording Guidelines for Phase II protocol.

| Recommended Adverse Event Recording Guidelines | | | | | |
|---|---|---|---|---|---|
| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| Unrelated | Phase I | Phase I | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| Unlikely | Phase I | Phase I | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| Possible | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| Probable | Phase I<br>Phase II | Phase I<br>Phase II | Phase I<br>Phase II | Phase I<br>Phase II | Phase I<br>Phase II |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Phase III | Phase III | | Phase III | Phase III |
| Definitive | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

### *7.1.2 SERIOUS ADVERSE EVENT REPORTING (SAE)*

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and

Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- The gene therapy reporting addendum ("Additional Reporting Form for Serious Adverse Events on Gene Transfer Trials") must be included with each SAE submitted.

### *7.1.3 REPORTING TO FDA:*

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

### 7.1.4 INVESTIGATOR COMMUNICATION WITH SUPPORTING COMPANIES:

**Expedited Reporting by Investigator to Onyx**

The Investigator must inform Onyx in writing by Fax at the contact information listed below of all Expedited Safety Reports submitted to the relevant Regulatory Agencies. These notifications should be performed in parallel to the Regulatory Agency submissions [e.g., within 7 calendar days for any Fatal or Life-threatening 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 will be documented on an MD Anderson Serious Adverse Event Form. This form must be completed and supplied to Onyx in English.

The initial report must be as complete as possible, at a minimum including the serious adverse event term (s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up Serious Adverse Event Form, and submitted to Onyx in the same timelines as outlined above. The institutional protocol number should be included on all 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. Onyx Drug Safety and Pharmacovigilance Contact Information:

**Onyx**Fax: (800) 783-7954
SAE hotline: (650)-266-2501)
e-mail: adverse.events@onyx-pharm.com

## 7.2 PREGNANCY

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of carfilzomib, Onyx Drug Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Onyx Drug Safety and Pharmacovigilance Contact information above). If the subject is pregnant, carfilzomib must be withheld.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

# 8 STATISTICAL ANALYSIS

**Statistical Considerations:**
*Goal:* This institutional, single-arm, phase II trial will investigate the progression-free survival (PFS) of a new therapy, carfilzomib, as post-first-line therapy for patients with recurrent or refractory clear cell renal cell carcinoma (CCRCC). Additionally, estimations of the treatment effect between patients with and without the VHL mutation will be calculated to build evidence for future trials.

*Endpoints:* The primary endpoint is PFS which is defined as the time from enrollment to progression or death, whichever comes first. Progression will be defined according to RECIST version 1.1. Any patients who are alive and free of disease at the time of analysis will be censored at the date of the most recent tumor assessment. Safety will be an important secondary endpoint. Adverse events will be recorded by CTCAE version 4.0 with information regarding relationship to the study drug. Whether or not a patient had to be discontinued from therapy due to predefined severe toxicity will also be recorded. Additional endpoints will include the response rate and overall survival. Response is defined as a CR or PR by RECIST. Overall survival will be defined as the time from enrollment to death, regardless of cause. Patients who are alive at the time of analysis will be censored on the date they were last in contact with study personnel.

*Sample Size:* Up to 40 patients will be enrolled on this trial. The number is small due an expectation of slow accrual. This is due to both the rarity of this disease as well as the fact that this treatment is delivered intravenously while other new treatments are oral. With the slow accrual, the choice of 40 patients is based on the feasibility of completing the trial within 2 years while retaining acceptable operating characteristics.

Using the monitoring method established by Thall et al,[22] PFS is assumed to follow an exponential distribution. Calculations were performed using TTEDesigner. Denote the historical median PFS as $m_H$ and the median PFS for this study as $m_E$. Under a Bayesian model, we will further assume that $m_H$ has an inverse gamma (IG) prior with parameters (shape, scale) = (3.25, 5.625), with median PFS=2.5 months and variance = 5. We also assume that $m_E$ follows IG prior with parameters (shape, scale) = (2.0625, 2.65625) with the same median PFS of 2.5 months, but with a much larger variance (100) to reflect the greater uncertainty about the PFS in patients treated with carfilzomib. The PFS data will be monitored continuously and the study will be terminated early if $Pr(m_H + d < m_E| \text{ data}) < 0.014$, where d= 2.5 months. Specifically, the trial will be stopped early if, given the current data, there is less than 1.4% chance that the median PFS in patients treated with carfilzomib will improve by more than 2.5 months over the historical control. While this is a large improvement in PFS, with a doubling of the median, 2 previous trials in this patient population have resulted in similar improvements. First, in a randomized phase III trial examining everolimus vs placebo, everolimus had a median PFS of 4.9 months vs 1.9 months in the placebo group. [7] In an earlier phase III trial examining sorafenib vs placebo, the PFS was 5.5 vs 2.8 months, respectively.[3] The operating characteristics of this decision rule are summarized in the table below.

