TITLE: A Phase I/II Study of the c-Met Inhibitor Cabozantinib as a Targeted Strategy to Reverse Resistance to the Proteasome Inhibitor Carfilzomib in Refractory Multiple Myeloma

Principal Investigator: Muhamed Baljevic, M.D.
The University of Nebraska Medical Center
Department of Internal Medicine
Division of Hematology/Medical Oncology
986840 Nebraska Medical Center
Omaha, NE 68198-6840
Telephone 402-559-8562, Fax 402-559-6520
E-mail muhamed.baljevic@unmc.edu

Co-Principal Investigator: Robert Z. Orlowski, Ph.D., M.D.
The University of Texas M. D. Anderson Cancer Center
Department of Lymphoma & Myeloma
1515 Holcombe Blvd., Unit 429
Houston, TX 77030
Telephone 713-745-8576, Fax 713-563-5067
E-mail rorlowski@mdanderson.org

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BioStatistician: Lynette Smith, PhD
Department of Biostatistics
UNMC College of Public Health
984375 Nebraska Medical Center
Omaha, NE 68198-4375
Telephone 402-559-4112
E-mail lmsmith@unmc.edu

Pathology/Biospecimens:
Clinical Studies Coordinator
The University of Texas M. D. Anderson Cancer Center
Department of Lymphoma & Myeloma
1515 Holcombe Blvd., Unit 429
Houston, TX 77030

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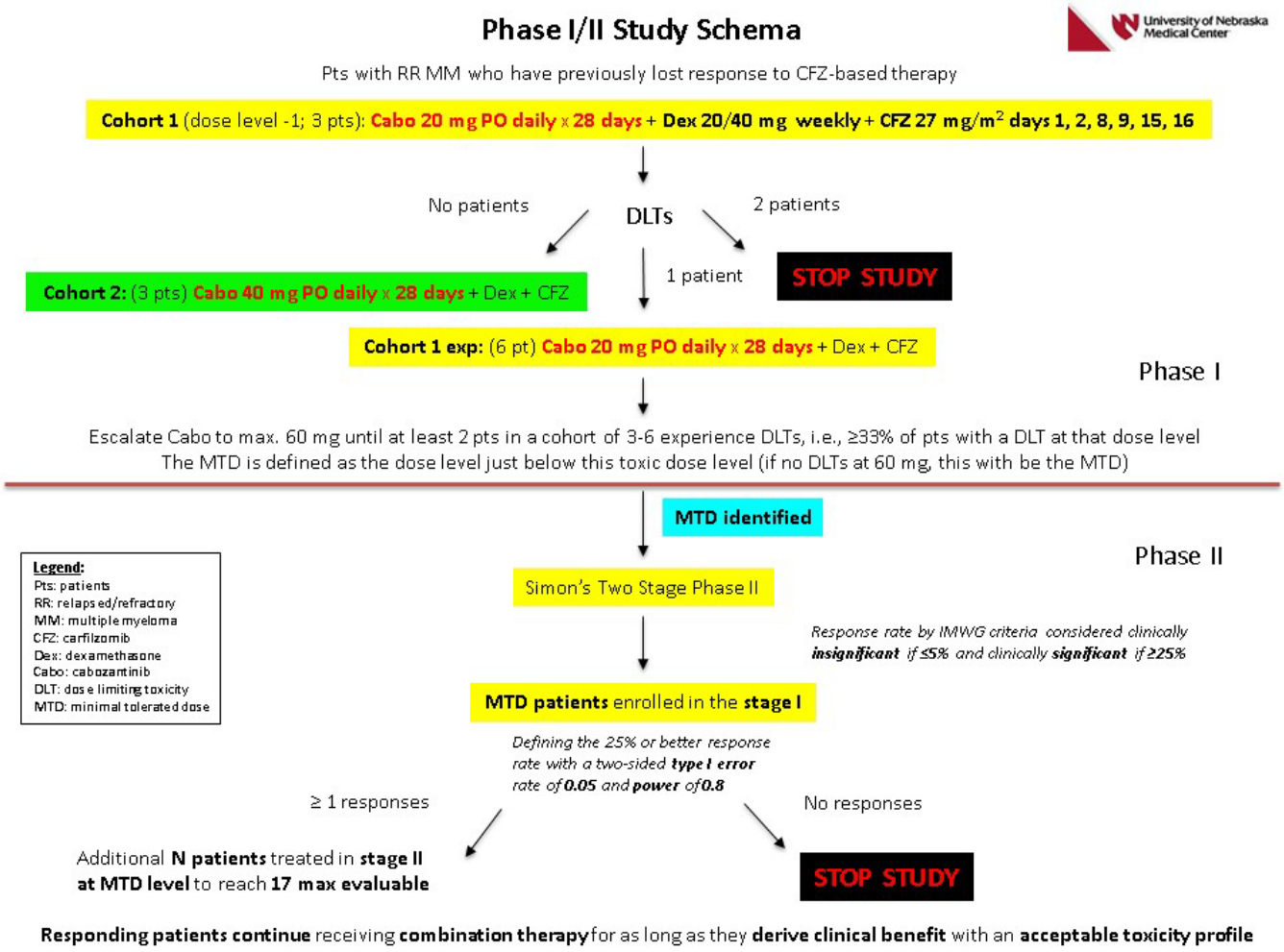
ABSTRACT
Much of the improvement in the median overall survival in multiple myeloma (MM) is owed to incorporation of proteasome inhibitors (PIs) and immunomodulators into the contemporary combination regimens. However, despite high remission rates in combination regimens, PI-based therapy faced limitation in both intrinsic and acquired PI resistance. Moreover, patients are currently treated empirically as no markers of PI sensitivity have been identified. Resting on novel pre-clinical observations from studying previously established MM cell lines with bortezomib and carfilzomib resistance, we identified *MUC20* expression as a viable biomarker modulating the intrinsic PI-sensitivity and/or relative resistance to PIs. In the currently proposed phase I/II study, we aim to treat patients with relapsed and/or relapsed refractory MM who have previously progressed on carfilzomib with an FDA approved c-MET inhibitor, *cabozantinib*. Our hypothesis is that the additional rescue blockade with cabozantinib added to the carfilzomib will (1) be safe and tolerable and (2) will show activity by demonstrating objective response to combination carfilzomib/cabozantnib therapy. In correlative studies, we aim to show that (1) the serum and marrow MUC20 levels which will be judged by genomic and flow cytometric studies will directly correlate with primary plasma cell MUC20/c-Met pathway activation and inversely correlate with PI resistance; and (2) a correlation of the gene and MUC20 expression profiles of patients with clinical outcomes may confirm the biomarker MUC20 as a predictor of disease sensitivity to PI, and allow future personalization of c-Met-targeted therapies, as well as combination approaches based on c-Met inhibitors.

SCHEMA



PROTOCOL THERAPY: 28-day Cycles

Cabozantinib:
Phase I: Level -1 = 20 mg or Level 0 = 40 mg or Level +1 = 60 mg, PO daily on days 1-28
Phase II: One of phase I dosing levels identified as MTD, PO daily on days 1-28

Carfilzomib: 27 mg/m^2 IV over 10 min on days 1, 2, 8, 9, 15, 16

Dexamethasone: 40 mg PO/IV on days 1, 8,15 and 22
(for patient age ≥ 75, acceptable to be given as 20 mg per week PO/IV)

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1. OBJECTIVES

1.1. PRIMARY OBJECTIVES

The **primary objectives** for this phase I/II study are:

Primary Objective(s):

(1) to determine the maximum tolerated dose (MTD) of daily cabozantinib given on days 1-28 added to a capped dose of carfilzomib of 27 mg/m^2 and capped dose of Dexamethasone a 40 mg (for patient age ≥ 75, acceptable to be given as 20 mg PO/IV) weekly every 4 weeks in patients with relapsed and refractory (RR) multiple myeloma (MM) who have lost response to carfilzomib

(2) to estimate the overall response rate (ORR) of patients with RR MM treated with the addition of cabozantinib to carfilzomib.

1.2. SECONDARY OBJECTIVES

The **secondary objectives** for this phase II study are:

(1) to identify biological correlates of clinical outcomes and toxicity, including the measurement of MUC20 levels at enrollment and after cycle 2, and activation status of the c-MET/ERK-1/2/ELK1/POMP pathway in primary MM cells at baseline and after each cycles of therapy on protocol, as defined by flow cytometry and GEP data;

(2) to estimate progression free survival (PFS), median duration of response (DOR), and median time to next treatment;

1.3. EXPLORATORY OBJECTIVES

The **exploratory objectives** for this phase I/II study are:

(1) To evaluate the symptom burden of RR MM patients undergoing therapy with addition of cabozantinib to carfilzomib in patients who have lost response to proteasome inhibition with carfilzomib, using the M. D. Anderson Symptom Inventory (MDASI) and its multiple myeloma module (MDASI-MM; please see Appendix B)

(2) To evaluate the impact of therapy with cabozantinib in combinbation with carfilzomib in patients who have lost response to proteasome inhibition with carfilzomib in the RR MM setting on patient reported outcomes using the European Organization for Research on the Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (QLQ-C30; please see Appendix C), and the myeloma-specific module QLQ-MY20 (please see Appendix D)

(3) To evaluate the impact of therapy with cabozantinib for RR MM on the ability to collect stem cells in any patients who go on to undergo subsequent stem cell mobilization

2. BACKGROUND

2.1 STUDY DISEASE

Multiple myeloma is characterized by an expansion of a clonal population of plasma cells in the bone marrow[1], and is the second most commonly diagnosed hematologic malignancy. Statistics from the American Cancer Society indicate that, in 2010, a total of 20,180 patients will be diagnosed with this plasma cell dyscrasia in the United States, including 11,170 men, and 9,010 women[2]. Notably, while the incidence of this disease appears to be stable, the total number of new cases yearly has more than doubled since 1983, when 9,600 patients were diagnosed[3], indicating that myeloma is becoming an increasing health care burden in the United States. This increase is in part due to the aging of the population, in that the average age at diagnosis of myeloma is usually 65-70[1]. Common disease-related symptoms include bony pain, due to either lytic disease or pathologic fractures, such as of the ribs or vertebrae; fatigue, due generally to anemia; renal insufficiency, due to cast nephropathy or amyloidosis, among others; and hypercalcemia, due to renal insufficiency and osteolysis. Other symptoms can include frequent infections due to granulocytopenia, functional hypogammaglobulinemia, and impaired cell-mediated immunity; peripheral neuropathy, due to amyloidosis or nerve root impingement; and manifestations of hyperviscosity, including dizziness, headaches, congestive heart failure, and bleeding diatheses[1].

Treatment for multiple myeloma is directed at reducing the total body disease burden, and therefore the symptoms associated with this disease process. Patients typically receive some kind of induction therapy regimen after developing symptomatic disease, which is often determined in part by whether they are candidates for high dose chemotherapy with autologous stem cell transplantation (ASCT). For those patients who are younger and/or fitter, and could be ASCT candidates, induction will typically consist of a regimen that avoids the use of the alkylating agent melphalan to avoid stem cell damage. Active and widely available chemotherapeutics in this setting include traditional cytotoxic agents, such as the alkylating agent cyclophosphamide, which is not toxic to stem cells, anthracyclines such as doxorubicin, corticosteroids such as dexamethasone or prednisone, and the microtubule targeting drug vincristine[1]. In addition, a number of novel drugs have been introduced over the past ten years that were initially validated in the relapsed and/or refractory setting, including immunomodulatory drugs such as thalidomide and lenalidomide[4], and proteasome inhibitors such as bortezomib[5]. These are now often incorporated into up-front regimens in combination with each other, as well as with some of the older cytotoxic agents. Among these various options, the National Comprehensive Cancer Network currently most strongly recommends the regimens of bortezomib with dexamethasone[6], bortezomib with doxorubicin and dexamethasone[7], bortezomib with thalidomide and dexamethasone[8], or lenalidomide with dexamethasone[9] prior to transplantation.

For those patients who are not ASCT candidates, usually because of advanced age, or compromised organ function and/or performance status, induction therapy will also typically incorporate novel agents and traditional cytotoxics, but are more likely to also include melphalan[1]. In this setting, the National Comprehensive Cancer Network currently most strongly recommends the regimens of bortezomib with melphalan and prednisone[10], thalidomide with melphalan and prednisone[11], and lenalidomide with dexamethasone[9].

With the introduction of novel agents, the outcomes for patients with multiple myeloma in both the up-front, and relapsed and/or refractory settings, have been improving[12–14]. Indeed, some studies suggest that median survival may have been increased from a previous average of three to four years, to seven to eight years, and that longer survival is now commonly possible, especially in

patients with good risk cytogenetic features who achieve a complete remission (CR). Unfortunately, myeloma is still felt to be incurable in the vast majority of patients, and even those who achieve a CR with front-line standard or high dose therapies eventually relapse. Options at that point include retreatment with their prior induction regimen, and the use of thalidomide[15] and lenalidomide[16–18], as well as bortezomib[19–22], either alone, or in various combinations. Second-line therapy can in many cases reestablish a complete remission, but this is typically of shorter duration than previously, due in part to the emergence of more drug-resistant disease clones. As a result, myeloma is characterized clinically by multiple relapses and decreasing remission durations with each additional line of therapy[23,24]. This indicates the need to continue to develop more novel and targeted agents that could be incorporated into our chemotherapeutic armamentarium against myeloma, and which could be used in a rational, molecularly adapted manner.

2.2 Cabozantinib

Receptor tyrosine kinases (RTKs) have emerged as an important class of molecular targets for anti-cancer therapy. The encouraging results from agents such as imatinib mesylate (Gleevec) against cancers with the constitutively active Bcr-Abl mutation, as well as erlotinib, an inhibitor of mutated and overexpressed epidermal growth factor (EGF) receptor kinase, have provided important clinical evidence that molecularly targeted RTK inhibitors are efficacious and can have a significant and broad effect against various cancers. As more RTKs are implicated in the pathophysiology of oncogenesis, the notion has been put forward that the signal transduction pathways that are served by these RTKs become dominant in initiating and maintaining the pro-proliferative and anti-apoptotic phenotype of the transformed cell. Indeed, there is growing evidence that dysregulated RTK signaling in cancer cells may result in so-called “oncogene addiction,” providing the opportunity to selectively kill cancer cells by ablating RTK signaling pharmacologically[25].

The c-Met RTK mediates the signals for a variety of physiological processes that have implications for oncogenesis, including migration, invasion, cell proliferation, and angiogenesis. A wide variety of human cancers exhibit constitutively dysregulated c-Met activity, either through over-expression of the c-Met kinase, activating mutations in c-Met, or increased autocrine or paracrine secretion of the c-Met ligand hepatocyte growth factor/scatter factor (HGF/SF). These alterations have been strongly implicated in tumor progression and metastasis in a variety of cancers, and a high constitutive activation of the c-Met RTK has been correlated with poor clinical prognosis[26,27].

c-Met can be activated in both a ligand-dependent manner, by the overexpression of c-Met and/or its ligand HGF, or a ligand-independent manner as in the case of activating mutations of c-Met such as those described in sporadic and hereditary papillary renal carcinoma[26]. Activation and autophosphorylation of c-Met results in the binding and phosphorylation of adaptor proteins such as Gab1, Grb2, Shc and c-Cbl, and results in the subsequent activation of signaling pathways, including the PI3K/Akt, FAK, STAT and Ras/MEK/Erk pathways that play various roles in cell survival, proliferation, invasion, and angiogenesis[28,29]. In the melanocyte lineage, c-Met expression is upregulated by microphthalmia-associated transcription factor (MITF), which has been implicated in the oncogenesis of melanoma and other cancers[30,31].

The presence of c-Met in most cancers, and its role in controlling multiple signal transduction pathways involved in tumor growth render this enzyme a logical therapeutic target for human cancer.

Cabozantinib is a FDA approved potent RTK inhibitor with selectivity against RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2 c-Met RTK, as determined by biochemical and cellular assays. A comprehensive review of cabozantinib can be found in the cabozantinib Exelixis FDA package insert (2012)[32].

2.2.1 NON-CLINICAL PHARMACOLOGY

***In Vitro* Efficacy**

Cabozantinib (XL184) is a potent inhibitor of MET and VEGFR2 that also inhibits RET, KIT, AXL, and FLT3, all of which have been implicated in tumor pathogenesis. Cabozantinib inhibits MET and VEGFR2 with IC_{50} values of 1.3 and 0.035 nmol/L respectively, while it also strongly inhibited KIT, RET, AXL, TIE2, and FLT3at IC_{50} values of 4.6, 5.2, 7, 14.3, and 11.3 nmol/L, respectively. IC_{50} determinations conducted at various concentrations of ATP revealed that cabozantinib is an ATP-competitive inhibitor of MET, VEGFR2, TIE2, and FLT3.

Cabozantinib inhibits endothelial cell tubule formation *in vitro*: HMVEC cells were incubated with VEGF in the presence of cabozantinib and tubule formation visualized by immunostaining for CD31. Cabozantinib inhibited tubule formation with an IC_{50} value of 6.7 nmol/L without cytotoxicity, indicating that cabozantinib exerts an antiangiogenic rather than cytotoxic effect.

Cabozantinib potently inhibited HGF-induced migration (IC_{50} 31 nmol/L) and invasion (IC_{50} 9 nmol/L) of B16F10 cells. VEGF- and HGF-mediated migration of proangiogenic murine MS1 endothelial cells were also sensitive to cabozantinib with IC_{50} values of 5.8 and 41 nmol/L, respectively[33].

Cabozantinib inhibits tumor cell proliferation in a variety of tumor types. The effect of cabozantinib on proliferation was evaluated in a number of human tumor cell lines. SNU-5 and Hs746T cells harboring amplified MET[34] were the most sensitive to cabozantinib (IC50 = 19 and 9.9 nmol/L, respectively); however, SNU-1 and SNU-16 cells lacking MET amplification were more resistant (IC50 = 5,223 and 1,149 nmol/L, respectively). MDAMB-231 and U87MG cells exhibited comparable levels of sensitivity to cabozantinib (IC50 = 6,421 and 1,851 nmol/L, respectively), whereas H441, H69, and PC3 cell lines were the least sensitive to cabozantinib with IC50 values of 21,700, 20,200, and 10,800 nmol/L, respectively. In addition, BaF3 cells expressing human FLT3-ITD, an activating mutation in acute myelogenous leukemia[35], were sensitive to cabozantinib (IC50 = 15 nmol/L) when compared with wild-type BaF3 cells (IC50 = 9,641 nmol/L).

***In Vivo* Efficacy**

Cabozantinib inhibits MET and VEGFR2 phosphorylation *in vivo*. A single 100 mg/kg oral dose of cabozantinib resulted in inhibition of phosphorylation of MET 2 to 8 hours post dose in H441 tumors that harbor constitutively phosphorylated MET. This result is consistent with data showing the sensitivity of these cells to inhibitors selective for MET and MET knockdown by siRNA[28,36].

This effect was reversible, as MET phosphorylation returned to basal levels by 48 hours after treatment. In separate experiments, cabozantinib inhibited in vivo stimulation of MET phosphorylation by HGF in liver hepatocytes and VEGF-stimulated phosphorylation of FLK1 with inhibition of both targets sustained through 8 hours postdose. Furthermore, cabozantinib eliminated endogenous levels of phosphorylated FLK1 that are present in the absence of VEGF stimulation.

Plasma concentrations of cabozantinib associated with maximal and sustained inhibition of MET and FLK1 were 17 - 34 mmol/L, greater than 3-fold above the MET cellular phosphorylation, VEGF tubule formation, and HGF invasion IC_{50} values described.

