Investigator Sponsored Trial

Protocol Information

Carfilzomib in combination with Thalidomide and Dexamethasone for remission induction and consolidation of Multiple Myeloma at first presentation
The Carthadex trial

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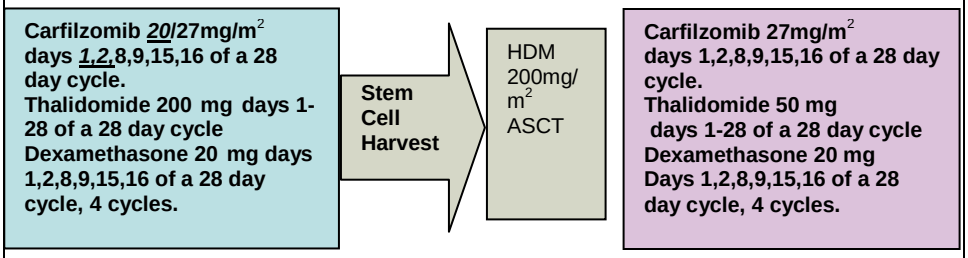
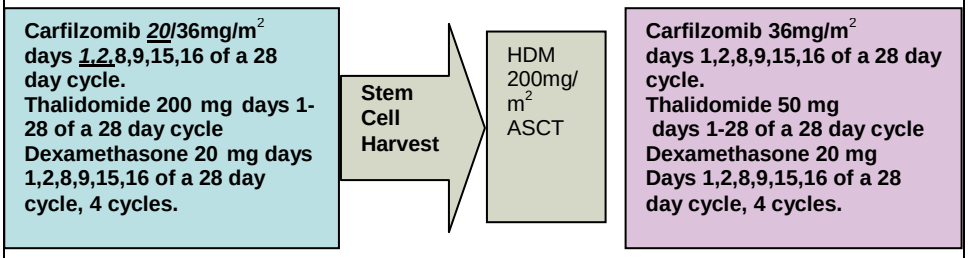
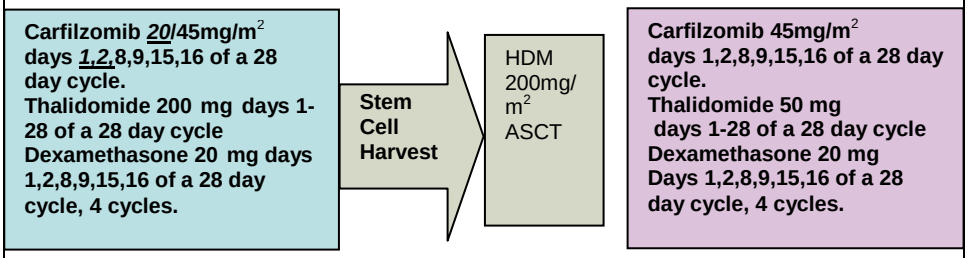
PROTOCOL SYNOPSIS	
TITLE	Carfilzomib in combination with Thalidomide and Dexamethasone for remission induction of Multiple Myeloma at first presentation.
OBJECTIVES	To assess the feasibility and efficacy of Carfilzomib in combination with Thalidomide and Dexamethasone in a phase II trial.
STUDY DESIGN	This trial will establish the feasibility and efficacy of Carfilzomib, in combination with Thalidomide and Dexamethasone as an induction therapy prior to therapy with High Dose Melphalan (HDM) and Autologous Stem Cell Transplantation (ASCT) in previously untreated patients with Multiple Myeloma. Stem cell harvest will be performed using high-dose Cyclophosphamide and standard G-CSF. In addition, the efficacy of a short (4 cycles) post-transplant consolidation schedule of Carfilzomib, in combination with lower dose Thalidomide and Dexamethasone will be investigated. The study will be conducted as a Phase II trial. Patients number 1 to 50:  For 20 additional patients (numbers 51 to 70):  For 20 additional patients (numbers 71 to 90): 