**Operating characteristics for futility monitoring based on PFS.**

| True median PFS (month) | Pr(stop early) | Average Number of Patients Treated |
|---|---|---|
| 1 | >0.99 | 4.3 |
| 2 | 0.99 | 9.9 |
| 2.5 | 0.84 | 18.0 |
| 3 | 0.55 | 25.6 |

| | | |
|---|---|---|
| 4 | 0.16 | 35.1 |
| 5 | 0.06 | 37.9 |
| 6 | 0.03 | 38.9 |
| 7 | 0.02 | 39.4 |

*Implementation:* Monitoring of PFS will be performed through the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to personnel responsible for enrolling patients and reviewing and analyzing patient data. Training on the use of the Clinical Trial Conduct website to enroll and monitor patients on the study will be provided by the study biostatistician for study personnel.

*Safety monitoring:* Toxicity will be monitored in all patients. Based on the method of Thall (1995)[23] continual monitoring after the 5th patient is planned. Calculations were performed in Multc Lean. Denote the probability of extreme toxicity by $\theta_E$, where extreme toxicity is defined as any toxicity that requires discontinuation of carfilzomib. This does not include voluntary patient withdrawals due to unpleasant symptoms, but patients meeting the definition of dose-limiting toxicity as defined in section 6.2 and then have required dose reductions/adjustments as defined in Section 6.3. Additionally, patients who later resume therapy will not be counted as being discontinued. We assume $\theta_E \sim$ beta (0.40, 1.6). Our stopping rule is given by the following probability statement: $Pr(\theta_E > 0.20 \mid \text{data}) > 0.95$. That is, we will stop the trial if, at any time during the study, we determine that there is more than a 95% chance that the extreme toxicity rate is more than 20%. Additionally, we denote the probability of extreme toxicity in standard therapies by $\theta_S$. We assume $\theta_S \sim$beta (200, 800). The stopping boundaries for this toxicity rule are to terminate the trial if the number of required treatment discontinuations compared to the number or patients on trial exceeds the limits in this table.

**Stopping Criteria for Excessive Treatment Discontinuations**

| If there are this many discontinuations | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|
| Stop if this many patients (or fewer) have been entered on the trial | 7 | 11 | 14 | 18 | 21 | 25 | 29 | 33 | 37 | 40 |

**The Operating Characteristics for Toxicity Monitoring**

| True toxicity rate | Probability of Stopping Early | Median (25th %ile, 75th %ile) |
|---|---|---|

| | | |
|---|---|---|
| 0.10 | 0.006 | 40 (40, 40) |
| 0.20 | 0.13 | 40 (40, 40) |
| 0.25 | 0.32 | 40 (27, 40) |
| 0.30 | 0.57 | 32 (13, 40) |
| 0.40 | 0.91 | 13 (7, 24) |
| 0.50 | 0.99 | 7 (6, 13) |

*Analysis Plan:* For discrete or categorical data, descriptive statistics will include tabulations of frequencies. For continuous data, summary statistics including n, mean, standard deviation, median, minimum and maximum will be computed. The estimate of the posterior median time to progression and its 95% credible interval will be estimated.

The Kaplan-Meier method[24] will be utilized to display progression-free and overall survival for the whole group and by the VHL mutation versus normal subgroups. Exact 95% binomial confidence intervals for the response rates will be computed overall and for VHL mutation subgroups. Patient adverse events will be tabulated by symptom grade and relationship to study drug.

# 9 INVESTIGATIONAL PRODUCT

## 9.1 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.

## 9.2 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®).

## 9.3 STORAGE

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

## 9.4 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.

# 10 REGULATORY OBLIGATIONS

## 10.1 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
2100 Powell St.
Emeryville, CA 94608

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.