Cabozantinib disrupts tumor vasculature and promotes tumor and endothelial cell death. Antiangiogenic-sensitive MDA-MB-231 cells expressing MET and VEGF were administered to tumor-bearing animals which were treated with a 100-mg/kg oral dose of Cabozantinib. Cabozantinib significantly increased tumor hypoxia and apoptosis when compared with vehicle-treated tumors. Cabozantinib induced cell death not only in tumor cells but also in endothelial cells in the tumor vasculature. These results showed that cabozantinib disrupts tumor vasculature by inducing endothelial cell death that negatively impacts tumor viability[33].

The *in vivo* efficacy of cabozantinib was evaluated in human tumor models in rodents over a period of time that corresponded to exponential tumor growth of each model. Cabozantinib treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors ($P < 0.001$) for all doses when compared with vehicle-treated tumors. Dose-dependent inhibition was observed for the 3- and 10-mg/kg doses ($P < 0.01$). Continuous treatment was associated with plasma concentrations of 9,000 to 16,000 nmol/L, which was ~2-fold above IC_{50} values for cellular proliferation and tubule formation with MDA-MB-231 conditioned media. Cabozantinib inhibited growth of H441 tumors at all doses ($P < 0.001$), with dose-dependent inhibition observed for the 10- and 30- mg/kg doses. The 60-mg/kg dose resulted in significant tumor regression (33%, $P < 0.005$) when compared with pre-dose tumor weights. The antitumor effect of cabozantinib in the MET-expressing rat C6 glioma cell line was also determined. Cabozantinib inhibited tumor growth ($P < 0.001$) for all doses when compared with vehicle-treated tumors. Moreover, the 3- and 10-mg/kg doses resulted in significant tumor regression (62 and 85%, $P < 0.0001$) when compared with pre-dose tumor weights[33].

On a body weight dosage basis, cabozantinib plasma exposures ranged from 6- to 10-fold higher in rats than in mice, which accounted for lower doses inducing tumor growth inhibition/regression in rats than in mice.

2.2.2 CLINICAL PHARMACOKINETICS

A population pharmacokinetic analysis of cabozantinib (COMETRIQ) was performed using data collected from 289 patients with solid tumors including MTC following oral administration of 140 mg daily doses. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr[32].

Absorption and Distribution:
Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma (≥ 99.7%). A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral cabozantinib dose[32].

Metabolism and Elimination:

Cabozantinib is a substrate of CYP3A4 in vitro. Inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by >80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine[32].

As such, because there is a potential for interaction of cabozantinib 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.

2.2.3 NON-CLINICAL TOXICOLOGY

In an embryo-fetal development study in which pregnant rats were administered daily doses of cabozantinib during organogenesis, increased loss of pregnancy compared to controls was observed at doses as low as 0.03 mg/kg (less than 1% of the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations at doses equal to or greater than 0.01 mg/kg/day (approximately 0.03% of the human exposure by AUC at the recommended dose)[32].

Please refer to investigators brochure for the remainder of the non-clinical toxicology.

2.2.4 CLINICAL EXPERIENCE

The pharmacokinetics, metabolism, safety, and efficacy of cabozantinib have been investigated in multiple phase 1 and phase 2 clinical trials in cancer patients. Two phase I dose escalation trials have defined the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) for continuous doses of cabozantinib as a single agent.

Pivotal phase III trial in medullary thyroid cancer patients has since also been completed.

2.2.5 PHASE I STUDIES

A phase I dose-escalation study of oral cabozantinib was conducted in patients with advanced solid tumors, including patients with medullary thyroid cancer (MTC)[37]. Primary end points included evaluation of safety, pharmacokinetics, and maximum-tolerated dose (MTD) determination. Additional end points included RECIST (Response Evaluation Criteria in Solid Tumors) response, pharmacodynamics, RET mutational status, and biomarker analyses.
Eighty-five patients were enrolled, including 37 with MTC. The MTD was 175 mg daily. Dose-limiting toxicities were grade 3 palmar plantar erythrodysesthesia (PPE), mucositis, and AST, ALT, and lipase elevations and grade 2 mucositis that resulted in dose interruption and reduction. Ten (29%) of 35 patients with MTC with measurable disease had a confirmed partial response. Overall, 18 patients experienced tumor shrinkage of 30% or more, including 17 (49%) of 35 patients with MTC with measurable disease. Additionally, 15 (41%) of 37 patients with MTC had

stable disease (SD) for at least 6 months, resulting in SD for 6 months or longer or confirmed partial response in 68% of patients with MTC.

Cabozantinib was also evaluated in a cohort of heavily pretreated patients with metastatic differentiated thyroid cancer (DTC)[38]. This single-arm open-label phase I trial assessed the safety, tolerability, and antitumor activity of cabozantinib in DTC patients taking part in a drug-drug interaction study. Adult patients with histologically confirmed metastatic or surgically unresectable DTC (including papillary, follicular, or Hürthle cell) were enrolled. Patients received daily oral dosing of 140 mg cabozantinib. Safety was assessed by evaluation of adverse events (AEs), vital signs, electrocardiograms, laboratory tests, and concomitant medications. Tumor response by magnetic resonance imaging or computed tomography scan was investigator assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.0. The study enrolled 15 patients who had failed standard radioactive iodine therapy. Patients had received a median of two prior systemic agents, and 11 patients (73%) had previously received at least one VEGF pathway inhibiting therapy. Common AEs included diarrhea, nausea, fatigue, and decreased appetite. Partial response was reported in eight patients (53%). Median progression-free survival (PFS) and median overall survival (OS) were not reached.

2.2.6 PHASE II STUDIES

Cabozantinib was subsequently evaluated for the activity in patients with castration-resistant prostate cancer (CRPC) in a phase II randomized discontinuation trial with an expansion cohort. Patients received 100 mg of cabozantinib daily. Those with stable disease per RECIST at 12 weeks were randomly assigned to cabozantinib or placebo. Primary end points were objective response rate at 12 weeks and PFS after random assignment[39]. One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 weeks was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) with cabozantinib and 5.9 weeks (95% CI, 5.4 to 6.6 weeks) with placebo (hazard ratio, 0.12; P < .001). Serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen were reduced by ≥ 50% in 57% of evaluable patients. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in narcotic use in 56%. The most common grade 3 adverse events were fatigue (16%), hypertension (12%), and hand-foot syndrome (8%). Cabozantinib was hence shown to have clinical activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and reductions in bone turnover markers, pain, and narcotic use

2.2.7 PHASE III STUDIES

The safety and efficacy of cabozantinib was assessed in an international, multi-center, randomized, double-blind, controlled trial of 330 patients with metastatic medullary thyroid carcinoma (MTC)[40]. Patients were required to have evidence of actively progressive disease within 14 months prior to study entry confirmed by an Independent Radiology Review Committee (IRRC) masked to treatment assignment (89%) or the treating physician (11%). Patients were randomized (2:1) to receive cabozantinib 140 mg (n = 219) or placebo (n = 111) orally once daily, without food, until disease progression determined by the treating physician or until intolerable toxicity. Randomization was stratified by age (≤ 65 years vs. > 65 years) and prior use of a tyrosine kinase inhibitor (TKI) (yes vs. no). No cross-over was allowed at the time of progression. The main efficacy outcome measures of progression-free survival (PFS), objective response (OR),

and response duration were based on IRRC-confirmed events using modified RECIST criteria. Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, 92% had undergone a thyroidectomy, and 48% were reported to be RET mutation positive according to research-use assays. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI. A statistically significant prolongation in PFS was demonstrated among cabozantinib-treated patients compared to those receiving placebo [HR 0.28 (95% CI: 0.19, 0.40); p <0.0001], with median PFS times of 11.2 months and 4.0 months in the cabozantinib and placebo arms, respectively. Partial responses were observed only among patients in the COMETRIQ arm (27% vs. 0; p<0.0001). The median duration of objective responses was 14.7 months (95% CI: 11.1, 19.3) for patients treated with cabozantinib. There was no statistically significant difference in OS between the treatment arms at the planned interim analysis. Toxicities >20% in the cabozantinib treatment arm included diarrhea (63.1% all grade, 15.9% grade ≥ 3), palmar-plantar erythrodysesthesia (hand-foot syndrome; 50% all grade, 12.5% grade ≥ 3), decreased weight (47.7% all grade, 4.7% grade ≥ 3), decreased appetite (45.8% all grade, 4.7% grade ≥ 3), nausea (43% all grade, 1.4% grade ≥ 3), fatigue (40.7% all grade, 9.3% grade ≥ 3), dysgeusia (34.1% all grade, 0.5% grade ≥ 3), hair color changes (33.6% all grade, 0.5% grade ≥ 3), hypertension (32.7% all grade, 8.4% grade ≥ 3), stomatitis (29% all grade, 1.9% grade ≥ 3), constipation (26.6% all grade, 0% grade ≥ 3), hemorrhage (25.2% all grade, 3.3% grade ≥ 3), vomiting (24.3% all grade, 2.3% grade ≥ 3), mucosal inflammation (23.4% all grade, 3.3% grade ≥ 3), asthenia (21% all grade, 5.6% grade ≥ 3), dysphonia (20.1% all grade, 0% grade ≥ 3). Serious adverse events (SAEs) were more frequent in cabozantinib- versus placebo-treated patients (42.1% v 22.9%). SAEs that occurred at a ≥ 2% frequency in cabozantinib- versus placebo-treated patients included mucosal inflammation (2.8% v 0%), hypocalcemia (2.8% v 0%), pulmonary embolism (2.3% v 0%), and hypertension (2.3% v 0%). AEs (not specified in report) were listed as the primary reason for treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients. Most deaths were attributed to disease progression (77% in the cabozantinib arm and 80% in the placebo arm).

More recently, cabozantinib versus Everolimus was compared in advanced renal-cell carcinoma in an open-label phase III event-driven trial (METEOR)[41]. Investigators randomly assigned 658 patients to receive cabozantinib at a dose of 60 mg daily or everolimus at a dose of 10 mg daily. The primary end point was PFS. Secondary efficacy end points were OS and objective response rate (ORR). Median PFS was 7.4 months with cabozantinib and 3.8 months with everolimus. The rate of progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; P<0.001). The ORR was 21% with cabozantinib and 5% with everolimus (P<0.001). Median overall survival was 21·4 months (95% CI 18·7-not estimable) with cabozantinib and 16·5 months (14·7-18·8) with everolimus (hazard ratio [HR] 0·66 [95% CI 0·53-0·83]; p=0·00026). Cabozantinib treatment also resulted in improved progression-free survival (HR 0·51 [95% CI 0·41-0·62]; p<0·0001) and objective response (17% [13-22] with cabozantinib vs 3% [2-6] with everolimus; p<0·0001) per independent radiology review among all randomised patients[84]. AEs were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib and in 25% of those who received everolimus. Discontinuation of study treatment owing to adverse events occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus.

Toxicities >20% in the cabozantinib treatment arm included diarrhea (74% all grade, 11% grade ≥ 3), fatigue (56% all grade, 9% grade ≥ 3), nausea (50% all grade, 4% grade ≥ 3), decreased appetite (46% all grade, 2% grade ≥ 3), palmar-plantar erythrodysesthesia (hand-foot syndrome; 42% all grade, 8% grade ≥ 3), hypertension (37% all grade, 15% grade ≥ 3), vomiting (32% all

grade, 2% grade ≥ 3), decreased weight (31% all grade, 2% grade ≥ 3), constipation (25% all grade, <1% grade ≥ 3), dysgeusia (24% all grade, 0% grade ≥ 3), stomatitis (22% all grade, 2% grade ≥ 3).

The most common adverse events (any grade) leading to dose reductions with cabozantinib were diarrhea (16%), the palmar–plantar erythrodysesthesia syndrome (11%), and fatigue (10%), and the most common with everolimus were pneumonitis (4%), fatigue (3%), and stomatitis (3%). Grade 5 adverse events occurred in 22 patients (7%) in the cabozantinib group and in 25 patients (8%) in the everolimus group and were primarily related to disease progression. Grade 5 events that were considered to be treatment-related occurred in 1 patient in the cabozantinib group (death not otherwise specified) and in 2 patients in the everolimus group (aspergillus infection and aspiration pneumonia).

2.2.8 PHARMACOKINETICS

A population pharmacokinetic analysis of cabozantinib was performed using data collected from 289 patients with solid tumors including MTC following oral administration of 140 mg daily doses. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr[32].

Cabozantinib is a noncompetitive inhibitor of CYP2C8 (Ki_{app} = 4.6 μM), a mixed-type inhibitor of both CYP2C9 (Ki_{app} = 10.4 μM) and CYP2C19 (Ki_{app} = 28.8 μM), and a weak competitive inhibitor of CYP3A4 (estimated Ki_{app} = 282 μM) in human liver microsomal (HLM) preparations. IC_{50} values >20 M were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control β-naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Cabozantinib at steady-state plasma concentrations (100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) in patients with solid tumors.

P-glycoprotein Inhibition: Cabozantinib is an inhibitor (IC_{50} = 7.0 M), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

The safety and effectiveness of cabozantinib in pediatric or geriatric patients aged 65 years and over have not been studied.

Cabozantinib should be used with caution in subjects with mild or moderate hepatic impairment (Child-Pugh class A and B, Appendix I). These subjects will be monitored closely for potential treatment-emergent drug toxicity that may necessitate a dose hold or reduction. If starting dose of Cabozantinib is >40 mg daily in patients with mild to moderate hepatic or renal impairment (Level +1 dose), candidacy for clinical trial will be discussed on a case-to-case basis. Cabozantinib will not be used in patients with severe hepatic impairment (Child-Pugh Class C)[85].

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is no experience with cabozantinib in patients with severe renal impairment.

Detailed preliminary pharmacokinetic data can be found in the most recent Cabozantinib Investigator's Brochure (2012).

2.3 Carfilzomib

2.3.1. 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®). 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[42,43].

2.3.2. 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[44]. Administration to rats at 12 mg/m^2, the severely toxic dose in 10% of animals (STD10), 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 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[44]. 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[45]. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems and appeared to relate to C_{max} 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 achievable 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.

2.4 RATIONALE FOR TARGETING c-MET IN CARFILZOMIB RESISTANT MULTIPLE MYELOMA

Multiple myeloma (MM) is a hematologic malignancy of monoclonal plasma cells and it remains incurable despite rapidly progressive armamentarium of therapeutic agents. Much of the improvement in the median overall survival in patients with MM is owed to incorporation of proteasome inhibitors (PIs)[46] and immunomodulators (IMiDs)[47,48] into the contemporary combination regimens.

Bortezomib is the first PI to gain regulatory approval when it became available as a single agent in the relapsed and/or refractory setting based on data from series of phase I through III trials[19–21], and was subsequently approved as part of front-line therapy with melphalan and prednisone[10]. Despite high remission rates in combination regimens, bortezomib-based therapy faced limitation in both intrinsic and acquired bortezomib resistance[49]. Mutation and overexpression of the proteasome subunit PSMB5 (proteasome subunit β type 5) have been demonstrated to be an important mechanism of bortezomib resistance[50,51]. Other causative factors play a role in development of proteasome resistance including persistent implication of NF-κB signaling pathways in *in vitro* and *in vivo* studies[52], antioxidant signaling in MM patient samples as well as MM cell lines[53,54] as well as bone marrow microenvironment with IGFs (insulin-like growth factors)[55,56] and Btk (Bruton's tyrosine kinase) pathway[57].

A more durable inhibition of the proteasome compared to reversible effect of bortezomib is achieved with second generation proteasome inhibitor Carfilzomib (Kyprolis), which is a peptide epoxy-ketone that binds the N-terminal threonine active site of the β5 subunit of the proteasome in an irreversible manner[58,59]. The efficacy of single-agent carfilzomib in patients with disease refractory to bortezomib and IMiD therapy was established in the PX-171-003-A1 study, a multicenter single-arm phase II trial, with an overall response rate of 24%, and the median duration of response of 7.8 months[60]. In a phase II trial (PX-171-004) of bortezomib naïve patients, the response rate with single-agent carfilzomib was approximately 50%[61]. Importantly, in the process of emergence of PI resistance that is poorly understood, even though carfilzomib shows activity in bortezomib resistant multiple myeloma cell lines and patient samples[62], resistance inevitably emerges to carfilzomib as well.

Given the need to identify mechanisms and develop biomarkers that could help guide the therapy past the point of proteasome resistance, as well as provide novel targets to overcome resistance, our group has made novel observations from studying previously established MM cell lines with bortezomib and carfilzomib resistance. We found that *MUC20 expression* may be a viable biomarker modulating the intrinsic proteasome inhibitor-sensitivity or relative–resistance. MUC20 levels were decreased in MM cell lines resistant to bortezomib or carfilzomib, and differential effect on MM cell viability was demonstrated with either shRNA knockdown or lentiviral over-expression of MUC20 (Figure 1.). Decreased levels of MUC20 lead to higher signaling through the c-MET/ERK-1/2/ELK1/POMP axis, which enhances the proteasome capacity and assembly, resulting in the ELK1-regulated enhancement of the POMP (proteasome maturation protein) expression, which in turn increases the assembly of the entire 20S proteasome, thereby reducing sensitivity to proteasome inhibition by bortezomib or carfilzomib. Crucially, MET inhibitor Cabozantinib was able to increase the sensitivity of PIs both *in vitro* (Figure 2.) and *in vivo* (data not shown), allowing for rescue of PI sensitivity in relapsed refractory MM. To validate the MUC20 as a candidate biomarker in the assessment of MM sensitivity to PI and overall outcome, samples from Millennium and Arkansas database in patients treated with bortezomib in the relapsed and relapsed and refractory settings were analyzed for MUC20 expression levels (Figure 3.). Patients who had higher expression of MUC20 had higher (CR+PR+MR) rate, which resulted in improved

PFS and OS. This analysis ultimately demonstrates that higher expression of MUC20 corresponded to superior OS in the myeloma patients, validating MUC20 as a viable and accurate indicator of not only PI sensitivity but also overall outcome in MM patients.

In the currently proposed study, we aim to treat the patients with RR MM who previously progressed on Carfilzomib-based therapy with an FDA approved c-MET inhibitor Cabozantinib. We hope to be able to rescue the PI by Carfilzomib in these patients, rendering them sensitive to the therapy that has proven to result in improved outcomes in MM patients.

Figure 1.