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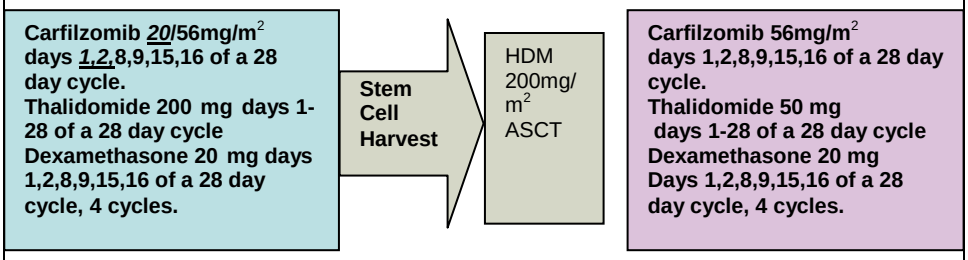
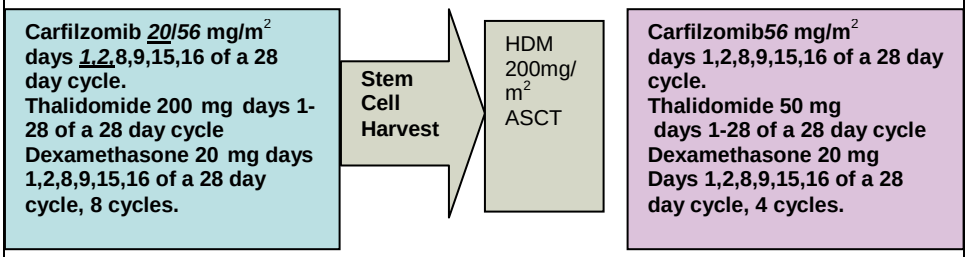


For 35 additional patients (numbers 111 to 145):


One hundred and forty five patients will be included in the study cohort. Molecular (FISH) characterization and gene expression profiling of the myeloma tumor cells will be performed at inclusion. All patients will be followed closely for toxicities and response assessment, as indicated. After completion of treatment, all patients will be followed two-monthly until relapse or progression. Thereafter every 6 months until 5 years after registration.
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<tr><td>STUDY POPULATION</td><td>Patients with Multiple Myeloma, ISS stage I -III age 18-65 yrs (must be transplant candidates) at first presentation;
145 patients.</td></tr>
<tr><td>EXCLUSION CRITERIA</td><td>
• Known intolerance of Thalidomide;
• Systemic AL amyloidosis;
• Non-secretory MM;
• Waldenstrom’s macroglobulinemia or IgM MM;
• Previous chemotherapy or radiotherapy except 2 cycles of Melphalan/Prednisone or local radiotherapy in case of local myeloma progression;
• Severe cardiac dysfunction (NYHA classification II-IV, see appendix III);
• Severe pulmonary dysfunction;
• Significant hepatic dysfunction (serum bilirubin ≥ 30 μmol/L or transaminases ≥ 3.0 times normal level), unless related to myeloma;
• Creatinine clearance (measured or calculated) <15cc/min;
• Alkaline Phosphatase >3x ULN;
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	• ANC < 1,0 x10^9/L, platelets < 75 x10^9/L, Hb < 4.9 mmol/L; • Non-secretory MM defined as SPEP < 5 g/L and UPEP < 200 mg/24 hr; • Intolerance to thromboprophylaxis; • Patients known to be HIV-positive; • Patients with active, uncontrolled infections; • Patients with neuropathy, CTC grade 3 or higher, or grade 2 painful peripheral neuropathy; • Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma; • Patients (all males and all pre-menopausal women) who are not willing or capable to use adequate contraception during the therapy; • Lactating women; • WHO Performance status > 3.
PROCEDURES	See appendix VII.
STUDY TREATMENT	**Study Cohort:** **<u>For patient numbers 1 to 50</u>** **Induction treatment (before HDM/ASCT):** Carfilzomib 20mg/m2 for days 1,2, then 45mg/m2 days 8,9,15,16 of cycle 1, then 27mg/m2 throughout next cycles. Thalidomide 200 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **Consolidation treatment (guideline 8 weeks after HDM/ASCT):** Carfilzomib 27mg/m2 days 1,2,8,9,15,16 of a 28 day cycle. Thalidomide 50 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **<u>For patient numbers 51 to 70</u>** **Induction treatment (before HDM/ASCT):** Carfilzomib 20mg/m2 for days 1,2, then 45mg/m2 days 8,9,15,16 of cycle 1, then 36mg/m2 throughout next cycles. Thalidomide 200 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **Consolidation treatment (guideline 8 weeks after HDM/ASCT):** Carfilzomib 36mg/m2 days 1,2,8,9,15,16 of a 28 day cycle. Thalidomide 50 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles.