## 10.2 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.

# 11 REFERENCES

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300, 2010
2. Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-24, 2007
3. Escudier B, Eisen T, Stadler WM, et al: Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125-34, 2007
4. Sternberg CN, Davis ID, Mardiak J, et al: Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 28:1061-8, 2010
5. Escudier B, Pluzanska A, Koralewski P, et al: Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 370:2103-11, 2007
6. Hudes G, Carducci M, Tomczak P, et al: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271-81, 2007
7. Motzer RJ, Escudier B, Oudard S, et al: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372:449-56, 2008

8. Bortezomib summary basis of approval (www.fda.gov/cder/foi/nda/2003/21602_Velcade.htm).
9. Arastu-Kapur S, Shenk KD, Parlati F, et al: Non-proteasomal targets of proteasome inhibitors bortezomib and carfilzomib, Am Soc Hematology, 2008, pp 2765
10. 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
11. Bross PF, Kane R, Farrell AT, et al: Approval summary for bortezomib for injection in the treatment of multiple myeloma. Clin Cancer Res 10:3954-64, 2004
12. Kirk CJ, Jiang J, Muchamuel T, et al: The selective proteasome inhibitor carfilzomib is well tolerated in experimental animals with dose intensive administration, Am Soc Hematology, 2008, pp 2765
13. Wang L, Siegel D, Kaufman JL, et al: Updated results of bortezomib-naive patients in PX-171-004, an ongoing open-label, phase II study of single agent carfilzomib (CFZ) in patients with relapsed or refractory myeloma (MM). , Am Soc Hematology Annual Meeting, 2009, pp 302
14. Alsina M, Trudel S, Vallone MK, et al: Phase I single agent antitumor activity of twice-weekly consecutive day dosing of the proteasome inhibitor carfilzomib (PR-171) in hematologic malignancies., Am Soc Hematology, 2007, pp 411
15. Jagannath S, VIj R, Stewart K, et al: The multiple myeloma research consortium (MMRC). Final results of PX-171-003-AO, part 1 of an open-label, single arm, phase II study of carfilzomib (CFZ) in patients with relapsed and refractory multiple myeloma (MM). , Am Soc Clinical Oncol Annual Meeting, 2009, pp 8504
16. Siegel D, Wang L, Orlowski RZ, et al: PX-171-004, an ongoing open label, phase II study of single-agent carfilzomib (CFZ) in patients with relapsed or refractory myeloma (MM): updated results form the bortezomib-treated cohort. , Am Soc Hematology Annual Meeting 2009, pp 303
17. Niesviszky R, Wang L, Orlowski RZ, et al: Base Ib multicenter dose escalation study of carfilzomib plus lenalinomide and low dose dexamethaosne (CRd) in relapsed and refractory multiple myeloma (MM), Am Soc Hematology Annual Meeting, 2009, pp 304
18. Badros AZ, VIj R, Martin TA, et al: Phase I study of carfilzomib in patients with relapsed and refractory multiple myeloma and varying degress of renal insufficiency. , Am Soc Hematology Annual Meeting, 2009, pp 3877
19. Ding, Z., Feng, Z., Fikes, N. A., Gao, M., Si, W., Sobieski, M. M., Stephan, C. C., Mills, G. B., and Jonasch, E. (2011). High throughput screening to identify molecules that alter VHL stability
20. Ding, Z., German, P., Bai, S., Feng, Z., Gao, M., Si, W., Sobieski, M. M., Stephan, C. C., Mills, G. B., and Jonasch, E. (2012). Agents That Stabilize Mutated von Hippel-Lindau (VHL) Protein: Results of a High-Throughput Screen to Identify Compounds That Modulate VHL Proteostasis. J Biomol Screen *17*, 572-580.

21. Kondagunta, G. V., Drucker, B., Schwartz, L., Bacik, J., Marion, S., Russo, P., Mazumdar, M., and Motzer, R. J. (2004). Phase II trial of bortezomib for patients with advanced renal cell carcinoma. J Clin Oncol *22*, 3720-3725.

22. Thall PF, Wooten LH, Tannir NM: Monitoring event times in early phase clinical trials: some practical issues. Clin Trials 2:467-78, 2005

23. Thall PF, Simon RM, Estey EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med 14:357-79, 1995

24. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

## **Appendix 1** – MSKCC Prognostic Factors

Risk factors associated with shorter survival

- Karnofsky performance status < 80% or ECOG  2
- High serum lactate dehydrogenase (> 1.5 X upper limit of normal)
- Low hemoglobin (< lower limit of normal)
- High corrected serum calcium (> 10 mg/dl; corrected calcium = total calcium – 0.707 [albumin –3.4])
- Absence of nephrectomy

Stratification

- Favorable risk: 0 risk factors
- Intermediate risk: 1 or 2 risk factors
- Poor risk: 3 risk factors