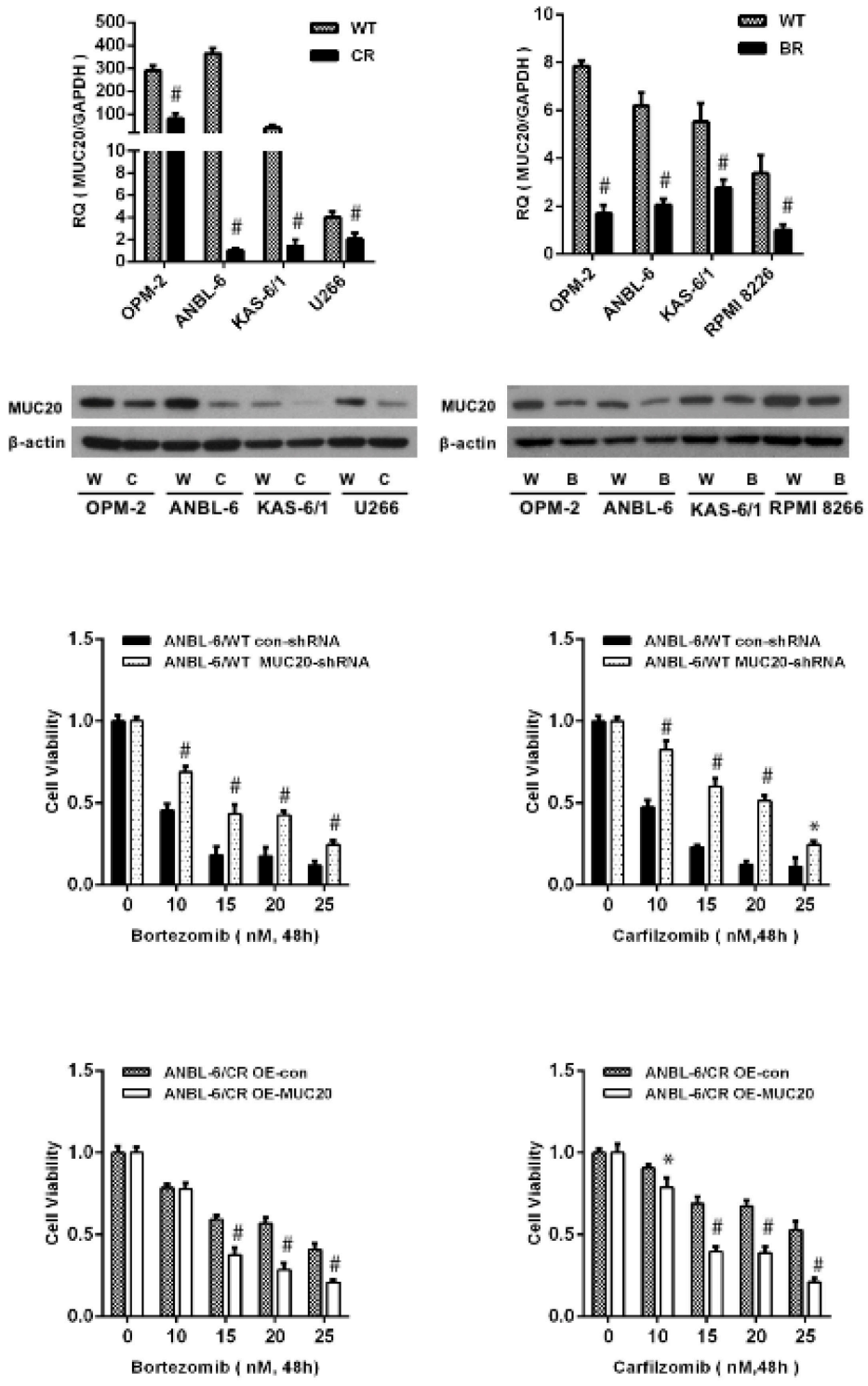


Figure 1. MUC20 expression impacted PI sensitivity in myeloma cell lines.

A. Using qPCR to detect MUC20 mRNA content in CR myeloma cells including OPM-2/CR, ANBL-6/CR, KAS-6/1/CR, U266/CR (left panel) and BR cells including OPM-2/BR, ANBL-6/BR, KAS-6/1/BR and RPMI 8226/BR(right panel) compared with their WT counterparts. Numbers represent relative quantitation (RQ) normalized to GAPDH (# $p < 0.01$ vs. WT).

B. Using Western blot to evaluate MUC20 protein levels in these same cell lines, and compared to β-Actin as a loading control. A representative autoradiograph from one of two independent experiments is shown.

C. ANBL-6/WT myeloma cell which has higher level of MUC20 expression harboring either a control shRNA not targeting a known genomic sequence (con-shRNA), or shRNA suppressing MUC20 (MUC20-shRNA), were exposed to the vehicle, or different concentration of either bortezomib (BTZ)(left panels) or carfilzomib (CFZ)(right panels) for 48 hours. Their viability was evaluated using WST-1 reagent. (* $p < 0.05$, # $p < 0.01$ vs. ANBL-6/WT con-shRNA).

D. ANBL-6/CR myeloma cell which has lower expression of MUC20 were infected with Lentiviral vectors without a cDNA insert (OE-con), or the cDNA for MUC20 (OE-MUC20). The viability to BTZ (left panels) or CFZ (right panels) for 48 hours were detected by WST-1. (* $p < 0.05$, # $p < 0.01$ vs. ANBL-6/CR OE-con).

Figure 2.

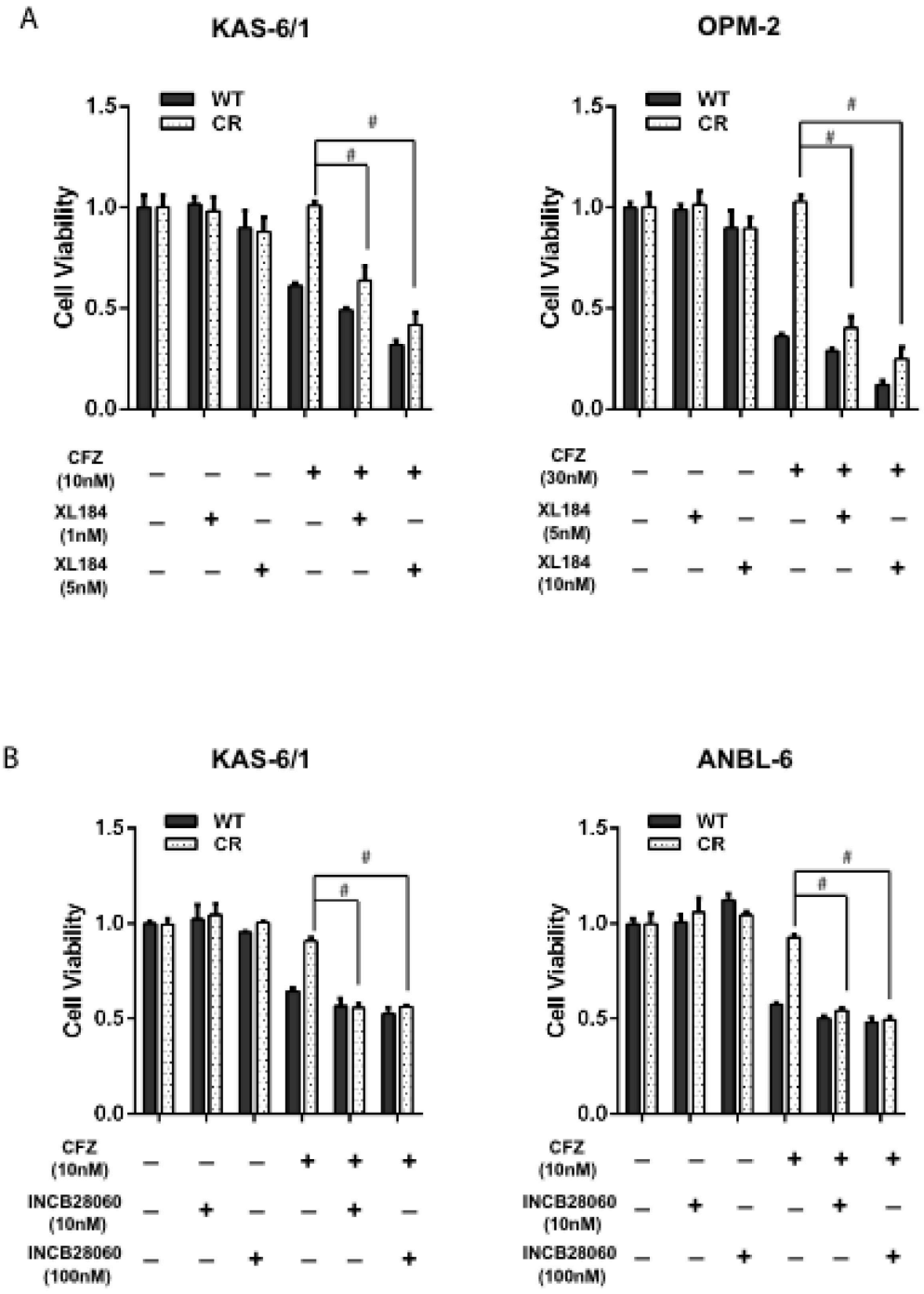
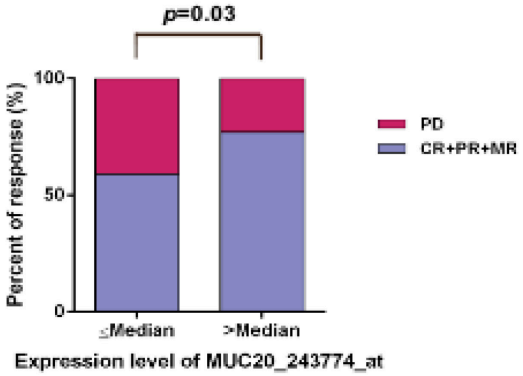


Figure 2. MET signaling pathways may regulate the Pls sensitivity

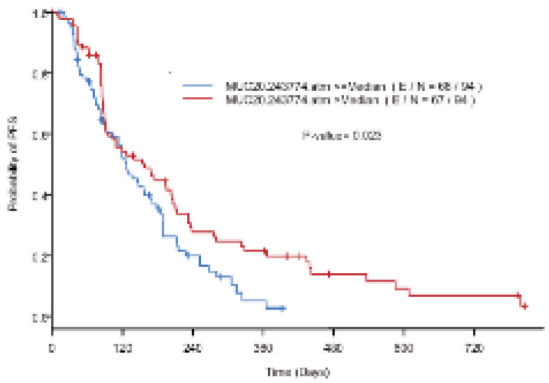
A. Cell viability of KAS-6/1 (left panel) and OPM-2 (right panel) both WT and CR cells to CFZ with or without XL-184 as a c-Met inhibitor for 48h were detected by using WST1. (# $p < 0.05$ vs. CFZ single treatment group).

B. Cell viability of KAS-6/1 (left panel) and ANBL-6 (right panel) both WT and CR cells to CFZ with or without INCB28060 as a c-Met inhibitor for 48h were detected by using WST1. (# $p < 0.05$ vs. CFZ single treatment group).

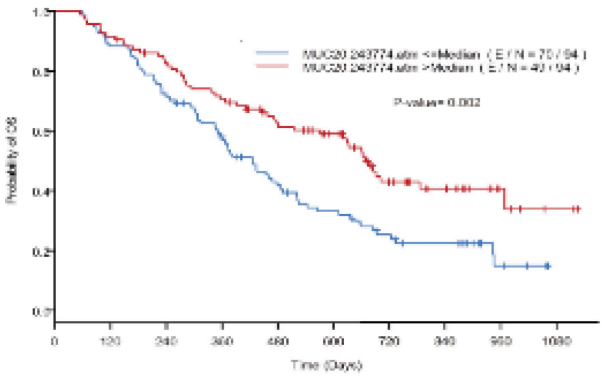
Figure 3.



Bortezomib Treatment



Bortezomib Treatment



Bortezomib Treatment

Figure 3. Influence of MUC20 expression on outcomes of patients treated with bortezomib

A. Response rate of patient

B. The progression-free survival (PFS) for patients with lower MUC20 expression levels (blue curves) or higher expression levels (red curves) were determined from Millennium Pharmaceuticals GEP database . All of the curves were plotted using Kaplan-Meier analyses, and significance was compared with the log rank test.

C. OS of patient analyzed in the same manner, high (red) vs. low (blue) MUC20 expression.

2.5 CORRELATIVE STUDIES BACKGROUND

We have briefly introduced above that POMP has an important role at the later steps of proteasome assembly and maturation. We indeed found the significantly higher expression of POMP protein in both bortezomib and carfilzomib resistant myeloma cells compared to wild to type cell lines. Further activation of c-Met by knock down of MUC20 lead to increasing of POMP and enhanced proteasome CT-L catalytic activity, while inhibition of c-Met signaling with ARQ-197 or over expression of MUC20 lead to the decrease. These data suggest the c-Met signaling regulates POMP expression which in turn affects the proteasome catalytic activity, resulting in PIs resistance. ETS-Like Gene 1 (ELK1) was further identified as a target for ERK-1/2 which binds to the POMP promoter region, regulating its expression. Taken together, our data support a role for signaling through the MUC20/c-MET/ERK-1/2/ELK1/POMP axis in enhancing proteasome assembly and capacity, thereby reducing sensitivity to proteasome inhibitors like carfilzomib or bortezomib in myeloma. Our research also identified a new pathway that involved in PIs resistance and may provide a target for the treatment.

These findings together support our **central clinical hypothesis**, that targeting the MUC20/c-MET/ERK-1/2/ELK1/POMP signaling axis with the c-Met inhibitor cabozantinib will be an active approach for patients with RR MM who have developed PI resistance to carfilzomib. Also, they support our **central correlative hypotheses**, which propose that:

1. The serum and marrow MUC20 levels which will be judged by genomic and flow cytometric studies will directly correlate with primary plasma cell MUC20/c-Met pathway activation and inversely correlate with PI resistance; and

2. A correlation of the gene and MUC20 expression profiles of patients with clinical outcomes may confirm the biomarker MUC20 as a predictor of disease sensitivity to PI, and allow future personalization of c-Met-targeted therapies, as well as combination approaches based on c-Met inhibitors.

3. ELIGIBILITY

3.1 Inclusion Criteria

1. Patients must have been previously diagnosed with histologically or cytologically confirmed symptomatic multiple myeloma, which require the **presence of all three** of the following International Myeloma Working Group criteria, except as noted:

- ❖ Clonal bone marrow plasma cells ≥ 10%
- ❖ A monoclonal protein in either serum or urine
- ❖ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder (to include one of the following)
  - o Hypercalcemia (corrected calcium > 2.75 mmol/L or 11.5 mg/dL); **OR**
  - o Renal insufficiency attributable to myeloma (serum creatinine >1.9 mg/dL); **OR**
  - o Anemia; normochromic, normocytic with a hemoglobin value ≥2 g/dL below the lower limit of normal, or a hemoglobin or <10 g/dL; **OR**
  - o Bone lytic lesions (MRI, CT or PET/CT with > 1 focal lesions ≥5 mm in size), severe osteopenia or pathologic fractures.
- ❖ Patients with a biopsy-proven plasmacytoma and either a serum or urine monoclonal protein will also be considered to have met the diagnostic criteria for multiple myeloma in the absence of clonal marrow plasmacytosis of ≥ 10%.
- ❖ Patient with bone marrow plasma cells of ≥ 60% or serum free light chain ratio of ≥ 100 will also be considered to have met the diagnostic criteria for multiple myeloma.

2. Patients must have measurable disease, as defined by at least one of the following:

- ❖ Serum monoclonal protein level ≥0.5 g/dL for IgG, IgA, or IgM disease
- ❖ Monoclonal protein or total serum IgD ≥0.5 g/dL for IgD disease
- ❖ Urinary M-protein excretion of ≥200 mg over a 24-hour period
- ❖ Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio

3. Patients prior lines of therapy must be separated by the documented disease progression. Using this definition, treatment with induction therapy, followed by high dose chemotherapy and autologous stem cell transplantation, and finally by maintenance therapy, would constitute one line, provided that multiple myeloma did not meet criteria for progression at any time during this period.

4. Patients eligible for this trial will be those who have previously failed carfilzomib at any point either as a single agent, or carfilzomib in combination with dexamethasone, or carfilzomib in combination with dexamethasone and any of the following agents: revlimid, cyclophosphamide, pomalidomide, daratumumab or bendamustine. Given the potential for compounding/worsening toxicities with the addition of cabozantinib to carfilzomib, patients eligible for the trial will have to have had very good tolerance to carfilzomib in the context of described regimens, with resolved prior toxicity to grade 1 or better, and **no toxicities due to carfilzomib that required dose reductions to less than 27 mg/m^2**.

5. Patients must have disease that has relapsed after carfilzomib therapy, with progressive disease (PD) being defined as an increase of 25% from the lowest response value in any one or more of the following:

- ❖ Serum M-component (the absolute increase must be ≥0.5 g/dL) **and/or**
- ❖ Urine M-component (the absolute increase must be ≥200 mg/24 hours) **and/or**

- Only in patients without a measurable serum and urine M protein level: the difference between involved and uninvolved FLC levels (absolute increase) must be >10 mg/dL
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Patients with relapsed disease will be considered to be those who have had progression, as defined above, off of any therapy, and who completed their therapy more than 60 days prior to the finding of progression. Patients with relapsed and refractory disease will be considered to be those who have had progression, as defined above, while still on their last line of therapy, or who progressed within 60 days of finishing their most recent therapy.

6. Patients must have completed their most recent drug therapy directed at multiple myeloma in the following timeframes:
- Chemotherapy, biological therapy, immunotherapy, monoclonal antibody or an investigational therapy at least 3 weeks prior to starting cabozantinib
- Corticosteroids at least 3 weeks prior to starting cabozantinib, except for a dose equivalent to dexamethasone of ≤4 mg/day
- Nitrosoureas, nitrogen mustards, mitomycin C, at least 6 weeks prior to starting cabozantinib
- Autologous stem cell transplantation or autologous chimeric antigen receptor (CAR) T cell therapy at least 12 weeks prior to starting cabozantinib
- Allogeneic stem cell transplantation or allogeneic CAR T cell at least 24 weeks prior to starting cabozantinib, and these patients must also not have moderate to severe active acute or chronic graft versus host disease

7. Patients must be age 19 or older (state of Nebraska), because no dosing or adverse event data are currently available on the use of cabozantinib in patients <19 years of age.

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; please see Appendix E)

9. Patients must have evidence of adequate bone marrow reserves, as defined by the following:
- Absolute neutrophil count (ANC) ≥1,000 cells/mm^3 without growth factors within 1 week of the initiation of treatment
- Total white blood cell count (WBC) ≥2,000 cells/mm^3 without growth factors within 1 week of the initiation of treatment
- Hemoglobin ≥8 g/dL without red blood cell transfusions within 2 weeks of the initiation of treatment
- Platelet counts of ≥100,000 cells/mm^3 for patients who have bone marrow plasmacytosis of <50%, or platelets ≥50,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥50%

10. Patients must have evidence of adequate hepatic function, as defined by the following:
- Total bilirubin ≤1.5 times the upper limit of the institutional normal values
- Total AST (SGOT) and ALT (SGPT) ≤2.5 times the upper limit of the institutional normal values

11. Patients must have evidence of adequate renal function, as defined by the following:
- Serum creatinine within the institutional normal limits, **OR** if the creatinine is elevated

- Creatinine clearance (CrCl) ≥30 mL/min., as measured by a 24-hour urine collection, or estimated by the Cockcroft and Gault formula:
  Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}} \times 0.85$
  Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}} \times 1.00$

  Worsening urinary paraproteinemia will be considered in the context of IMWG disease response criteria on a monthly basis. Any patient with urinary protein (otherwise unrelated to urinary myeloma associated M-protein) with excretion > 3.5 g/day will be considered to have developed nephrotic-range proteinuria, and will be taken off study.

12. Patients must have evidence of adequate cardiac function, as defined by the following:
- Absence of New York Heart Association (NYHA) class II, III, or IV congestive heart failure (please see Appendix F for the NYHA classification system)
- Absence of uncontrolled angina or hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment
- Absence of the following in the previous 6 months:
  - myocardial infarction;
  - unstable angina pectoris;
  - clinically-significant cardiac arrhythmias;
  - stroke (including transient ischemic attack (TIA), or other ischemic event);
  - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (eg, vena cava filter) are not eligible for this study)
- Absence of clinically significant bradycardia, or other uncontrolled cardiac arrhythmia defined as grade 3 or 4 according to National Cancer Institute (NCI) Common Terminology
- Absence of history of congenital long QT syndrome

13. Patients who have received radiation therapy must have completed this at **least 4 weeks** prior to starting therapy with cabozantinib, with the following exceptions:
- Local radiation therapy to enhance bone healing of a pathologic fracture may have been performed, as long as it was completed at least 2 weeks prior to starting cabozantinib
- Local radiation therapy to treat post-fracture pain that is refractory to analgesics may have been performed, as long as it was completed at least 2 weeks prior to starting cabozantinib

14. Patients who have undergone any recent major surgery must have done so **at least 4 weeks** prior to starting therapy with cabozantinib, with the following exceptions:
- Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to starting cabozantinib
- Planned elective surgery unrelated to the patient's diagnosis of multiple myeloma, such as hernia repair, may be allowed, at the discretion of the principle investigator, as long as it was performed at least 2 weeks prior to starting cabozantinib, and patients have recovered fully from this procedure

15. HIV seropositive patients with acceptable organ function who meet the patient selection criteria, and who are not on combination antiretroviral therapy, and whose absolute $CD4^+$ count is ≥400 cells per cubic millimeter of blood, will be eligible. However, HIV positive patients on combination antiretroviral therapy will be ineligible, because of the potential for pharmacokinetic interactions with cabozantinib.