	<u>For patient numbers 71 to 90</u> **Induction treatment (before HDM/ASCT):** Carfilzomib 20mg/m2 for days 1,2, then 45mg/m2 days 8,9,15,16 of cycle 1, then 45mg/m2 throughout next cycles. Thalidomide 200 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **Consolidation treatment (guideline 8 weeks after HDM/ASCT)**: Carfilzomib 45mg/m2 days 1,2,8,9,15,16 of a 28 day cycle. Thalidomide 50 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **<u>For patient numbers 91 to 110</u>** **Induction treatment (before HDM/ASCT):** Carfilzomib 20mg/m2 for days 1,2, then 56mg/m2 days 8,9,15,16 of cycle 1, then 56mg/m2 throughout next cycles. Thalidomide 200 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **Consolidation treatment (guideline 8 weeks after HDM/ASCT)**: Carfilzomib 56mg/m2 days 1,2,8,9,15,16 of a 28 day cycle. Thalidomide 50 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles. **<u>For patient numbers 111 to 145</u>** **Induction treatment (before HDM/ASCT):** Carfilzomib 20mg/m2 for days 1,2, then 56mg/m2 days 8,9,15,16 of cycle 1, then 56mg/m2 throughout next cycles. Thalidomide 200 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. **8 cycles**. **Consolidation treatment (guideline 8 weeks after HDM/ASCT):** Carfilzomib 56mg/m2 days 1,2,8,9,15,16 of a 28 day cycle. Thalidomide 50 mg days 1-28 of a 28 day cycle. Dexamethasone 20 mg days 1,2,8,9,15,16 of a 28 day cycle. 4 cycles.
PRIMARY ENDPOINT	Response (Complete response (CR), very good partial response (VGPR), overall response (OR)): • After induction prior to HDM/ASCT; • After HDM/ASCT prior to consolidation treatment; • At end of consolidation treatment.

SECONDARY ENDPOINTS	Efficacy and toxicity of induction treatment; Efficacy and toxicity of consolidation treatment; Feasibility of good quality stem cell harvest; Progression-free survival (PFS); Overall Survival (OS).
STATISTICAL METHODS	Phase II, non randomized design.

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INTRODUCTION

1.1. Disease Specific Background

Multiple myeloma is a malignancy of the plasma cells. It represents the second most common hematological malignancy. The annual incidence rates in northern Europe are 4-5/100.000. Approximately 850 cases of multiple myeloma are diagnosed in the Netherlands each year. Multiple myeloma is uniformly fatal. As the disease progresses, morbidity and eventual mortality are caused by reduced immunoresistance to infections, significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, and, less commonly, neurological complications and hyper viscosity. Despite the use of high-dose chemotherapy and autologous stem cell transplantation, this cancer remains incurable. The 5-year survival rate for patients with multiple myeloma among patients treated with conventional chemotherapy is 25%, while with intensified therapy this may increase to 50 %. Novel agents are urgently needed to improve the treatment results of this disease.

1.2. Induction treatment with novel agents

In the last few years, Thal/Dex has emerged as one of the most commonly used induction regimen for the treatment of newly diagnosed myeloma. The use of Thal/Dex was initially based on three phase II clinical trials which showed significant activity.[20-22] Response rates with Thal/Dex range 64-76% in these studies, comparable or better than those obtained with infusional VAD. Thal/Dex had the advantage over VAD of not requiring intravenous administration.

The Eastern Cooperative Oncology Group (ECOG) recently reported the results of a randomized trial comparing Thal/Dex to dexamethasone (Table 7).[18] Two hundred seven patients were studied. The best response within four cycles of therapy was significantly higher with Thal/Dex compared to dexamethasone alone; 63% versus 41%, respectively, P=0.0017. Adjusted response rates allowing for the use of serum M protein values alone in patients in whom a measurable urine protein at baseline was unavailable at follow-up were 72% with Thal/Dex versus 50% with dexamethasone alone. Stem cell harvest was successful in 90% of patients in each arm. DVT was more frequent with Thal/Dex (17% versus 3%). Overall, grade 3 or higher non-hematologic toxicities were seen in 67% of patients within four cycles with Thal/Dex and 43% with dexamethasone alone (P <0.001). Early mortality (first 4 months) was 7% with Thal/Dex and 11% with dexamethasone alone. Based on this trial, the United States Food and Drug Administration (FDA) granted accelerated approval for Thal/Dex for the treatment of newly diagnosed myeloma. Confirmatory results are available from a separate randomized, double-blind, placebo-controlled study comparing Thal/Dex versus placebo/dexamethasone (Placebo/Dex) as primary therapy in 470 patients with newly diagnosed myeloma.[23] Based on EBMT criteria, overall (complete plus partial) response to therapy was significantly higher with Thal/Dex compared with placebo/Dex, 63% versus 46%, respectively, p<0.001. Based on the IMWG criteria, the proportion of patients achieving CR or VGPR was 43.8% with Thal/Dex versus 15.8% with placebo/Dex, p<0.001, and the proportion of patients achieving CR was 8.1% with Thal/Dex vs.

3.0% with placebo/Dex, p=0.02. Response to therapy with Thal/Dex was rapid, with a median time to best response (CR or PR) of 8.3 weeks compared to 20.1 weeks for placebo/Dex. As in the ECOG study, grade 4 adverse events were more frequent with Thal/Dex than with Placebo/Dex (30.3% v 22.8%). With these two phase III trials discussed above Thal/Dex emerged as a reasonable induction regimen for front-line therapy in transplant candidates. Studies show that therapy with Thal/Dex does not significantly affect stem cell yield.[5,11]

A Dutch study compared thalidomide, Adriamycin, dexamethasone (TAD) with VAD as induction therapy.[1424] After induction patients in both arms proceeded to stem cell transplantation. A total of 556 patients were randomized and progression free survival was superior with TAD compared with VAD, median 33 months to 25 months, respectively (P<0.001). However no difference in overall survival was seen.

Patients receiving thalidomide in combination with high-dose steroids or chemotherapy need routine thromboprophylaxis with coumarin (target International Normalization Ratio (INR) of 2-3) or low-molecular weight heparin (equivalent of enoxaparin 40mg once daily). Aspirin can be used instead in patients receiving only low doses of dexamethasone (40mg once a week or lower) or prednisone in combination with thalidomide, provided no concomitant erythropoietic agents are used [25].

Despite the high activity of Thal/Dex, the regimen has limitations because of high non-hematologic toxicity seen in approximately two-thirds of patients. Thal/Dex is not superior to MP in elderly patients; results of a randomized trial show MP is preferable to Thal/Dex (using high dose Dex) in such patients because of increased death rate from infection associated withThal/Dex.[26 27] In younger patients, the increased response rates, TTP, and PFS seen with Thal/Dex and other thalidomide based regimens need to be considered in the context of other rapid advances occurring in the treatment of myeloma (see below). One option to reduce toxicity is to reduce the dose of dexamethasone to 40 mg once a week ("low dose dexamethasone"), based on findings with lenalidomide plus dexamethasone discussed below. However, there are no good data with this approach.

Bortezomib has been studied extensively in newly diagnosed myeloma, both in patients who are candidates for transplantation and in elderly patients. In newly diagnosed myeloma, bortezomib produces response rates of approximately 40% as a single-agent.[34] Significantly higher response rates (approximately 70-90%) have been observed with bortezomib plus dexamethasone (Vel/Dex) in phase II studies.[35,36] The CR plus VGPR rate is approximately 30% with Vel/Dex. Harousseau and colleagues reported preliminary results of a randomized trial comparing VAD versus Vel/Dex as pre-transplant induction therapy.[16] With 482 patients enrolled, preliminary results show superior response rates and progression-free survival with Vel/Dex compared to VAD. The incidence of grade 3-4 adverse events was comparable between the two regimens. No adverse effect on stem cell mobilization has been noted with Vel/Dex.

PAD (proteasome-inhibitor (bortezomib), adriamycin, dexamethasone) has shown high activity in newly diagnosed myeloma in a phase II study with an overall response rate of 95% and a complete response rate of 24%.[37] Sonneveld and colleagues tested PAD versus VAD in a randomized, open-label, phase III trial.[17] Patients with newly diagnosed myeloma ages 18-65 were randomly assigned to 3