16. Screen subjects prior to treatment whose baseline hepatitis B serologic status is unknown. Subjects, who are chronic carriers of hepatitis B virus, please screen with hepatitis B DNA to exclude active viral replication and monitor hepatitis B DNA at regular intervals while on study.

17. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s). **Male subjects must agree to not donate sperm for at least 90 days after the last dose of Carfilzomib**.

18. Female subjects of childbearing potential must not be pregnant at screening. Female patients must be either postmenopausal, free from menses for ≥2 years, surgically sterilized, or willing to use two adequate barrier methods of contraception to prevent pregnancy, or must agree to abstain from heterosexual activity throughout the study. Female patients of childbearing potential must have a negative serum (βHCG) or urine pregnancy test before receiving the first dose of cabozantinib or carfilzomib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Women of reproductive potential will be counseled to use effective contraceptive measures to prevent pregnancy during treatment with either cabozantinib or carfilzomib. Patients shall be advised not to take cabozantinib or carfilzomib treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, she will be advised to discuss the appropriate timing with her physician.

19. Understand and able to willingly provide voluntary written informed consent, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

3.2 EXCLUSION CRITERIA

1. Patients who are receiving any concurrent investigational agent with known or suspected activity against multiple myeloma, or those whose adverse events due to agents administered more than 4 weeks earlier have not recovered to a severity of grade 0 or grade 1.

2. Patients who have known central nervous system involvement with multiple myeloma will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3. Patients who have previously been treated with another agent targeting the *MUC20*/c-Met axis, including either monoclonal antibodies to *MUC20* or c-Met, or small molecule inhibitors of c-Met.

4. Patients with a known history of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib.

5. Cabozantinib is metabolized by CYP3A4. The metabolism and consequently overall pharmacokinetics of cabozantinib could be altered by inhibitors and/or inducers or other substrates of CYP3A4. It is recommended that chronic concomitant treatment with strong

CYP3A4 inhibitors (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) or inducers should be avoided because it may significantly decrease cabozantinib concentrations. If patients are taking any strong CYP3A4 inhibitors, alternate medications with no or minimal CYP3A4 inhibitors should be sought prior to trial enrolment. While mild inhibitors/inducers of these cytochrome P450 isoenzymes are not specifically excluded, investigators should be aware that cabozantinib exposure may be altered by the concomitant administration of these drugs, and avoidance is also recommended. Lists including medications and substances known or with the potential to interact with CYP3A4 are provided in Appendix G.

6. Uncontrolled or ongoing/active infection. Due to side effect profile of cabozantinib, patients with the following history will also not be eligible for the trial: patients with a recent history of hemorrhage or hemoptysis; patients with dehiscence or wound healing complications requiring medical intervention; patients with severe hypertension that cannot be controlled (blood pressure of > 150 systolic or > 100 diastolic mmHg) with anti-hypertensive therapy within 7 days of first dose of therapy.

7. Pregnant or lactating women are excluded from this study because cabozantinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib, breastfeeding should be discontinued if the mother is treated with cabozantinib.

8. Patients with non-secretory multiple myeloma, active plasma cell leukemia, defined as either having 20% of peripheral white blood cells comprised of $CD138^{+}$ plasma cells, or an absolute plasma cell count of 2×10^{9}/L, known amyloidosis, or known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

9. Patients who have required plasmapheresis and exchange less than 2 weeks prior to initiation of therapy with cabozantinib

10. Patients with known moderate or severe hepatic impairment, active hepatitis A, B, and/or C infection, due to the difficulty that would be faced in assessing the attribution of any events of hepatic toxicity while on cabozantinib therapy.

11. Patients with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for >5 years, and are considered by their physician to be at less than 30% risk of relapse. In addition, patients with basal cell carcinoma of the skin, superficial carcinoma of the bladder, carcinoma of the prostate with a current PSA value of <0.5 ng/mL, or cervical intraepithelial neoplasia will be eligible. Finally, patients who are on hormonal therapy for a history of either prostate cancer or breast cancer may enroll, if there has been no evidence of disease progression during the previous three years.

12. Allergy to carfilzomib or cabozantinib or any excipients

13. Uncontrolled intercurrent illness including medical, psychiatric, cognitive or other conditions, psychiatric illness/social situations that would compromise the patient's ability to understand the patient information, to give informed consent, to comply with the study protocol or to complete the

study or, in the judgment of the Principal Investigator, would make the patient inappropriate for study participation.

14. The subject has experienced any of the following:
    - ❖ clinically-significant GI bleeding within 6 months before the first dose of study treatment;
    - ❖ GI disorders particularly those associated with a high risk of perforation or fistula formation including:
        - o Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction
        - o Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization,

      Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization
    - ❖ hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment;
    - ❖ any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment.
    - ❖ Patient who have developed or have had history of pulmonary hemorrhage while on carfilzomib will be excluded (fatal pulmonary hemorrhage has been observed with carfilzomib).

15. The subject has radiographic evidence of cavitating pulmonary lesion(s);

16. The subject has tumor invading or encasing any major blood vessels;

17. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib;

18. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment *Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility*.

19. Inability to swallow intact tablets

20. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment;

21. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel);

Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted if started > 6 months prior to randomization. LMWH used as therapeutic anticoagulation may increase observed PTT levels in subjects. Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least

24 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.

22. Subjects who have Carfilzomib-related posterior reversible encephalopathy syndrome (PRES) and thrombotic microangiopathy (TMA) should not be challenged with Carfilzomib.

3.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial. Accrual targets for men and women, as well as for various ethnic categories, are up to 32 subjects to obtain 17 evaluable subjects.

4. REGISTRATION PROCEDURES

4.1 Recruitment

Subjects who are referred to the Nebraska Medical Center (NMC) / UNMC, or other IRB approved participating sites (MD Anderson), with relapsed and refractory (RR) multiple myeloma (MM) who have lost response to carfilzomib may be eligible for this study.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of encounter. On initial presentation assessment of ECOG performance Status will be completed.

After offering consent, the patient's primary Oncologist will make the decision as to screened eligibility of the candidate based on the eligibility criteria listed above. If the patient is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the patient after thorough review of the study is completed by the physician and his/her designee.

Some insurance carrier's may decline to cover the costs of usual medical care if the patient is participating in a clinical trial. The patient will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The patient can then decide if they wish to participate.

4.2 Eligibility Verification/Registration:

Before patients are registered to the study, an eligibility checklist (Appendix A) must be completed to verify the subject meets the eligibility criteria. Informed consent must be obtained by following procedures defined in section 12.6 entitled Process of Informed Consent.

Subjects will be registered through the sponsor PI by contacting the UNMC Fred & Pamela Buffett Cancer Center Research Project Coordinator.

All Study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC Research Project Coordinator if a patient appears to meet the eligibility criteria. They will email or fax the completed eligibility checklist (Appendix A). The Eligibility Check list will be

maintained in a study file. If the UNMC Multi-site Project Manager confirms that the subject meets criteria and target accrual has not been met, approval for the subject will be given. A confirmation of Registration will be forwarded by the UNMC Multi-site Project Manager.

In the event of an after-hours potential enrollment (i.e., clinic coast time differences), or an immediate need-to-treat based on potential subject condition, registration can be accomplished by contacting the sponsor PI Dr. Muhamed Baljevic, MD directly by email: muhamed.baljevic@unmc.edu (response required) or by phone/pager 402-559-4000 or 402-888-0345. Additionally, the UNMC Research Project Coordinator must be notified in or to meet UNMC Protocol Review Monitoring System (PRMS) reporting requirements.

Participating/Collaborating Sites:
Participating/Collaborating sites must have both local *and* UNMC IRB approval, and have met all other UNMC criteria to enroll. Study personnel from non-UNMC IRB approved sites will provide the UNMC Multi-site Project Manager with the following information:

- Demographics fax/scan cover sheet (located in the Study Manual)
- Copy of the signed and dated consent form (subject signature obliterated with signature line and subject initials visible)
- Signed Eligibility Checklist

Registration Date: eligibility verification and notification of assigned subject number (by UNMC) will be known as the Registration date.

Date of enrollment: is defined as the date of the start of study treatment / first protocol related intervention.

The listed documents/ information for subjects enrolled will be provided to the PRMS office within one (1) week of enrollment as applicable:

- UNMC and Participating Site Protocol Numbers
- Investigator/Participating Site Identifier (ID)
- Subject ID: Assigned by UNMC [Site ID followed by subject number (##-###)]
- Consent Date: Date subject signed consent
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity
- Re-consent Date: (If applicable)
- Ineligibility Status: (If known)
- Off Study Date: (If applicable)

4.3 Pathology Requirements

Pathology material will be reviewed, and the diagnosis confirmed by each site's Pathology department as outlined in protocol.

Additional bone marrow aspirate pathology material is required to be captured at screening and after cycle 2 for correlative studies. See Section 5.8 for details of the required samples.

4.4 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a subject does not receive any assigned protocol treatment after consenting, baseline and

follow-up data will still need to be collected and submitted according to the instructions in the protocol. The reason he/she did not receive any treatment and the date and type of the first non-protocol treatment that the subject receives must also be reported.

4.5 Requirements for Submitting Regulatory Documents UNMC and Participating Institutions:

Before an institution may enroll patients, all site activation criteria must be met by submitting required protocol specific regulatory documents to the study project manager at UNMC Fred & Pamela Buffett Cancer Center.

4.6 Required Protocol Specific Regulatory Documents

1. Confirmation that the UNMC Team Designee(s) conducted an initial site teleconference prior to opening a protocol to accrual at the participating site.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. Copy of each participating/collaborating site's IRB Approval Letter and current IRB Roster, Federal Wide Assurance (FWA) Number or IRB Statement of Compliance.

NOTE: The above submissions must include the following details:
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

5. TREATMENT PLAN

5.1 AGENT ADMINISTRATION

The recommended starting daily dose of cabozantinib is 20 mg (one 20-mg capsules). It will not be administered with food. Patients will be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Capsules will be swallowed as whole and will not be opened. Patients will be instructed to not take a missed dose within 12 hours of the next dose. cabozantinib will not be ingested with grapefruit, grapefruit juice or nutritional supplements that are known to inhibit cytochrome P45.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 9. Appropriate dose modifications are described in Section 5.7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

To assess compliance with treatment, all patients will be requested to maintain a medication diary of each dose of medication. This medication diary will be returned to the research staff at the end of each cycle of therapy. A sample patient study medication diary is provided in Appendix H.

5.1.1 Cabozantinib

Cabozantinib tablets should be administered by mouth (PO) daily (one 20-mg capsules for the initial testing dose). Tablets should be taken with water and swallowed whole, and missed or vomited dose should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time. Patients will receive cabozantinib daily continuously during entire 28-day treatment cycle (Days 1-28 on therapy).

Refer to Section 8.2.4 for further details on administrations of other study drugs, carfilzomib and dexamethasone.

5.2 PATIENT ASSESSMENTS

5.2.1 SCREENING

The screening period for the following assessments will be considered to be any time **within** the **twenty eight days prior to day 1** of study-directed treatment:

- A comprehensive history, including a description of prior anti-neoplastic treatment regimens, and current use of supportive therapies as well as concomitant medications
- A comprehensive physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature) along with height and weight
- ECOG performance status determination
  12-lead electrocardiogram *Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.*
- Echocardiogram (TTE)
- Postero-anterior and lateral chest radiography
- Myeloma skeletal/bony survey to document lytic disease
- Computed tomography or magnetic resonance to evaluate the size and location of plasmacytomas, if clinically indicated by standard of care(SOC)
- Samples for clinical laboratory evaluations as follows:
  - Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, platelet count)
  - $CD4^+$ cell count in patients with known HIV-seropositivity
  - Hepatitis B serology status, if unknown
  - Serum chemistry (creatinine, blood urea nitrogen (BUN), uric acid, total bilirubin, aspartate aminotransferase (AST (SGOT)), alanine aminotransferase (ALT (SGPT)), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)
  - Serum β-HCG or urine pregnancy test for women of child-bearing potential
  - Coagulation parameters, including prothrombin time (PT) and activated partial thromboplastin time (aPTT)
  - Serum β-2-microglobulin

- ❖ Evaluation of serum and/or urine parameters of measurable disease, including serum protein electrophoresis with immunofixation, quantitative immunoglobulins, serum free κ and λ light chain concentrations as well as the κ/λ ratio, and a 24-hour urine collection for total volume with total protein and electrophoresis with immunofixation for Bence Jones proteinuria
- ❖ Bone marrow aspiration and biopsy, with samples obtained for hematopathology review, flow cytometry, cytogenetic studies by routine karyotyping and fluorescence *in situ* hybridization (FISH; including probes for del 13q14, t(4,14), t(14,16), t(14,20) and del 17p), and correlative studies.
- ❖ Serum sample for evaluation of baseline *MUC20* level
- ❖ An oral examination will be performed prior to initiation of cabozantinib and periodically during therapy, and patients advised regarding good oral hygiene practices.
    - o Note: the oral examination can be completed as part of an ENT referral visit

5.2.2 CYCLE 1 ASSESSMENTS

Prior to initiation of any study-directed therapy, the following assessments will be performed **within three days of day 1 of cycle 1** to confirm the patient's eligibility:

- ❖ Samples for clinical laboratory evaluations as follows:
    - o Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)
    - o Serum chemistry (creatinine, BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)
    - o Serum β-HCG or urine pregnancy test for women of child-bearing potential
    - o PT and aPTT
- ❖ Evaluation of serum and/or urine parameters of measurable disease, including serum protein electrophoresis with immunofixation, quantitative immunoglobulins, serum free κ and λ light chain concentrations as well as the κ/λ ratio, and a 24-hour urine collection for total volume with total protein and electrophoresis with immunofixation for Bence Jones proteinuria. Please note that these tests should not be repeated if they were performed within fourteen days during the screening period.
- ❖ Urine protein should be monitored regularly during treatment and treatment discontinued in patients who develop nephrotic syndrome.

In addition, prior to initiation of any study-directed therapy, the following assessments will be performed on **day 1 of cycle 1** to confirm the patient's eligibility:

- ❖ An abbreviated interval medical history, including a description of current supportive therapies as well as concomitant medications
- ❖ An abbreviated, symptom-directed physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature) along with weight
- ❖ Any additional studies that the physician, physician assistant, nurse practitioner, or research nurse feels are medically appropriate
- ❖ ECOG performance status determination
- ❖ Electrocardiography (ECG) will be performed
- ❖ Measurement of symptom burden using the MDASI-MM tool (Appendix B)

- ❖ Determination of the quality of life using the QLQ-C30 (Appendix C) and QLQ - MY20 (please see Appendix D) tools
- ❖ The patient will be provided with a study medication diary for cycle 1 that will allow them to document compliance with the treatment schedule (please see Appendix H for a sample patient study medication diary)

Once cabozantinib has been initiated in **cycle 1**, the patient will return on **days 8 and 22 (± 3 day)** for the following assessments:

- ❖ Samples for clinical laboratory evaluations as follows:
  - o Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)

Once cabozantinib has been initiated in **cycle 1**, the patient will return on **day 15 (± 3 days)** for the following assessments:

- ❖ An abbreviated interval medical history, including a description of current supportive therapies as well as concomitant medications, and an evaluation of any possible toxicities due to therapy and their severity
- ❖ An abbreviated, symptom-directed physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature)
- ❖ Any additional studies that the physician, physician assistant, nurse practitioner, or research nurse feels are medically appropriate
- ❖ ECOG performance status determination
- ❖ Measurement of symptom burden using the MDASI-MM tool
- ❖ Samples for clinical laboratory evaluations as follows:
  - o Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)
  - o Serum chemistry (creatinine, BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)

5.2.3 CYCLE 2 ASSESSMENTS

Prior to continuing further therapy with cabozantinib in cycle 2, the following assessments will be performed **within three days of day 1 of the cycle**:

- ❖ Samples for clinical laboratory evaluations as follows:
  - o Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)
  - o Serum chemistry (creatinine, BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)
  - o Serum β-HCG or urine pregnancy test for women of child-bearing potential

- ❖ Any additional studies that the physician, physician assistant, nurse practitioner, or research nurse feels are medically appropriate
- ❖ Evaluation of serum and/or urine parameters of measurable disease, including serum protein electrophoresis with immunofixation, quantitative immunoglobulins, serum free κ and λ light chain concentrations as well as the κ/λ ratio, and a 24-hour urine collection for total volume with total protein and electrophoresis with immunofixation for Bence Jones proteinuria. Please note that these data will be collected after cycle 1 to evaluate the kinetics of any responses to cabozantinib, but patients will be treated for a total of two full

cycles before a formal assessment of disease response is made. Subsequent disease response assessments will be made with every cycle (i.e. after cycle 3, 4, 5, etc.).

In addition, prior to continuation of any study-directed therapy, the following assessments will be performed on **day 1 of each cycle**:

- An abbreviated interval medical history, including a description of current supportive therapies as well as concomitant medications, and an evaluation of any possible toxicities due to therapy and their severity
- An abbreviated, symptom-directed physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature) along with weight
- ECOG performance status determination
- Electrocardiography (ECG) will be performed in patients to monitor QTcF
- Measurement of symptom burden using the MDASI-MM tool
- Determination of the quality of life using the QLQ-C30 and QLQ – MY20 tools
- Collection of the study medication diary for the previous cycle of therapy from the patient to document treatment compliance

In addition, the following assessments will be performed on **day 15 of each cycle (± 3 days):**

- Measurement of symptom burden using the MDASI-MM tool (Appendix B)

5.2.4 ASSESSMENTS DURING TREATMENT CYCLE 3 AND LATER

Prior to continuing further therapy with cabozantinib in cycle 3, and in all subsequent cycles of therapy, the following assessments will be performed **within three days of day 1 of the cycle**:

- Samples for clinical laboratory evaluations as follows:
  - Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)
  - Serum chemistry (creatinine, BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)
  - Serum β-HCG or urine pregnancy test for women of child-bearing potential

- Serum sample for evaluation of MUC20 level (prior to start of cycle 3 only)
- Any additional studies that the physician, physician assistant, nurse practitioner, or research nurse feels are medically appropriate
- Evaluation of serum and/or urine parameters of measurable disease, including serum protein electrophoresis with immunofixation, quantitative immunoglobulins, serum free κ and λ light chain concentrations as well as the κ/λ ratio, and a 24-hour urine collection for total volume with total protein and electrophoresis with immunofixation for Bence Jones proteinuria. Please note that these data will be collected after cycle 1 to evaluate the kinetics of any responses to cabozantinib, but patients will be treated for a total of two full cycles before a formal assessment of disease response is made. Subsequent disease response assessments will be made with every cycle (i.e. after cycle 3, 4, 5, etc.).
- Bone marrow aspiration and biopsy **will be performed** to confirm a possible complete remission, with samples obtained for hematopathology review, flow cytometry, cytogenetic studies by routine karyotyping and FISH, including probes for del 13q14, t(4,14), t(14,16), and del 17p, and correlative studies (performed once only at cycle 3).