cycles of VAD or PAD. VAD was administered at a dose of vincristine 0.4 mg, adriamycin 9 mg/m^2 days 1-4, dexamethasone 40 mg days 1-4, 9-12, and 17-20 (high dose dexamethasone). PAD was administered at a dose of bortezomib 1.3 mg/m^2 days 1,4,8,11, adriamycin 9 mg/m^2 days 1-4, and dexamethasone 40 mg days 1-4, 9-12, and 17-20. After induction therapy, all patients were to receive ASCT (one or two transplants) followed by maintenance with either thalidomide 50 mg daily in the VAD arm or bortezomib, 1.3 mg/m^2 *once every 2 weeks* in the PAD arm for 2 years. A total of 833 patients were randomized, and preliminary results on the first 300 patients are available. The overall response rate prior to ASCT was superior with PAD compared with VAD, 83% versus 59%, P<0.001. Corresponding CR rates were 5% versus 1%. Post transplant CR rates were 23% versus 9%, respectively, P<0.001. Eighty percent of patients achieved at least VGPR with this regimen of PAD followed by ASCT. Again, following PAD, stem cell harvest was adequate in all patients.
Cavo et al have compared Thal/Dex to bortezomib, thalidomide, dexamethasone (VTD) as pre transplant induction therapy in a randomized controlled trial.[38] A total of 399 pts (199 randomized to VTD and 200 to TD) could be evaluated for primary study and secondary end points. On an intent to treat basis, VTD had significantly higher response rates compared with Thal/Dex, 92% versus 78.5% respectively, P<0.001) following the 3 cycles of induction. CR rates were also better, CR (21% versus 6% respectively, P<0.001. Serious adverse events occurred in 14% of patients randomized to VTD versus 13% with Thal/Dex. There were no problems with stem cell mobilization, with median yields of9.3 and 10.6 (x10^6 CD34+ cells/Kg), respectively. On an intention-to-treat basis, post-transplant CR was higher with VTD compared with Thal/Dex, 41% vs. 20%, respectively, P<0.001. PFS was significantly superior with VTD as compared to Thal/Dex, P=0.04, but overall survival is similar so far. VTD thus is a highly active induction regimen, and has the additional advantage of not requiring major dose modifications in renal failure. [10]
Taken together, these results indicate that the combination of a proteasome inhibitor, thalidomide and dexamethasone offers some of the highest response rates in first-line multiple myeloma treatment. The clinical use of bortezomib in this setting is however hampered by the high incidence (~20%) of CTC grade 2-4 peripheral polyneuropathy, which is reason to prematurely discontinue bortezomib in the majority of these patients. It is anticipated that the combination of a non-neurotoxic proteasome inhibitor, such as carfilzomib, with Thalidomide and Dexamethasone will lead to a high response rate with low toxicity in first-line as well as relapsed multiple myeloma treatment.

1.3. Carfilzomib Background

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). 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[1,2].

1.3.1. Carfilzomib Toxicology Studies

In our initial Good Laboratory Practice (GLP)-compliant toxicity studies, carfilzomib was administered to rats and monkeys as two complete two-week cycles of QDx5 for five days with nine days rest. Administration to rats at 12 mg/m^2, the severely toxic dose in 10% of animals (STD_{10}), caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomib. Daily administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The dose-limiting toxicities (DLTs) of carfilzomib in both the rat and monkey 28 day GLP toxicity studies included toxicity to the gastrointestinal tract, bone marrow, pulmonary, and cardiovascular systems. No behavioral or histopathological signs of neurotoxicity were observed, and carfilzomib does not cross the blood-brain barrier.

In 6-month rat and 9-month chronic toxicity studies, carfilzomib was administered on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle, mimicking the most active anti-tumor regimen, as well as the currently preferred clinical regimen. Tolerability was excellent, with no evidence of peripheral (or central) neurotoxicity observed, even at high doses. This is in stark contrast to that observed with bortezomib[3,4]. DLTs included effects on the gastrointestinal, renal, pulmonary, and cardiovascular systems. 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. 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 maximum tolerated dose on a less intensive schedule[3].

1.3.2. Carfilzomib Preclinical Antitumor Activity

Based upon the results of *in vitro* and *in vivo* studies, it is anticipated that the more intense and longer duration of proteasome inhibition that can be achieved with carfilzomib will result in enhanced anti-tumor activity relative to bortezomib. Continuous (72 hr) exposure to carfilzomib is associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture.[1] Incubation of hematologic tumor cell lines with carfilzomib for as little as one hour leads to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib has also been demonstrated to be cytotoxic in bortezomib-resistant tumor cell lines.[5]

The anti-tumor efficacy of carfilzomib has been tested in immunocompromised mice implanted with a variety of tumor cell lines. In a human colorectal adenocarcinoma model HT-29, administration of carfilzomib on a twice-weekly Day 1, Day 2 schedule resulted in significant reduction in tumor size and was superior to a twice-

weekly Day 1, Day 4 schedule using the same dose of carfilzomib, and a once-weekly dosing schedule using twice the dose level. Bortezomib at its MTD has no activity in this xenograft model using the standard Day 1, Day 4 schedule.