In addition, prior to continuation of any study-directed therapy, the following assessments will be performed on **day 1 of each cycle**:

- An evaluation of disease response to determine eligibility to continue therapy will be performed after the first two cycles, and then every cycle after that. Patients with evidence of disease progression after cycle 2 or later, which is confirmed according to the Uniform criteria, will be removed from the study at the time of confirmation of disease progression is obtained.
- An abbreviated interval medical history, including a description of current supportive therapies as well as concomitant medications, and an evaluation of any possible toxicities due to therapy and their severity
- An abbreviated, symptom-directed physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature) along with weight
- ECOG performance status determination
- Electrocardiography (ECG) will be performed every 12 weeks
- Measurement of symptom burden using the MDASI-MM tool
- Determination of the quality of life using the QLQ-C30 and QLQ – MY20 tools
- Collection of the study medication diary for the previous cycle of therapy from the patient to document treatment compliance

In addition, the following assessments will be performed on **day 15 of each cycle (± 3 days):**

- Measurement of symptom burden using the MDASI-MM tool

5.2.5 END OF STUDY ASSESSMENT

Patients who will be discontinuing therapy with cabozantinib due to any of the circumstances detailed in Section 5.4 will have an end-of-study assessment. This will occur **within thirty days of discontinuing therapy**, and will include:

- An comprehensive interval medical history, including a description of current supportive therapies as well as concomitant medications, and an evaluation of any possible remaining toxicities due to therapy and their severity
- An comprehensive physical examination including vital sign measurements (systolic and diastolic blood pressure, respiratory rate, pulse, temperature) along with weight
- ECOG performance status determination
- 12-lead ECG
- Measurement of symptom burden using the MDASI-MM tool
- Determination of the quality of life using the QLQ-C30 and QLQ-MY20 tools
- Samples for clinical laboratory evaluations as follows:
    - Hematology (white blood cell count with automated differential, hemoglobin, hematocrit, red blood cell count, platelet count)
    - Serum chemistry (creatinine, BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate, magnesium, glucose, calcium, phosphorous, total protein and albumin)
    - Serum β-HCG or urine pregnancy test for women of child-bearing potential
- Any additional studies that the physician, physician assistant, nurse practitioner, or research nurse feels are medically appropriate
- Evaluation of serum and/or urine parameters of measurable disease, including serum protein electrophoresis with immunofixation, quantitative immunoglobulins, serum free κ

and λ light chain concentrations as well as the κ/λ ratio, and a 24-hour urine collection for total volume with total protein and electrophoresis with immunofixation for Bence Jones proteinuria

5.2.6 DATA COLLECTED AFTER THE END OF STUDY ASSESSMENT

To evaluate the impact of therapy with cabozantinib and carfilzomib for RR MM on the ability to harvest stem cells in any patients who go on to undergo subsequent stem cell mobilization, pilot data will be collected about the mobilization regimen used, the number of stem cells collected, and the number of days of apheresis necessary. In addition, in those patients who proceed to stem cell transplantation, data will be collected about the kinetics of stem cell engraftment, including the number of days to neutrophil and platelet recovery.

5.3 CONCOMITANT MEDICATION

5.3.1 Anticancer Therapy

Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (eg, palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

5.3.2 Other Medications

All concomitant medications used by the subject (including prescription and over-the-counter medications, transfusions, vitamins, herbal remedies, and nutritional supplements) during the period from 28 days before the first dose of study treatment through 30 days after the date of the last dose of study treatment are to be recorded in the case report forms.

5.3.3 PERMITTED CONCOMITANT MEDICATIONS

Standard Therapies

Standard therapies for concurrent medical conditions are allowed, except for the use of corticosteroids beyond the limits allowed in the inclusion and exclusion criteria (Sections 3.1 and 3.2). Transfusions, hormone replacement, and short term higher doses of corticosteroids should be utilized as indicated by standard clinical practice

Erythropoiesis Stimulating Agents (ESA)

Please follow ASCO or MEDICARE guidelines for the use of ESA in patients diagnosed with cancer, drug labels and the Food and Drug Administration (FDA) alerts dated March 9, 2007; November 8, 2007; March 12, 2008; July 31, 2008; and December 2, 2008.

Hematopoietic growth factors

Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, American Society of Clinical Oncology [ASCO] or [European Society for Medical Oncology] ESMO guidelines)

Antiemetics and Antidiarrheal

Prophylactic and supportive antiemetics and antidiarrheal medications may be administered according to standard clinical practice if clinically indicated.

Bisphosphonates

Drugs used to control bone loss (eg, bisphosphonates and denosumab) are allowed if started before screening activities but may not be initiated or exchanged during the course of the study and require Sponsor approval.

Thromboembolism Prophylaxis:
Because cabozantinib treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in cabozantinib-treated and placebo-treated patients, respectively), patients will be on prophylactic dose of Aspirin while on therapy (**ASA 81-325 mg PO daily**). If patients are on a greater dose of Aspirin for other medical reasons, that dose of Aspirin will be continued.

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

    - *Low dose heparins for prophylactic use* are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* at the time of first dose are allowed if the subject has no evidence of brain metastasis, has been on a stable dose of LMWH for at least 12 weeks, and has had no complications from a thromboembolic event or the anticoagulation regimen.

    - *Therapeutic doses of low molecular weight heparins (LMWH)* after first dose are allowed if clinically indicated (eg, for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 5.7

    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction);

For restrictions on oral anticoagulants see Section 5.3.4.

Gastric pH modifying agents

Administration of the PPI esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers (Study XL184-018). Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib. Cimetidine should be avoided due to potential CYP interactions

5.3.4 CONCOMITANT MEDICATIONS TO AVOID IF POSSIBLE

The following therapies *should be avoided* if possible, while the subject is on study:

- Palliative external radiation to bone metastasis for bone pain should not be performed while on study. Subjects who have such an intervention may be considered not evaluable (and may be assigned a censoring or progression date) for certain efficacy endpoints;

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended;

- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, because this could significantly increase the exposure to cabozantinib;

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations and should be avoided. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 5.3.5.

5.3.5 Potential for Drug Interactions

Cytochrome P450 (CYP): Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma drug concentration time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in

the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

In addition, cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib.

Please refer to Section 8.1.5 of the protocol for more information.

5.4 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue without a limitation on the number of cycles, unless one of the following criteria applies:

- Disease progression after two cycles or later of therapy
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient becomes pregnant
- Patient loses the ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical illness
- Patient achieves complete remission (CR), and the patient and investigator feel that discontinuation of cabozantinib is in the patient’s best interests, or
- Patient achieves a level of response that qualifies him or her for another therapy for which they provide consent, such as high dose therapy with autologous stem cell transplantation.

5.5 DURATION OF FOLLOW-UP

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.7. DOSING DELAYS / DOSE MODIFICATIONS

In Phase I of this study we will determine the MTD among three doses. DLTs will be based solely on adverse events that occur during cycle 1. The definition of DLT includes:

a. Any non-hematological toxicity Grade ≥ 3, except for alopecia and nausea uncontrolled by medical management.

b. Grade 4 neutropenia lasting more than 5 days.

c. Febrile neutropenia of any duration (ANC <1.0 x 109/L fever ≥ 38.5°C)

d. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion

e. Grade 4 anemia, unexplained by underlying disease.

We will study three dose levels using the 3+3 algorithm, so that we will accrue a minimum of 3 patients and a maximum of 18 patients in Phase I. The initial dose of cabozantinib for all patients treated on this study will be 20 mg P.O. daily, which is designated dose level -1. In the event that dose modifications are needed for toxicities, the following additional dose levels will be used:

Dose Level	Cabozantinib Dose
-1	20 mg p.o., daily
0	40 mg p.o., daily
+1	60 mg p.o., daily

To allow for optimal experimental design, capped dose of carfilzomib of 27 mg/m^2 will be used in the study without dose escalations or de-escalations. Given the potential for compounding/worsening toxicities with the addition of cabozantinib to carfilzomib, patients eligible for the trial will have to have had very good tolerance to carfilzomib in the context of treatment regimens they were receiving, with resolved prior carfilzomib toxicities to grade 1 or better, and no toxicities due to carfilzomib that required dose reductions to less than 27 mg/m^2 as dose adjustments will be allowed in the carbozantinib only. Stopping of carfilzomib however will be allowed if the adverse events secondary to carfilzomib that require its stopping are observed/met.

Specific dose modifications guidelines will be followed for the adverse events nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia, and are detailed below. If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Event Name	Diarrhea
Grade of Event	**Management/Next Dose for Cabozantinib**
≤Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1. Resume at same dose level.
Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: Loperamide anti-diarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Event Name	Vomiting
Grade of Event	**Management/Next Dose for Cabozantinib**
≤Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1. Resume at same dose level.
Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > one dose reductions should go off protocol therapy.	
Recommended management: Antiemetics.	

Event Name	Nausea
Grade of Event	**Management/Next Dose for Cabozantinib**
≤Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1. Resume at same dose level.
Grade 3	Hold* until <Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > one dose reductions should go off protocol therapy.	
Recommended management: Antiemetics.	

5.7.1 PRECAUTIONS, WARNINGS, AND OTHER SUPPORTIVE CARE GUIDELINES

Gastrointestinal Disorders

The most common non-hepatobiliary GI AEs reported in clinical studies with cabozantinib regardless of causality are diarrhea, nausea, decreased appetite, vomiting, constipation, stomatitis and abdominal pain.

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced per above table.

In addition, general supportive measures should be implemented including hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals, and alcohol.

Nausea and Vomiting

Antiemetic agents are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care in accordance to clinical practice guidelines. The 5-HT3 receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure (see Sections 5.3.5). Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4. When therapy with antiemetic agents does not control the nausea or vomiting to tolerable levels, study treatment should be temporarily interrupted or dose reduced per the above table.

Dehydration may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented.

Stomatitis and Mucositis

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis.

During treatment with cabozantinib good oral hygiene and standard local treatments such as nontraumatic cleansing and oral rinses (eg, with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as indicated by local guidelines. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered per the table For other non-hematologic adverse events, and for hematologic adverse events, the following criteria for dose reduction should be used:

Table 5-1: Recommended carfilzomib and cabozantinib dose modification plan for hematologic and non-hematologic toxicities.

Event Grade (NCI CTC V4.03) and Category		Action by Agent	
Grade	**Adverse Event**	**Carfilzomib**	**Cabozantinib**
Grade 2	**Pulmonary Hypertension or Pulmonary Complications**	Withhold carfilzomib until resolved or returned to baseline. Restart at the dose used prior to the event or reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2), at the discretion of the physician. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	
	Congestive heart failure or myocardial ischemia	Withhold carfilzomib until resolved or returned to baseline. Restart at the dose used prior to the event or reduced dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2), at the discretion of the physician. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	
	Rash, or hand-foot syndrome only		Withhold cabozantinib until recovery to Grade 1 or screening value. Administer cabozantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer cabozantinib at lower dose for subsequent cycles.

Event Grade (NCI CTC V4.03) and Category		Action by Agent	
Grade	**Adverse Event**	**Carfilzomib**	**Cabozantinib**
	Non-hematologic toxicities		Continue current dose level.
Grade 3	**Hematologic (neutropenia, thrombocytopenia, anemia)**	Withhold carfilzomib dose. If fully recovered before next scheduled dose, continue at same dose level. If recovered to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce dose by one dose level: from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. **TMA**: If TMA is suspected, hold carfilzomib and manage per standard of care. If TMA is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If TMA is excluded, may restart carfilzomib.	Withhold cabozantinib. If the relevant lab value recovers to: 1.0×10^9/L for ANC, 8 g/dL for hemoglobin, or 50×10^9/L for platelets, resume cabozantinib treatment at same dose level. If the relevant lab value takes more than 3 weeks to recover to the level described above, restart cabozantinib administration at the next lower dose. If a second hold is required for the same event, administer cabozantinib at the next lower dose for subsequent cycles (for those subjects starting at 40 mg dose, cabozantinib would be discontinued is second hold required).
	Hepatic Toxicity	25% dose reduction in case of baseline or treatment emergent mild or moderate hepatic impairment. Withhold carfilzomib until resolved or returned to baseline. After resolution, consider if restarting is appropriate. May be restarted at the dose (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2) with frequent monitoring of liver function. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.	

Event Grade (NCI CTC V4.03) and Category		Action by Agent	
Grade	**Adverse Event**	**Carfilzomib**	**Cabozantinib**
	Renal	Serum creatinine ≥2 times baseline, CrCl <15 mL/minute or CrCl decreases to ≤50% of baseline, or patient requires dialysis: Withhold dose and monitor renal function. If renal toxicity is due to carfilzomib, resume dosing when renal function has improved to within 25% of baseline; resume with a reduced dose by 1 dose level.	
	Cardiac Toxicity: Grade 3 or 4, new onset or worsening of: **1. Congestive heart failure;** **2. Decreased left ventricular function** **3. Myocardial ischemia**	Withhold until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	
	Peripheral Neuropathy	Withhold until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	
	Clinically significant Non-hematologic	Withhold until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	Withhold cabozantinib until recovery to Grade 1 or screening value. Administer cabozantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer cabozantinib at lower dose for subsequent cycles. For those subjects starting at 40 mg dose, cabozantinib would be

Event Grade (NCI CTC V4.03) and Category		Action by Agent	
Grade	**Adverse Event**	**Carfilzomib**	**Cabozantinib**
		PRES: If PRES is suspected, hold carfilzomib. Consider evaluating with MRI for onset of symptoms suggestive of PRES. If PRES if confirmed, permanently discontinue carfilzomib. If PRES is excluded, may resume carfilzomib at same dose if clinically appropriate.	discontinued if second hold required.
Grade 4	**Non-hematologic (including hemorrhage and peripheral neuropathy)**	Withhold carfilzomib until resolved or returned to baseline. Consider restarting at the next scheduled treatment with one dose level reduction (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	Withhold cabozantinib until recovery to Grade 1 or screening value. Consult with the Medical Monitor or designee prior to restarting cabozantinib. If the Investigator and Medical Monitor concur, administer cabozantinib at the next lower dose for subsequent cycles, unless further dose reduction is required. If a second hold is required for the same event, administer cabozantinib at lower dose for subsequent cycles. For those subjects starting at 40 mg dose, cabozantinib would be discontinued if second hold required.
	Hematologic (neutropenia, thrombocytopenia, anemia, febrile neutropenia)	Hold drug. If fully recovered before next scheduled dose, continue carfilzomib at same dose level. If recovered to Grade 2 neutropenia or Grade 3 thrombocytopenia, reduce dose by one dose level (from 27 mg/m^2 to 20 mg/m^2, OR from 20 mg/m^2 to 15 mg/m^2). If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.	Withhold cabozantinib. If the relevant lab value recovers to: 1.0×10^9/L for ANC, 8 g/dL for hemoglobin, or 50×10^9/L for platelets, resume treatment at next lower dose for subsequent cycles, unless further dose reduction is required.
Permanently discontinue for any of the following		**1. Hypertensive crisis** **2. Hypertensive emergency** **3. Malignant hypertension**	**1. Development of visceral perforation or fistula formation** **2. Severe hemorrhage** **3. Serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)** **4. Nephrotic syndrome**

Event Grade (NCI CTC V4.03) and Category		Action by Agent	
Grade	**Adverse Event**	**Carfilzomib**	**Cabozantinib**
			5. Malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management **6. Osteonecrosis of the jaw** **7. Reversible posterior leukoencephalopathy syndrome.**
	Hepatitis B reactivation	**Any subject who becomes HBV DNA positive or develops reactivation of HBV should have carfilzomib treatment interrupted and receive appropriate anti-viral treatment as per a specialist in Hepatitis B.**	
	Progressive Multifocal Leukoencephalopathy (PML)	Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue Kyprolis if PML diagnosis is confirmed.	

Fatigue, Anorexia, and Weight Loss

Fatigue has been reported during treatment with cabozantinib. Common causes of fatigue such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, sleep disturbance, and hypothyroidism should be ruled out and/or these causes treated in accordance to standard of care. Individual non-pharmacological and/or pharmacologic interventions directed to the contributing and treatable factors should be given. Note: Chronic use of modafinil should be avoided because of its potential to reduce cabozantinib exposure (see Investigator's Brochure).

Anorexia and weight loss should be managed in accordance to local standard of care including nutritional support. If fatigue, anorexia, or weight loss cannot be adequately managed, study treatment should be temporarily interrupted or dose reduced per protocol.

Perforations and Fistulas:
Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of cabozantinib treated patients, respectively. All were serious and one GI fistula was fatal (< 1%). Non-GI fistulas including tracheal/esophageal were reported in 4% of cabozantinib-treated patients. Two (1%) of these were fatal. **Cabozantinib should be discontinued in patients who experience a perforation or a fistula**.

Hemorrhage:
Serious and sometimes fatal hemorrhage occurred with cabozantinib. The incidence of Grade 3hemorrhagic events was higher in cabozantinib-treated patients compared with placebo (3% vs.1%). **Cabozantinib should be avoided in patients with a recent history of hemorrhage or hemoptysis**.

Thrombotic Events:
Cabozantinib treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in cabozantinib-treated and placebo-treated patients, respectively). **Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication**.

Subjects who develop a PE or DVT should have cabozantinib treatment held until therapeutic anticoagulation with heparins (eg, LMWH) is established. LMWH are the preferred management for thrombotic events, warfarin is not recommended. Cabozantinib treatment may be resumed in subjects who are stable and have uncomplicated PE or DVT and are deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator/Sponsor.

Wound Complications:
Wound complications have been reported with cabozantinib. Treatment with cabozantinib should be stopped at least 28 days prior to scheduled surgery. Therapy can be resumed after surgery based on clinical judgment of adequate wound healing. **In patients with dehiscence or wound healing complications requiring medical intervention, therapy should be withheld**.

Hypertension:
Cabozantinib treatment results in an increased incidence of treatment-emergent hypertension with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (modified JNC criteria) stage 1 or 2 hypertension identified in 61% in cabozantinib-treated patients compared with 30% of placebo-treated patients in the randomized trial. Blood pressure should be monitored prior to initiation and regularly during cabozantinib treatment. It should be withheld for hypertension that is not adequately controlled with medical management; when controlled, cabozantinib can be resumed at a reduced dose. **It should be discontinued for severe hypertension that cannot be controlled with anti-hypertensive therapy**.

Osteonecrosis of the Jaw:
Osteonecrosis of the jaw (ONJ) occurred in 1% of cabozantinib-treated patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection,

toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy, and patients advised regarding good oral hygiene practices. For invasive dental procedures, cabozantinib should be withheld for at least 28 days prior to scheduled surgery, if possible.

Palmar-Plantar Erythrodysesthesia Syndrome:
Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 50% of patients treated with cabozantinib and was severe (Grade 3) in 13% of patients. Cabozantinib should be witheld in patients who develop intolerable Grade 2 PPES or Grade 3-4 PPES until improvement to Grade 1 when it can be resumed at a reduced dose.

Proteinuria:
Proteinuria was observed in 4 (2%) of patients receiving cabozantinib, including one with nephrotic syndrome, as compared to none of the patients receiving placebo. Urine protein should be monitored regularly during cabozantinib treatment and treatment **discontinued in patients who develop nephrotic syndrome**.

Reversible Posterior Leukoencephalopathy Syndrome:
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one (<1%) patient. An evaluation for RPLS should be performed in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. **Discontinuation of cabozantinib should occur in patients who develop RPLS.**

Corrected QTc Prolongation
Cardiac arrest within 1 day of carfilzomib administration has been reported. If there is QT prolongation, we will consider holding carfilzomib.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms or increased by > 60 ms above baseline, the following actions must be taken:

- Interrupt study treatment
- Hospitalize symptomatic subjects (eg, with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated
- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec and the average increase is ≤ 60 ms above baseline, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Study treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- Study treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 msec or return to ≤ 60 ms above baseline.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved
- Sponsor has reviewed all available information and has agreed to the continuation of study treatment

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

All study treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation (confirmed by central ECG lab) after reinitiation of study treatment at a reduced dose

Hypophosphatemia

Hypophosphatemia has been reported during treatment with cabozantinib. Serum phosphorus should be monitored frequently while receiving cabozantinib. Other causes of hypophosphatemia should be ruled out and/or these causes treated in accordance to standard of care. Mild to moderate hypophosphatemia should be managed by oral replacement including food that are high in phosphate (diary items, meats, beans) and/or oral phosphate supplements in accordance to standard clinical practice guidelines.

Clinically relevant hypophosphatemia should be managed in accordance to the dose modification guidelines as outlined in the protocol.

Thyroid Function Disorders

Changes in thyroid function tests (TFTs) and hypothyroidism have been reported with cabozantinib therapy and other tyrosine kinase inhibitors as a result of altered thyroid hormone regulation by mechanisms that seem to be specific for each agent[86]. Currently available data are insufficient to determine the mechanism of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended before initiation and during treatment with cabozantinib. Management of thyroid dysfunction (eg, symptomatic hypothyroidism) should follow accepted clinical practice guidelines and dose modification guidelines as outlined in the protocol.

Angioedema

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

Musculoskeletal and Connective Tissue Disorders

Cabozantinib appears to represent minimal risk of adverse musculoskeletal effects based on nonclinical GLP-compliant toxicology studies. The development of new or progressive, unexplained musculoskeletal symptoms such as pain or weakness should be assessed for underlying causes.

Rhabdomyolysis has been reported. Cabozantinib should be discontinued in subjects with serious and life-threatening rhabdomyolysis and interrupted if less severe forms occur when there are no other clear causes. Reinitiation of cabozantinib treatment must be discussed with and approved by the sponsor. Therapy of rhabdomyolysis should include supportive care and standard medical intervention.

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea has been reported in clinical studies with cabozantinib. Symptoms should be managed according to locally accepted clinical practice including an assessment for underlying causes. Pulmonary embolism should be considered as possible causes for new onset dyspnea given the risk of thrombosis associated with inhibition of VEGF signaling. Furthermore, fistula formation and pneumonia have been reported in subjects treated with cabozantinib and should be considered as clinically indicated in subjects presenting with pulmonary symptoms.

Other

Treatment of emergent toxicities is at the investigator's discretion.

5.8 LABORATORY CORRELATIVE STUDIES

Our **central correlative hypotheses** propose that:

1. The serum and marrow MUC20 levels which will be judged by flow cytometry and genomic studies will directly correlate with primary plasma cell MUC20/c-Met pathway activation and inversely correlate with PI resistance; and

2. A correlation of the gene expression and flow cytometry profiles of patients with clinical outcomes may confirm the biomarker MUC20 as a predictor of disease sensitivity to PI, and allow future personalization of c-Met-targeted therapies, as well as combination approaches based on c-Met inhibitors.

We plan to quantitate endogenous levels of MUC20 in marrow aspirates and in patient serum samples at enrollment and after cycle 2 (prior to start of cycle 3) of therapy using a sensitive flow cytometry and GEP assays.

5.8.1 SAMPLES FOR LABORATORY ENDPOINTS

Bone marrow aspirates will be performed on all patients at baseline and after cycle 2 of therapy, and these will be purified into $CD138^+$ and $CD138^-$ fractions through the Department of Lymphoma & Myeloma's Myeloma Tissue Bank using standard immunomagnetic bead approaches[63]. Supernatants from marrow aspirate preparations will also be collected, as will concurrent serum samples from each patient's peripheral blood, these samples will be stored at each site, until Phase II of the study when efficacy will be assessed.

5.8.2 GENE EXPRESSION PROFILING

Plasma cells purified from the baseline bone marrow aspirate will be subjected to gene expression profiling using the "bead array" technology from Illumina. In this approach, cDNA is first generated by priming of mRNA with an oligo-dT primer containing a binding site for T7 RNA polymerase[64] using a kit from Ambion. This enables the subsequent amplification and generation of biotin-labeled cRNA. The starting material is total RNA, and since as little as 25 ng is required, based on the published average yield of total RNA[65], as well as our own experience[63], this can be obtained from as few as 5,000 $CD138^+$ myelomatous plasma cells. Specific transcripts within the cRNA are then measured by fluorescent imaging after direct hybridization to HT-12 bead arrays, which contain 12 arrays per slide, each with an average of 15 beads for each of >48,000 probes measuring >25,000 annotated genes and additional transcripts. These studies will be performed by Dr. Orlowski in collaboration with Dr. R. Eric Davis, the Co-Director of the SPORE Myeloma Tissue Core Facility, and an expert in gene expression profiling of primary samples[66,67]. Data from these studies will be analyzed as described in the subsequent section 10. Subject to the availability of sufficient residual nucleic acid, the expression levels of genes of special interest, such as MUC20 and c-Met, will be confirmed by Dr. Orlowski using quantitative real-time polymerase chain reaction[68,69].

5.8.3 CORRELATION OF MUC20 LEVELS AND RESPONSE TO THERAPY

We plan to quantitate endogenous levels of MUC20 in marrow aspirate supernatants and in patient serum samples using a sensitive flow cytometry and ELISA assay. Given the published literature in this area, we anticipate finding that MUC20 levels will be directly inversely correlated with PI resistance. MUC20 will inversely correlate with the activation status of the c-Met pathway, with the latter to be determined by gene expression profiling.

5.8.4 POTENTIAL PITFALLS

Patients with relapsed, or relapsed and refractory multiple myeloma have varying levels of marrow plasmacytosis, and it is therefore possible that, on at least some patients, a low yield of plasma cells will be obtained that may limit the ability to do both genomic and proteomic analyses. However, our current methods allow for gene expression profiling from as few as 5,000 $CD138^+$ myeloma cells[63,65]. Our experience with these techniques, therefore, gives us confidence that we will be able to obtain a fully informative dataset from the vast majority of patients treated on this study.

The intent is to utilize all of the marrow aspirate and serum samples collected for the correlative studies, however, should we not see a clinical response (efficacy) in Phase II of the study, the above correlative analysis may not be performed and the samples will be maintained at each site for future unspecified used.

5.9 SYMPTOM INVENTORY AND QUALITY OF LIFE

5.9.1 M. D. ANDERSON SYMPTOM INVENTORY (MDASI)

Symptoms will be measured by the multiple myeloma module of the MDASI (MDASI-MM, Appendix B). The MDASI is a multiple-symptom assessment tool for measuring of cancer-related symptoms[70] that is sensitive to disease and treatment changes[71]. This instrument is brief, easily understood, and validated in the cancer population. Patients rate the severity of 13 physical, affective, and cognitive symptoms on 0–10 numeric scales, ranging from "not present" to "as bad as you can imagine." The recall period is for the last 24 hours. The MDASI-MM has 7 additional items known to be important in assessing multiple myeloma patients (constipation, muscle weakness, diarrhea, sore mouth or throat, rash, concentration and bone aches). The MDASI-MM takes less than 5 minutes to complete either by self-report or study staff personal interview, using paper format, tablet PC, or via an automated system, such as a telephone-based interactive voice response (IVR). Symptom severity and interference will be the variables of interest to correlate to clinical outcomes and biomarkers.

This tool is to be administered at baseline, at the start of each cycle, half-way through each cycle, and at the end-of-study visit.

5.9.2 QUALITY OF LIFE / PATIENT REPORTED OUTCOMES

The European Organization for Research and Treatment of Cancer (EORTC) sought, starting in 1986, to develop an integrated, modular approach to evaluate the quality of life of patients with malignant disorders who were participating in clinical trials. This effort resulted in the Quality of Life Questionnaire (QLQ) Core 30 (QLQ-C30) tool, which was initially tested in an international field study to determine its practicality, reliability, and validity[72]. Nine multi-item scales were incorporated into QLQ-C30, including five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. In the first validation study, the questionnaire was administered to 305 patients with unresectable lung cancer in 13 countries. Notably, the average time needed to complete the questionnaire was about 11 minutes, and most patients could do this without assistance. Validity was supported by the fact that all interscale correlations were statistically significant, the correlation was moderate, indicating that the scales were assessing different quality-of-life construct components; that most of the functional and symptom measures discriminated clearly between patients differing in clinical status as defined by the ECOG performance status scale, weight loss, and treatment toxicity; and that there were statistically significant changes in physical and role functioning, global quality of life, fatigue, and nausea and vomiting, for patients whose performance status had improved or worsened[72].

Since this initial version of QLQ-C30, a number of other, later versions have been developed, which incorporated changes such as the addition of single items assessing other symptoms and perceived financial impact of the disease. Later, four-point scales were used for the first five items, and some questions were rephrased, leading to the current version, 3.0, which is the standard that is used for all new studies[73]. Notably, the QLQ-C30 has been successfully used in a number of multiple myeloma studies, including trials targeting younger and older patients, newly diagnosed and relapsed or relapsed/refractory patients, and patients undergoing standard or high dose therapies[70,71].

A multiple myeloma-specific module has also been designed, and is intended to be used in clinical trials with the EORTC QLQ-C30. This questionnaire uses a one-week time frame, and response categories are consistent with the EORTC QLQ-C30. After testing studies in patients with multiple myeloma, a review of the results obtained in each stage of development resulted in an initial 24-item myeloma-specific module, the EORTC QLQ-MY24[74], which assesses disease-specific symptoms and their impact on everyday life, treatment side-effects, social support, and future

perspective. Like the QLQ-C30, the QLQ-MY24 has been successfully used in a number of different clinical trial settings.

These tools will be administered at baseline, at the start of each cycle, and at the end-of-study visit.

6. MEASUREMENT OF EFFECT

Restaging will be performed at start and after cycle 2 using the serum and/or urine protein electrophoresis with immunofixation and serum free light chains to assess disease burden. Disease response quality will also be assessed after completion of three cycles of therapy, and then every cycle after that. Bone marrow aspiration and biopsy will be performed after the baseline sampling only to confirm the achievement of a complete remission (CR). Responses will be determined using the European Group for Blood & Marrow Transplantation (EBMT)[75] and International Myeloma Working Group *(*IMWG) Uniform Response Criteria[76].

6.1 RESPONSE QUALITY

Responses to cabozantinib will be determined predominantly using the recently published[76] consensus recommendations for the uniform reporting of clinical trials from the **International Myeloma Working Group**. These guidelines provide for the following response categories:

- Complete Response (CR)
  - Negative immunofixation of the serum and urine, **and**
  - Disappearance of any baseline soft tissue plasmacytomas, **and**
  - < 5% plasma cells in the bone marrow
- Stringent Complete Response (sCR)
  - CR as defined above, **plus**
  - Normal serum free light chain (FLC) ratio, **and**
  - Absence of clonal plasma cells (PC) by immunohistochemistry, or by immunophenotyping with 2 - 4 color flow cytometry
- Very Good Partial Response (VGPR)
  - Serum and urine M-component still detectable by immunofixation but not on electrophoresis, **or**
  - ≥ 90% or greater reduction in serum M-component plus a urine M component of < 100 mg per 24 hours
- Partial Response (PR)
  - ≥ 50% reduction of the serum M-protein and a reduction in the 24 hour urinary M-protein by ≥ 90%, or to < 200 mg per 24 hours
  - If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
  - If serum and urine M-proteins are not measurable, and serum free light assay is also not informative, ≥ 50% reduction in bone marrow plasma cells is required in place of the M-protein, provided the baseline percentage was ≥ 30%
  - In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of any soft tissue plasmacytomas is also required
- Stable Disease (SD)
  - Any measurements not meeting criteria for CR, VGPR, PR or progressive disease

- ❖ Progressive Disease (PD)
    - An increase of 25% from the lowest response value in any one or more of the following:
        - Serum M-component (the absolute increase must be ≥0.5 g/dL) **and/or**
        - Urine M-component (the absolute increase must be ≥200 mg/24 hours) **and/or**
        - Only in patients without a measurable serum and urine M protein level: the difference between involved and uninvolved FLC levels (absolute increase) must be >10 mg/dL
        - Only in patients without a measurable serum and urine M protein level, and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute %) must be >10%
        - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
        - Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Notably, all of the response categories (CR, sCR, VGPR, PR, and PD) require two consecutive assessments made at anytime before the institution of any new therapy. Also, the CR, PR, and SD categories require no known evidence of progressive or new bone lesions if radiographic studies were performed, and the VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both or neither. Radiographic studies are not required to satisfy these response requirements, and bone marrow assessments need not be confirmed.

In addition to the above definitions, a modification of the uniform criteria will be made for the purposes of this study by introducing the following criterion:

- ❖ Minor Response (MR)
    - Between 25 - 49% reduction in serum M protein, maintained for a minimum of 6 weeks
    - Between 50 - 89% reduction in urinary light chain excretion which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks
    - For subjects with non-secretory myeloma only, between 25 - 49% reduction in plasma cells in a bone marrow aspirate or a bone trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks
    - Between 25 - 49% reduction in the size of extramedullary plasmacytomas
    - If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

6.2 RESPONSE QUANTITY

Using the above measures of response quality, the current study will seek to define, on an intent to treat basis, the following parameters:

- ❖ Overall Response Rate (ORR)
    - CR + sCR + VGPR + PR
- ❖ Clinical Benefit Response Rate (CBR)
    - CR + sCR + VGPR + PR + MR

6.3 RESPONSE DURABILITY

In addition to response quality and quantity, the current study will measure response durability based on the following:

- Time to Progression (TTP)
  - Duration from the start of treatment to disease progression, with deaths due to causes other than progression censored
- Progression-free Survival (PFS)
  - Duration from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first
- Duration of Response (DOR)
  - Duration from first observation of partial response to the time of disease progression, with deaths due to causes other than progression censored
- Time to Next Treatment (TTNT)
  - Time from registration on trial to next treatment or death due to any cause, whichever comes first

7. STUDY CALENDAR AND ASSESSMENTS

Table 7.1. Study Time and Events Table

Study Phase	Screening	Treatment								End
Study Cycle	/	c1				2		≥3		/
Study Day	-28 to -1	1	8	15	22	1	15	1	15	
Assessment			±3	±3	±3	±3		±3	±3	Within 30 days of D/C
Informed consent	X									
Comprehensive history	X									X
Comprehensive physical examination	X									X
Interval (abbreviated) medical history		X		X		X		X		
Symptom-directed (abbreviated) physical examination		X		X		X		X		
Oral Examination[13]	X	[----------as clinically indicated----------]								
Verification of study eligibility	X	X								
Vital signs, including weight	X	X		X		X		X		X
Height	X									
ECOG performance status	X	X		X		X		X		X
Echocardiogram (TTE)	X									
12-lead electrocardiogram	X[10]	X[1]				X[1]		X[1, 11]		X
Posteroanterior & lateral chest radiograph	X									
Skeletal survey for lytic lesions	X									
Computed tomography of plasmacytomas, if indicated by SOC	X[2]							X[2]		
Complete blood count, differential, platelet count	X	X[3,4]	X[3]	X[3]	X[3]	X		X		X
$CD4^+$ cell count in patients who are HIV-positive	X									
Hep B screen[12]	X									
Hep B-DNA monitoring[12]		[----------as clinically indicated----------]								
Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose	X	X[4]		X		X		X		X
Calcium, phosphorous, magnesium	X	X[4]		X		X		X		X
Alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, lactate dehydrogenase, uric acid	X	X[4]		X		X		X		X
Total protein, albumin	X	X[4]		X		X		X		X
β-2-microglobulin	X									
Thyroid stimulating hormone (TSH)	X[8]									
β-human chorionic gonadotropin level	X[5]	X[5]				X[5]		X[5]		X[5]
Prothrombin & activated partial thromboplastin times	X	X[4]				X[9]		X[9]		
Serum protein electrophoresis and immunofixation, quantitative immunoglobulins	X	X[6]				X		X		X
Serum free κ and λ light chains and κ/λ ratio	X	X[6]				X		X		X
24-hour urine protein electrophoresis & immunofixation	X	X[6]				X		X		X
Disease status to determine eligibility to continue with further therapy with cabozantinib								X		
Bone marrow aspiration and biopsy (study samples taken also)	X							X[7]		
Serum sample for MUC20	X[4]							X[4]		
M. D. Anderson Symptom Inventory – Multiple Myeloma tool (MDASI–MM)		X		X		X	X	X	X	X
Quality of Life Questionnaires (QLQ-C30, QLQ–M20)		X				X		X		X
Dispense/collect patient study medication diary	X					X		X		X

[1] To evaluate if there is an increase in QTcF to an absolute value > 500 ms or an increase of > 60 ms above baseline. See section 5.7.1 for more details.
[2]If indicated for initial measurement, and then for confirmation of complete response as directed by SOC.
[3]Complete blood cell counting will be performed weekly in cycle 1 only.
[4]These studies can be performed within 3 days of the indicated day. In cycles ≥ 3 serum sample will be drawn prior to cycle 3 only.
[5]Only in women of child-bearing potential.
[6]These tests should not be repeated if they were performed within fourteen days during the screening period.
[7]To evaluate response, a bone marrow aspiration and biopsy will be performed once, as well as bone marrow aspirate extra tube for MUC20 correlative studies. In cycles ≥ 3 study sample will be taken prior to cycle 3 only.
[8]TSH will be tested every three cycles if subject continues past cycle 3.
[9] Subjects receiving LMWH for therapeutic anticoagulation or thromboprophylaxis, will have PT/PTT coagulation parameters at the start of each cycle while on study treatment.
[10] Baseline ECG see Exclusion criteria #18 for details. Of note, the ECG should be performed 1 to 14 days prior to starting treatment.
[11] Beyond C3 ECG is performed every 12 weeks.
[12] If baseline hepatitis B serology status is unknown, please perform. For monitoring, carriers of HBV who being treatment with carfilzomib should be closely monitored for signs and symptoms of active HBV infection throughout treatment. Any subject who becomes HBV DNA positive or develops reactivation of HBV should have carfilzomib treatment interrupted and receive appropriate anti-viral treatment as per a specialist in Hepatitis B.
[13] Note: the oral examination can be completed as part of an ENT referral visit

8. Drug Formulation and Procurement

A list of the adverse events and potential risks associated with the investigational agent administered in this study found below in Section 8.1.7.

8.1 Cabozantinib

Please consult the most current Investigator's Brochure and package insert for complete drug information. At study sites, all study medication will be stored and inventoried in accordance with applicable state and federal regulations.

8.1.1 Chemical Name

N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

8.1.2 Cabozantinib Tablets

For this clinical trial cabozantinib is supplied as film coated tablets containing cabozantinib malate equivalent to 20 mg of cabozantinib and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. All tablet strengths are prepared from a common blend and are distinguished by shape. The 20 mg tablets are round.

Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w
Cabozantinib malate (25% drug load as cabozantinib)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4
Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910/Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

8.1.3 Preparation and storage:
Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). Stability information submitted includes forced degradation, heat stress, light stress and long-term studies. These studies indicate sensitivity to acid hydrolysis (formation of ordinary impurities) and high heat (formation of genotoxic impurities).

8.1.4 Administration:
Oral. Patients will receive cabozantinib at a starting dose of 20 mg P.O. once daily continuously during days 1-28 of a 28-day cycle. Should unacceptable toxicities occur at 20 mg, there will be no de-escalation dose and the study will be halted. If there are no toxicities observed on initial dose of 20 mg PO daily, the dose will be escalated to 0 level of 40 mg PO daily in the same manner. If no toxicities observed, further dose escalation to +1 level of 60 g PO daily will be done. Cabozantinib will be given 1-2 days prior to carfilzomib in three additional patients enrolled.

Cabozantinib must be taken on an empty stomach. Patients taking cabozantinib tablets should be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should be swallowed whole with water, and cannot be crushed or broken. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Section 5.7.

8.1.5 Potential Drug Interaction:
Cabozantinib is metabolized via a drug metabolizing enzyme system associated with cytochrome P450 (CYP3A4). Interactions with drugs metabolized via the same enzyme system are possible. Drugs which inhibit CYP3A4 may markedly increase the plasma concentration of cabozantinib.

Drugs and substances which inhibit CYP3A4 may increase the plasma concentrations of cabozantinib.

Please refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

http://medicine.iupui.edu/flockhart/table.htm

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Protein Binding*:* Cabozantinib is highly bound (≥ 99.7%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect).

8.1.6 Other Interactions:

Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. Subjects should fast (with the exception of water) for at least 2 hours after eating the evening meal before taking their dose of cabozantinib. After the 2-hour fast and before going to bed, subjects are to take cabozantinib with a full glass of water (minimum of 8 oz or 240 mL) with no more food intake for one hour post-dose.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

8.1.7 Known potential toxicities:

Cabozantinib treatment-emergent adverse events/serious adverse events of particular interest

- Gastrointestinal disorders (diarrhea, nausea and vomiting , dehydration [prostate cancer studies], stomatitis and mucositis)
- Hepatobiliary disorders (elevated ALT and AST)
- Hematological disorders
- Fatigue, anorexia, and weight loss
- Skin disorders (palmar-plantar erythrodysesthesia syndrome [PPES] and rash)

- Wound healing and surgery
- Hypertension
- Thromboembolic events (venous and arterial)
- Proteinuria
- QTc prolongation
- Hypophosphatemia
- Thyroid function disorders
- Hemorrhagic events
- Osteonecrosis of the jaw (ONJ)
- Angioedema
- Musculoskeletal and connective tissue disorders
- Respiratory, thoracic, and mediastinal disorders

8.1.8 Drug procurement:
Cabozantinib is an investigational agent supplied to investigators by Exelixis, Inc.

8.2 Carfilzomib

8.2.1 Preparation and storage:
Carfilzomib is currently FDA approved for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. KYPROLIS (carfilzomib) is administered intravenously over 10 minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle.

8.2.2 Known potential toxicities:
Carfilzomib each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Very Common (may affect more than 1 in 10 patients)

• swelling of hands, feet or ankles • headache • high blood pressure • pain • muscle spasms • fever • fatigue • nausea • stomach pain	• vomiting • diarrhea • constipation • respiratory tract infections • lung infection • • low blood cell counts (red, platelets, white) • runny nose or nasal congestion • decreased blood levels of potassium • high blood sugar and/or creatinine	• dizziness • weakness • numbness • difficulty sleeping • infusion reaction • back pain • joint pain • pain in limbs (hands or feet)

Common (may affect up to 1 in 10 patients)

• heart failure and heart problems including rapid strong or irregular heart beat • possible fluid in the lung • chills • pulmonary hypertension • rash • itchy or redness of skin • increased sweating	• blood clot in the lungs • nose bleed • change in voice; hoarseness • wheezing decreased blood levels of sodium, magnesium, protein, calcium or phosphate • high blood levels of calcium, uric acid, potassium, bilirubin, or c-reactive protein	• low blood pressure • blood clots in veins • bone and muscle pain muscle weakness • kidney problems, decreasing ability to make urine and failure • anxiety

Uncommon (may affect up to 1 in 100 patients)

• decreased or worsening of heart function • severe increase in blood pressure • stroke • build-up of fluid around the heart • inflammation of the tissue around the heart • decreased blood supply to the heart • bleeding around the brain • bleeding in the stomach and bowels	• hole in the intestines (possible leaking contents into the abdomen) • itchy skin, yellowing of the skin and/or eyes caused by blocking of bile flow from the liver • liver failure • bleeding in the lungs • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • lung inflammation (possible difficulty breathing) • multi organ failure	• blockage in the lung (possible pain and/or shortness of breath) allergic reaction to carfilzomib • breakdown products of the cancer cells entering the blood stream (Tumor Lysis Syndrome)

Rarely, Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome (TTP/HUS); Thrombotic microangiopathy; Posterior reversible encephalopathy syndrome (PRES) have been reported in patients taking carfilzomib.

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib:

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML).
- Tenderness of pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, nausea and vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs

Driving and Using Machines
You may experience fatigue, dizziness, fainting, and/or a drop in blood pressure after treatment with carfilzomib. This may impair your ability to drive or operate machinery. If you have these symptoms, you should not drive a car or operate machinery.

Hydration Risks
There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your doctor's instructions regarding how much water or other fluids you should drink. Over hydration can cause side effect to your heart, lungs, and kidneys.

8.2.3 Drug procurement: Commercially available.

8.2.4 Nursing guidelines

In order to control the dosing of carfilzomib while combined with cabozantinib in this trial, patients will receive carfilzomib at a maximum capped starting dose of 27 mg/m^2 intravenously over 10 minutes provided that they tolerated that dose with only grade 1 toxicities as specified above in the inclusion criteria.. Carfilzomib will be administered on two consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28).

Patients will also be allowed to continue with Dexamethasone at a capped dose of 40 mg (for patient age ≥ 75, acceptable to be given as 20 mg PO/IV) weekly.

9. Toxicity and Adverse Event Reporting Guidelines

Adverse event monitoring and reporting is a routine part of every clinical trial.

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All patients will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication. Adverse event and serious adverse events will be followed until baseline or ≤ grade 1 levels. Toxicity will be assessed using the revised NCI CTCAE version 4.03.

All adverse events will be followed to a satisfactory conclusion. Serious adverse events should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to UNMC DSMC.

In addition to complying with all applicable regulatory reporting laws and regulations, all serious adverse events and toxicities will be reported to the University of Nebraska Medical Center, Institutional Review Board (IRB), participating sites own IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Definitions:
Adverse Event
An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

An adverse event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 5.0, Treatment Plan) and/or if the investigator considers them to be adverse events. In general, if a laboratory abnormality or change in vital sign is associated with a specific diagnosis that is being reported concurrently as an adverse event (e.g. elevated creatinine with renal failure or sinus tachycardia in febrile neutropenia) the findings that support the diagnosis do not need to be reported as separate adverse events unless the investigator feels it is appropriate.

Treatment-emergent Adverse Event
Treatment-emergent adverse event is defined as any adverse event with onset or worsening from the time that the first dose of study drug is administered until 30 days after the final dose of study drug is administered.

Unexpected Adverse Event
An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event
A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such 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. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.1 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) and Exelixis

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTC-

AE) version 4.03.

9.1.1 IRB REPORTING

All internal serious adverse events (AEs) must be reported to the local IRB promptly per institutional human research protection program policies.

9.1.2 FRED & PAMELA BUFFETT CANCER CENTER DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

All adverse events whether internal or external, will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) as noted in Section 9.3.2. In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per DSMC policy.

All adverse events ≥ grade 3 (expected or unexpected, regardless of attribution) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) in accordance with DSMC guidelines.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.03).

AEs will be collected from the time the subject signs the consent form and ending 30 days following the final chemotherapy. All AEs will be followed until resolution or a cause is identified. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final chemotherapy.

Transplant related Adverse Experiences (AE's) or Serious Adverse Experiences (SAE's) will NOT be collected.

Copies of the AE report will be submitted to the IRB as indicated in Section 9.1.1.

Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

9.1.3 FOOD AND DRUG ADMINISTRATION (FDA) REPORTING

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.1.4 Exelixis and Amgen Reporting requirements

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this should be documented to the extent that information is available.

- Investigator shall notify Exelixis and Amgen within twenty-four (24) hours of making such discovery by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form;

- For multicenter studies the Investigator must notify the IND/CTA Sponsor by submitting a completed SAE report form and any other pertinent SAE information as indicated on the SAE reporting form within 24 hours. The site will also submit the SAE report form to Exelixis and Amgen no later than 2 business days.

- This report must be submitted by Institution to Exelixis at e-mail: drugsafety@exelixis.com or fax 650-837-7392, even if it is not felt to be drug related; and to Amgen Global Safety Toll-free 1-888-814-8653.

- Pregnancy (for a subject or for the partner of a subject), although not itself an SAE, should also be reported on a pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities;

- SAEs that must be recorded on an SAE Reporting form include the following:

    - all SAEs that occur after informed consent and through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure);

    - any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 30 days after the decision to discontinue study treatment;

    - although most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

Pregnancy
If a subject becomes pregnant during the study, she will be taken off study treatment and will be followed through the end of her pregnancy. The investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis and Amgen or designee. Any birth defect or congenital anomaly must be reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Medication Errors/Overdose
Any study drug administration error or overdose that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis and Amgen or designee.

9.2 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point process during the trial.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

For participating site(s) that are NCI Cancer Centers, the protocol specific finding of the participating site's Audit Committee will be submitted to the UNMC Audit Committee for review on a schedule to be determined by the UNMC Audit Committee. For participating site(s) that are not NCI Cancer Centers, the audit process will be established by the UNMC Audit Committee on a site-by-site basis.

Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html.

9.3 Monitoring

9.3.1 Various methods will be implemented by the sponsor (UNMC) to exchange information with participating sites:

• Site Initiation/Orientation
• Regular Teleconferences including group wide progress within the agenda
• Investigator meetings as feasible (remote or TBA, possibly in conjunction with larger meetings)
• Email distributions/reports as needed
• Drug company Safety Updates

9.3.2 Ongoing data monitoring for all the subjects in this study:

For this study, data monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s). Monitoring is a Quality Control, continuous process during the entire trial.

UNMC or a representative for UNMC will monitor the data of participating sites in adherence to applicable research regulations, the protocol, and the site agreement. The sponsor may request de-identified source documents that support data entered by mail, fax, or electronic means for centralized compliance monitoring.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Sample Size Description

This Phase I/II study has two primary aims. The first primary aim is to determine the MTD that will be chosen as RP2D among three doses. DLTs will be based solely on adverse events that occur during cycle 1, while the RP2D will be chosen taking into consideration any toxicities that may potentially arise beyond cycle 1. A DLT is defined as treatment-related unmanageable toxicities, including grade 3 non-hematologic effects, or grade 4 hematologic effects, that require delay or termination of the treatment during cycle 1. We will study three dose levels using the 3+3 algorithm. Overall, depending on the dose escalation portion, the minimum number of study patients enrolled should both phases (I and II) be successful is 26 (23+3), and the maximum 32 (29+3); additional 3 patients represent adjustment to meet the goal of total evaluable patients at the end of the study, accounting for the treatment discontinuation rate of 7% in the METEOR study.

The second primary aim of the study is to determine the ORR. Response will be determined by the IMWG response criteria guidelines. All subjects in phase I that receive the RP2D will be included in phase II study analysis. We will use a Simon two-stage design to compare response rates of 0.25 versus 0.05 with alpha=0.05 and power of 0.80[83]. A minimum of nine patients will be enrolled in the first stage. The first interim analysis would be performed, as the hypothesis will be rejected and enrollment will cease if no response is seen in the first 9 patients enrolled on the Phase II portion of the study. Otherwise, another 14 patients will be accrued for a total of 17 evaluable patients. If, there has already been at least one documented response in the first 9 patients, then accrual will be continued into the second stage without interruption. However, if there have not been any documented responses in the first 9 patients, accrual will be halted to allow for all patients to complete at least two cycles of therapy, at which time they will be considered evaluable for disease response. At the end of the trial, the drug will be rejected if no more than 2 responses are seen in the total of 17 evaluable patients.

This study has several secondary aims:
(1) To describe and tabulate the toxicities of cabozantinib in this specific patient population, which will be graded according to the CTCAE, version 4.03;
(2) To describe GEP values as well as *MUC20* level of expression in patients at baseline and after cycle 2 of therapy;
(3) response durability, the earliest of progression, death, or loss to follow-up, and the time to next treatment;
(4) symptom burden as quantified by the MD Anderson Symptom Inventory and its MM module;

(5) evaluation of the impact of cabozantinib on signaling through the c-MET/ERK-1/2/ELK1 /POMP using genomic assays by comparing primary plasma cells obtained from bone marrow aspirates obtained at baseline, and after cycle 2 of therapy.

10.2 Analytic Plan

For the phase I study, we will examine three doses, with the first cohort assigned to 20 mg orally daily dose. The MTD will be defined via the 3+3 algorithm, i.e. as the dose level below the one at which 1/3 or 2/6 patients experience DLTs. At the completion of the phase II section, the ORR will be estimated as the proportion of patients with ORR and will be accompanied by a 95% confidence interval.

All observed toxicities will be tabulated by type and grade. All remaining secondary aims will be assessed with descriptive statistics and graphical displays to evaluate changes in outlined serum and bone marrow markers between pre- and post-treatment. A paired t-test will be used to examine differences pre- and post-treatment.

10.3 ACCRUAL

Total accrual targets for this study are 32 with flexibility based on enrollment in phase I of the study. This study is planned as a 2-institution study, University of Nebraska Medical Center being the lead site, and MD Anderson Cancer Center a secondary site. Based on prior phase I and II studies at both sites, in a similar patient population, we estimate that 3 patients will be accrued every two months, suggesting that a total of 12-18 months will be needed to meet the sample size.

10.4 Stopping Rules

A response rate of 5% or less will be considered as clinically insignificant, while a response rate of 25% will be considered as clinically significant. With alpha= 0.05 and power of 0.80, the Simon optimal 2-stage design requires minimum enrollment of 9 patients in the first stage. The hypothesis will be rejected and enrollment will cease if no response is seen in the 9 patients. If at least 1 response is seen in the first 9 patients, another 14 patients will be accrued, for a total of 17 evaluable patients. At the end of the trial, the drug will be rejected if no more than 2 responses are seen in the total of 17 evaluable patients.

Cabozantinib will be taken in 20-mg capsules to reach the target dose levels as determined during the phase I and phase II portions of the study. This therapy will be continued without a cap on the number of allowed cycles, unless one of the following occurs:

- Disease progression after two cycles or later of therapy
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient becomes pregnant
- Patient loses the ability to freely provide consent through imprisonment or involuntary incarceration for treatment of a psychiatric or physical illness
- Patient achieves complete remission (CR), and the patient and investigator feel that discontinuation of cabozantinib is in the patient’s best interests, or

- ❖ Patient achieves a level of response that qualifies him or her for another therapy, such as high dose therapy with autologous stem cell transplantation.

10.5 ANALYSIS OF GENE EXPRESSION PROFILING

Our central hypothesis for the correlative laboratory studies is that inhibition of c-Met with cabozantinib will show anti-tumor efficacy especially in patients who have greater activation of the MU20/c-Met pathway at baseline, as determined by genomic and flow cytometry approaches.

10.5.1 DATA PREPROCESSING

For gene expression data*,* we will apply appropriate normalization methods for the expression profiles, which include quantile normalization[77] and locally weighted scatterplot smoothing[78], in order to make analyses comparable across arrays. We shall use robust quantification methods such as the robust multichip analysis[79] to produce a set of expression measurements, which will be used for subsequent downstream statistical analysis.

10.5.2 DATA ANALYSIS

To assess differential expression, we will use t-tests or Mann-Whitney tests if appropriate. When there are more than two groups, an ANOVA (or non-parametric Kruskall-Wallis ANOVA) model will be used to test for biomarker expression differences among groups. The significance threshold will be chosen based on standard methods that have been developed to adjust for multiple testing for such univariate tests; for example, bounding the false discovery rate (FDR)[80] using either Significance Analysis of Microarrays (SAM)[81] or Beta-Uniform Mixture (BUM)[82] models.

10.5.3 PATHWAY ANALYSIS

The candidate signatures identified in the analysis associated with treatment/disease groups will be uploaded into the Ingenuity Pathway Analysis Application (IPA) for pathway analysis. Ingenuity's knowledge base is a repository of molecular interactions, regulatory events, gene-to-phenotype associations, and chemical knowledge that provides the building blocks for pathway construction. The pathways associated with treatment that are identified by the IPA software are ranked according to p-values. The p-values are calculated by Fisher's exact test, and can be adjusted to account for multiple testing using the methods outlined above.

10.6 ANALYSIS OF SYMPTOM BURDEN AND QUALITY OF LIFE STUDIES

The current study will examine the impact of therapy on each patient's symptom burden using the MDASI-MM tool, and about each patient's quality of life using the EORTC QLQ-C30 and QLQ-MY20 tools. Since studies using these tools in multiple myeloma patients treated with cabozantinib have not previously been performed, we are unable at this time to predict the impact of this agent on these parameters. Therefore, we hope to collect pilot data in the course of this protocol which would be hypothesis generating, and which could be confirmed in future, larger, possibly randomized trials. As a result, these studies are exploratory in nature, and their results will be examined using descriptive statistics.

10.7 REPORTING AND EXCLUSIONS

10.7.1 EVALUATION OF TOXICITY

All patients will be evaluable for toxicity from the time of their first treatment with cabozantinib.

10.7.2 EVALUATION OF RESPONSE

All patients included in the study must 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. Those patients who do not receive a single dose of the investigational drug will be replaced in this trial with new patients. 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.

All conclusions should be based on all eligible patients. Subanalyses 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 subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

11.0 Records to be Kept

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms. De-identified source documents which support data entered must be provided to the sponsor by mail, fax, or electronic means for centralized compliance monitoring. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form. Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 9.0 (Adverse Events: List and Reporting Requirements).

11.1 Quality Assurance

Complete records must be maintained in a research chart on each patient treated on the protocol. These records should include primary documentation (e.g., lab. report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).

- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate).

Note: **All** adverse events that have occurred on the study must be reported via the monitoring method identified above.

11.2 Forte Electronic Data Capturing (EDC) System

Data will be stored electronically for this study on the Forte secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Forte logo.

Forte EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Forte through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

12.0 Patient Consent

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Subjects are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Pathology material will be reviewed, and the diagnosis confirmed by each site's Pathology department as outlined in protocol.

12.4 Recruitment and Informed Consent

Subjects who are referred to the Nebraska Medical Center (NMC) / UNMC, or other IRB approved participating sites (MD Anderson), with relapsed and refractory (RR) multiple myeloma (MM) who have lost response to carfilzomib may be eligible for this study.

These potential subjects will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine - http://clinicaltrials.gov (NCT03201250)
National Cancer Institute - http://www.cancer.gov (NCI--2017-02024)

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the patient chooses to be a participant in this study informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there are any indications that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld.

The results of the tests done solely for research purposes will not be disclosed to the

subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is anticipated that the use of the protocol chemotherapy in this patient population may help control the disease. There are risks associated with chemotherapy, but the risk to benefit ratio is considered acceptable for patients with cancer.

12.10 Potential Benefits to Society

Information obtained from this study may help other patients by contributing to the knowledge of the biology of cancers, and to understand the potential clinical benefit of this regimen.

12.11 Potential Risks

The use of cytototoxic chemotherapy are associated with numerous potential risks. Combined chemotherapy is considered a valid treatment option for patients with advanced cancers. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment.

12.12 Therapeutic Alternatives

If subjects choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include other chemotherapy drugs, radiation, surgery, or a combination of these approaches. The treatment recommendations may or may not be similar to treatment as described in this protocol.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy, the risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

The consent document used in this study will include the adult consent document.

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14.0 Data Collection Forms

Attached.

APPENDIX A: **ELIGIBILITY CHECKLIST**

IRB# 434-17-FB Title: A Phase I/II Study of the c-Met Inhibitor Cabozantinib as a Targeted Strategy to Reverse Resistance to the Proteasome Inhibitor Carfilzomib in Refractory Multiple Myeloma

Date Completed:	Institution: Investigator:	Subject ID:	Checklist #: Protocol v5.2 dated 08-23-19

Inclusion Criteria:	**Yes**	**No**	**N/A**
1. Patients must have been previously diagnosed with histologically or cytologically confirmed symptomatic multiple myeloma, which require the presence of all three of the following International Myeloma Working Group criteria, except as noted: ❖ Clonal bone marrow plasma cells ≥ 10% ❖ A monoclonal protein in either serum or urine ❖ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder (to include one of the following) o Hypercalcemia (corrected calcium > 2.75 mmol/L or 11.5 mg/dL); **OR** o Renal insufficiency attributable to myeloma (serum creatinine >1.9 mg/dL); **OR** o Anemia; normochromic, normocytic with a hemoglobin value ≥2 g/dL below the lower limit of normal, or a hemoglobin or <10 g/dL; **OR** o Bone lytic lesions, severe osteopenia or pathologic fractures. (MRI, CT or PET/CT with > 1 focal lesions ≥5 mm in size) ❖ Patients with a biopsy-proven plasmacytoma and either a serum or urine monoclonal protein will also be considered to have met the diagnostic criteria for multiple myeloma in the absence of clonal marrow plasmacytosis of ≥ 10%. ❖ Patient with bone marrow plasma cells of ≥ 60% or serum free light chain ratio of ≥ 100 will also be considered to have met the diagnostic criteria for multiple myeloma. ❖	[ ]	[ ]	**1.**
2. Patients must have measurable disease, as defined by at least one of the following: ❖ Serum monoclonal protein level ≥0.5 g/dL for IgG, IgA, or IgM disease ❖ Monoclonal protein or total serum IgD ≥0.5 g/dL for IgD disease ❖ Urinary M-protein excretion of ≥200 mg over a 24-hour period ❖ Involved free light chain level ≥10 mg/dL, along with an abnormal free light chain ratio	[ ]	[ ]	**2.**
3. Patients prior lines of therapy f must be separated by the documented disease progression. Using this definition, treatment with induction therapy, followed by high dose chemotherapy and autologous stem cell transplantation, and finally by maintenance therapy, would constitute one line, provided that multiple myeloma did not meet criteria for progression at any time during this period.	[ ]	[ ]	**3.**
4. Patients eligible for this trial will be those who have previously failed carfilzomib at any point either as a single agent, or carfilzomib in combination with dexamethasone,			

or carfilzomib in combination with dexamethasone and any of the following agents: revlimid, cyclophosphamide, pomalidomide, daratumumab or bendamustine. Given the potential for compounding/worsening toxicities with the addition of cabozantinib to carfilzomib, patients eligible for the trial will have to have had very good tolerance to carfilzomib in the context of described regimens, with resolved prior toxicity to grade 1 or better, and no toxicities due to carfilzomib that required dose reductions to less than 27 mg/m^2.	**[ ] [ ] 4.**
5. Patients must have disease that has relapsed after carfilzomib therapy, with progressive disease (PD) being defined as an increase of 25% from the lowest response value in any one or more of the following: ❖ Serum M-component (the absolute increase must be ≥0.5 g/dL) **and/or** ❖ Urine M-component (the absolute increase must be ≥200 mg/24 hours) **and/or** ❖ Only in patients without a measurable serum and urine M protein level: the difference between involved and uninvolved FLC levels (absolute increase) must be >10 mg/dL ❖ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas ❖ Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder Patients with relapsed disease will be considered to be those who have had progression, as defined above, off of any therapy, and who completed their therapy more than 60 days prior to the finding of progression. Patients with relapsed and refractory disease will be considered to be those who have had progression, as defined above, while still on their last line of therapy, or who progressed within 60 days of finishing their most recent therapy.	**[ ] [ ] 5.**
6. Patients must have completed their most recent drug therapy directed at multiple myeloma in the following timeframes: ❖ Chemotherapy, biological therapy, immunotherapy, monoclonal antibody or an investigational therapy at least 3 weeks prior to starting cabozantinib ❖ Corticosteroids at least 3 weeks prior to starting cabozantinib, except for a dose equivalent to dexamethasone of ≤4 mg/day ❖ Nitrosoureas, nitrogen mustards, mitomycin C at least 6 weeks prior to starting cabozantinib ❖ Autologous stem cell transplantation or autologous chimeric antigen receptor (CAR) T cell therapy at least 12 weeks prior to starting cabozantinib ❖ Allogeneic stem cell transplantation or allogeneic CAR T cell at least 24 weeks prior to starting cabozantinib, and these patients must also not have moderate to severe active acute or chronic graft versus host disease	**[ ] [ ] 6.**
7. Patients must be age 19 or older (state of Nebraska), because no dosing or adverse event data are currently available on the use of cabozantinib in patients <19 years of age.	**[ ] [ ] 7.**
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; please see Appendix E)	**[ ] [ ] 8.**
9. Patients must have evidence of adequate bone marrow reserves, as defined by the following:	**[ ] [ ] 9.**

_____ Absolute neutrophil count (ANC) ≥1,000 cells/mm^3 without growth factors within 1 week of the initiation of treatment _____ Total white blood cell count (WBC) ≥2,000 cells/mm^3 without growth factors within 1 week of the initiation of treatment _____ Hemoglobin ≥8 g/dL without red blood cell transfusions within 2 weeks of the initiation of treatment _____ Platelet counts of ≥100,000 cells/mm^3 for patients who have bone marrow plasmacytosis of <50%, or ≥50,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥50%	
10. Patients must have evidence of adequate hepatic function, as defined by the following: _____ Total bilirubin ≤1.5 times the upper limit of the institutional normal values _____ Total AST (SGOT) and ALT (SGPT) ≤2.5 times the upper limit of the institutional normal values	**[ ] [ ] 10.**
11. Patients must have evidence of adequate renal function, as defined by the following: _____ Serum creatinine within the institutional normal limits, **OR** if the creatinine is elevated _____ Creatinine clearance (CrCl) ≥30 mL/min., as measured by a 24-hour urine collection, or estimated by the Cockcroft and Gault formula: Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL Worsening urinary paraproteinemia will be considered in the context of IMWG disease response criteria on a monthly basis. Any patient with urinary protein (otherwise unrelated to urinary myeloma associated M-protein) with excretion > 3.5 g/day will be considered to have developed nephrotic-range proteinuria, and will be taken off study.	**[ ] [ ] 11.**
12. Patients must have evidence of adequate cardiac function, as defined by the following: ❖ Absence of New York Heart Association (NYHA) class II, III, or IV congestive heart failure (please see Appendix F for the NYHA classification system) ❖ Absence of uncontrolled angina or hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 100 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment ❖ Absence of the following in the previous 6 months: o myocardial infarction; o unstable angina pectoris; o clinically-significant cardiac arrhythmias; o stroke (including transient ischemic attack (TIA), or other ischemic event); o thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (eg, vena cava filter) are not eligible for this study) ❖ Absence of myocardial infarction in the previous 6 months	**[ ] [ ] 12.**

❖ Absence of clinically significant bradycardia, or other uncontrolled cardiac arrhythmia defined as grade 3 or 4 according to National Cancer Institute (NCI) Common Terminology ❖ Absence of history of congenital long QT syndrome	
13. Patients who have received radiation therapy must have completed this **at least 4 weeks** prior to starting therapy with cabozantinib, with the following exceptions: ❖ Local radiation therapy to enhance bone healing of a pathologic fracture may have been performed, as long as it was completed at least 2 weeks prior to starting cabozantinib ❖ Local radiation therapy to treat post-fracture pain that is refractory to analgesics may have been performed, as long as it was completed at least 2 weeks prior to starting cabozantinib	**[ ] [ ] 13.**
14. Patients who have undergone any recent major surgery must have done so **at least 4 weeks** prior to starting therapy with cabozantinib, with the following exceptions: ❖ Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to starting cabozantinib ❖ Planned elective surgery unrelated to the patient's diagnosis of multiple myeloma, such as hernia repair, may be allowed, at the discretion of the principle investigator, as long as it was performed at least 2 weeks prior to starting cabozantinib, and patients have recovered fully from this procedure	**[ ] [ ] 14.**
15. HIV seropositive patients with acceptable organ function who meet the patient selection criteria, and who are not on combination antiretroviral therapy, and whose absolute $CD4^+$ count is ≥400 cells per cubic millimeter of blood, will be eligible. However, HIV positive patients on combination antiretroviral therapy will be ineligible, because of the potential for pharmacokinetic interactions with cabozantinib.	**[ ] [ ] 15.**
16. Screen subjects prior to treatment whose baseline hepatitis B serologic status is unknown. Subjects, who are chronic carriers of hepatitis B virus, please screen with hepatitis B DNA to exclude active viral replication and monitor hepatitis B DNA at regular intervals while on study.	**[ ] [ ] 16.**
17. Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s). Male subjects must agree to not donate sperm for at least 90 days after the last dose of Carfilzomib.	**[ ] [ ] 17.**
18. Female subjects of childbearing potential must not be pregnant at screening. Female patients must be either postmenopausal, free from menses for ≥2 years, surgically sterilized, or willing to use two adequate barrier methods of contraception to prevent pregnancy, or must agree to abstain from heterosexual activity throughout the study. Female patients of childbearing potential must have a negative serum (βHCG) or urine pregnancy test before receiving the first dose of cabozantinib or carfilzomib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her	**[ ] [ ] 18.**

treating physician immediately. Women of reproductive potential will be counseled to use effective contraceptive measures to prevent pregnancy during treatment with either cabozantinib or carfilzomib. Patients shall be advised not to take cabozantinib or carfilzomib treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, she will be advised to discuss the appropriate timing with her physician. 19. Understand and able to willingly provide voluntary written informed consent, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care. *<u>All of the above must be **yes** to be eligible</u>*	**[ ] [ ] 19.**
Exclusion Criteria: 1. Patients who are receiving any concurrent investigational agent with known or suspected activity against multiple myeloma, or those whose adverse events due to agents administered more than 4 weeks earlier have not recovered to a severity of grade 0 or grade 1.	**[ ] [ ]1.**
2. Patients who have known central nervous system involvement with multiple myeloma will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.	**[ ] [ ]2.**
3. Patients who have previously been treated with another agent targeting the *MUC20*/c-Met axis, including either monoclonal antibodies to *MUC20* or c-Met, or small molecule inhibitors of c-Met.	**[ ] [ ]3.**
4. Patients with a known history of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib.	**[ ] [ ]4.**
5. Cabozantinib is metabolized by CYP3A4. The metabolism and consequently overall pharmacokinetics of cabozantinib could be altered by inhibitors and/or inducers or other substrates of CYP3A4. It is recommended that chronic concomitant treatment with strong CYP3A4 inhibitors (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) or inducers should be avoided because it may significantly decrease cabozantinib concentrations. If patients are taking any strong CYP3A4 inhibitors, alternate medications with no or minimal CYP3A4 inhibitors should be sought prior to trial enrolment. While mild inhibitors/inducers of these cytochrome P450 isoenzymes are not specifically excluded, investigators should be aware that cabozantinib exposure may be altered by the concomitant administration of these drugs and avoidance is also recommended. Lists including medications and substances known or with the potential to interact with CYP3A4 are provided in Appendix G.	**[ ] [ ]5.**
6. Uncontrolled or ongoing/active infection. Due to side effect profile of cabozantinib, patients with the following history will also not be eligible for the trial: patients with a recent history of hemorrhage or hemoptysis; patients with dehiscence or wound healing complications requiring medical intervention; patients with severe	**[ ] [ ]6.**

hypertension that cannot be controlled (blood pressure of > 150 systolic or > 100 diastolic mm) with anti-hypertensive therapy within 7 days of first dose of therapy.	
7. Pregnant or lactating women are excluded from this study because cabozantinib is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib, breastfeeding should be discontinued if the mother is treated with cabozantinib.	**[ ] [ ]7.**
8. Patients with non-secretory multiple myeloma, active plasma cell leukemia, defined as either having 20% of peripheral white blood cells comprised of $CD138^{+}$ plasma cells, or an absolute plasma cell count of 2 x 10^{9}/L, known amyloidosis, or known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).	**[ ] [ ]8.**
9. Patients who have required plasmapheresis and exchange less than 2 weeks prior to initiation of therapy with cabozantinib	**[ ] [ ]9.**
10. Patients with known moderate or severe hepatic impairment, active hepatitis A, B, and/or C infection, due to the difficulty that would be faced in assessing the attribution of any events of hepatic toxicity while on cabozantinib therapy	**[ ] [ ]10.**
11. Patients with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for >5 years, and are considered by their physician to be at less than 30% risk of relapse. In addition, patients with basal cell carcinoma of the skin, superficial carcinoma of the bladder, carcinoma of the prostate with a current PSA value of <0.5 ng/mL, or cervical intraepithelial neoplasia will be eligible. Finally, patients who are on hormonal therapy for a history of either prostate cancer or breast cancer may enroll, if there has been no evidence of disease progression during the previous three years.	**[ ] [ ]11.**
12. Allergy to carfilzomib or cabozantinib or any excipients	**[ ] [ ]12.**
13. Uncontrolled intercurrent illness including medical, psychiatric, cognitive or other conditions, psychiatric illness/social situations that would compromise the patient's ability to understand the patient information, to give informed consent, to comply with the study protocol or to complete the study or, in the judgment of the Principal Investigator, would make the patient inappropriate for study participation.	**[ ] [ ] 13.**
14. The subject has experienced any of the following: ❖ clinically-significant GI bleeding within 6 months before the first dose of study treatment; ❖ GI disorders particularly those associated with a high risk of perforation or fistula formation including: o Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction	**[ ] [ ] 14.**

○ Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization, Note: Complete healing of an intra-abdominal abscess must be confirmed prior to randomization ❖ hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood within 3 months before the first dose of study treatment; ❖ any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment. ❖ Patient who have developed or have had history of pulmonary hemorrhage while on carfilzomib will be excluded (fatal pulmonary hemorrhage has been observed with carfilzomib).	
15. The subject has radiographic evidence of cavitating pulmonary lesion(s);	**[ ] [ ] 15.**
16. The subject has tumor invading or encasing any major blood vessels;	**[ ] [ ] 16.**
17. The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib;	**[ ] [ ] 17.**
18. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment. *Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility.*	**[ ] [ ] 18.**
19. Inability to swallow intact tablets	**[ ] [ ] 19.**
20. The subject has prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 7 days before the first dose of study treatment;	**[ ] [ ] 20.**
21. Concomitant anticoagulation at therapeutic doses with oral anticoagulants (eg, warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (eg, clopidogrel); Note: Low-dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (< 1 mg/day), and low dose, low molecular weight heparins (LMWH) are permitted **if started > 6 months prior to randomization. LMWH used as therapeutic anticoagulation may increase observed PTT levels in subjects.** . Anticoagulation with therapeutic doses of LMWH is allowed in subjects without radiographic evidence of brain metastasis, who are on a stable dose of LMWH for at least 24 weeks before randomization, and who have had no complications from a thromboembolic event or the anticoagulation regimen.	**[ ] [ ] 21.**
22. **Subjects who have Carfilzomib-related posterior reversible encephalopathy syndrome (PRES) and thrombotic microangiopathy (TMA) should not be challenged with Carfilzomib**. *All of the above must be **no** to be eligible.*	**[ ] [ ] 22.**
Eligibility: [ ] Patient satisfies all criteria. [ ] Patient not formally eligible, but admitted to study because (state reason);	

Patient Initials: _____MR #_____DOB _____ **ELIGIBILITY reviewed and confirmed** **Site Investigator Signature _____Date_____**	

Appendix B: MDASI - MM TOOL

M. D. Anderson Symptom Inventory (MDASI - MM)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering** things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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MM

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **muscle weakness** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **diarrhea (loose stools)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **sore mouth or throat** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your problem with **Paying Attention (Concentrating)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your **bone aches** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
21. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
22. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
23. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
24. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
25. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
26. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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APPENDIX C: EORTC QLQ-C30 TOOL

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ | | | ⌋
Your birthdate (Day, Month, Year): ⌊ | | | | | | | | ⌋
Today's date (Day, Month, Year): 31 ⌊ | | | | | | | | ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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APPENDIX D: EORTC QLQ-MY20 TOOL

ENGLISH

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

APPENDIX E: ECOG PERFORMANCE STATUS SCALE

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 F: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION SYSTEM

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX G: LIST OF POTENTIAL DRUG INTERACTIONS

When drugs classified as ‘substrates’ are co-administered with cabozantinib, there is the potential for higher concentrations of the ‘substrate.’ When cabozantinib is co-administered with compounds classified as ‘inhibitors,’ increased plasma concentrations of cabozantinib is the potential outcome. The co-administration of ‘inducers’ would potentially lower plasma cabozantinib concentrations.

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

CYP3A4 Inhibitors

Strong inhibitors:	**Moderate inhibitors:**	**Weak inhibitors:**	**All other inhibitors:**
indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir suboxone telithromycin cobicistat boceprevir mibefradil telaprevir troleandomycin posaconazole	aprepitant amprenavir amiodarone atazanavir ciprofloxacin crizotinib darunavir/ritonavir dronedarone erythromycin diltiazem fluconazole grapefruit juice Seville orange juice verapamil voriconazole imatinib	cimetidine fluvoxamine	chloramphenicol delaviridine diethyl-dithiocarbamate gestodene mifepristone norfloxacin norfluoxetine star fruit

CYP3A4 Inducers

Aminoglutethimide Carbamazepine Fosphenytoin Nafcillin	Nevirapine Oxcarbazepine Pentobarbital Phenobarbital	Phenytoin Primidone Rifabutin Rifampin	Rifapentine St. John's wort (3)

When drugs classified as 'substrates' are co-administered with cabozantinib, there is the potential for higher concentrations of the 'substrate'. When cabozantinib is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of cabozantinib is the potential outcome. The co-administration of 'inducers' would potentially lower plasma cabozantinib concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

(1) Wang *et al*. (2004). *Clin Pharmacol Ther*. 75:191-197
(2) Malhotra *et al*. (2001). Clin Pharmacol Ther. 69:14-23.
(3) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249.
(4) Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329.

APPENDIX H: STUDY MEDICATION DIARY

CYCLE_______________ Date__________ Study ID: ____________

Your prescribed dose of cabozantnib is _________________. Number of Pills Dispensed: _________________

- If you miss a dose please add the comment "missed dose" on the corresponding date. Dose should not be replaced.
- If your Study Doctor has asked you to change your dose, please add the new dosage on the corresponding date.
- Return all study drug bottles, any unused drug and completed diaries to the Study Coordinators at the study site.

Cabozantinib tablets should be taken by mouth, at least 2 hours before and at least 1 hour after eating. Tablets should be taken with water and swallowed whole.

You are to take your study medication as follows:

# of Pills	# of time(s) per day	Duration: days/weeks/months	Special instruction

Month ___________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time _____am/pm
# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time _____am/pm
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# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time _____am/pm
# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time ____am/pm	# of pills_______ Time _____am/pm	# of pills_______ Time _____am/pm
		Notes:				

Drug Diary for Oral Dexamethasone:

Record Date and Time taken	Record Dose of Dexamethasone taken	If dose of any drug was missed or changed, provide a reason
	mg	
	mg	
	mg	
	mg	
	mg	
	mg	
	mg	
	mg	

APPENDIX I: Child-Pugh Classifications

Clinical and Lab Criteria	Points		
	1	2	3
Encephalopathy **	(grade 0)	(grade 1 or 2)	(grade 3 or 4)
Ascites *	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

GRADE[2]	DESCRIPTION	POINTS
A	Mild; well-compensated disease	5-6
B	Moderate; significant functional compromise	7-9
C	Severe; decompensated disease	10-15