1.3.3. Phase 1 Experience with Carfilzomib as a Monotherapy

A Phase 1 clinical trial, PX-171-002, testing carfilzomib in subjects with relapsed/refractory hematologic malignancies, is being completed[6]. During the dose escalation portion of the trial, 36 subjects received carfilzomib on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Subjects with Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Waldenström's Macroglobulinemia, and Hodgkin's Lymphoma (HL) were enrolled on the study.

No dose limiting toxicities (DLTs) were observed in the initial seven cohorts (doses ranged from 1.2 to 15 mg/m^2) of three subjects each. At the 20 mg/m^2 dose level, one of eight patients had a Grade 3 renal failure at Cycle 1, Day 2 which was considered possibly related to study drug and lasted for six days. The patient continued on study for the remainder of Cycle 1 before having disease progression. At the 27 mg/m^2 dose level, one of six subjects experienced a DLT during Cycle 1, consisting of severe hypoxia with pulmonary infiltrates following Day 2 of dosing. In subjects where the 27 mg/m^2 dose was efficacious, a "first dose effect" was seen that included a constellation of findings that appeared to be the clinical sequelae of rapid tumor lysis syndrome (TLS) and/or cytokine release. This effect was notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion. On the second day, three of five subjects with multiple myeloma experienced an increase in creatinine to Grade 2 (including the subject with the DLT). This elevation was rapidly reversible and all three subjects were rechallenged with carfilzomib without recurrence of the events. Interestingly, all three subjects had a rapid decline in serum and/or urine M-protein levels; two subjects achieved a PR and the third subject achieved a minimal response (MR). There were no consistent changes in potassium, calcium, phosphorous, or uric acid levels. Because of the possible TLS and reversible creatinine elevations, hydration and very-low dose dexamethasone prophylaxis were instituted in subsequent studies (see Section 1.5) and have essentially eliminated clinically significant TLS/creatinine elevations and the other "first-dose" effects.

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

Of the 36 evaluable patients enrolled in PX-171-002, 20 had MM[6]. Four MM patients achieved a partial response (PR), one of two at the 15 mg/m^2 dose, one of six at the 20 mg/m^2 dose, and two of five at the 27 mg/m^2 dose. The responses have been

rapid in onset, beginning in some subjects after 1-2 doses. The duration of response (DOR) ranged from 134 to 392 days. The minimal effective dose was 15 mg/m^2 wherein >80% proteasome inhibition in peripheral blood and mononuclear cells was observed one hour after dosing. The median number of prior therapies for subjects on this trial was five, and responses were seen in subjects who had relapsed from (including some refractory to) bortezomib and/or immunomodulatory agents. Stable disease also occurred in four NHL and five MM subjects, with subjects on therapy for up to 409 days. Such prolonged therapy, at "full" twice-weekly doses, is not possible with bortezomib. These results led to the initiation of two Phase 2 studies.

1.3.4. Phase 2 Experience with Carfilzomib as a monotherapy

Two Phase 2 clinical studies are ongoing with carfilzomib in MM patients, PX-171-003-A0 (N=46) in relapsed and refractory MM and PX-171-004 (N=39) in relapsed MM. In both studies, patients were dosed with 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 on a 28 day schedule. In these studies there were four cases of suspected or documented TLS prior to institution of the prophylaxis guidelines. No further cases of TLS have been reported. In both studies, the most common adverse events were fatigue, anemia, thrombocytopenia (primarily cyclical), gastrointestinal, and dyspnea. Almost all were Grades 1 or 2. There were reported cases of increased in serum creatinine that were primarily < Grade 2 and were transient, rapidly reversible, and non-cumulative. A very low rate of treatment-emergent peripheral neuropathy, 2.2% Grade 3/4, was observed in PX-171-003-A0 despite the fact that 78% of patients had Grade 1/2 neuropathy upon study entry.[7].

The response rate in PX-171-003-A0 was 18% PR, 7% MR and 41% SD in these patients that entered the study with progressive disease and were refractory to their most recent therapy, often including bortezomib and/or an immunomodulatory drug (usually lenalidomide). The median time to progression on the PX-171-003-A0 study was 5.1 months with a DOR of 7.4 months (mean follow up of 7.6 months). A "stepped up" dosing schedule, referred to as 20/27 mg/m^2, has subsequently been incorporated into the PX-171-003 study (referred to as PX-171-003-A1) in order to maximize the clinical benefit of carfilzomib. Patients receive 20 mg/m^2 for the first cycle and 27 mg/m^2 thereafter. To date, this dosing schedule has been well tolerated[7]. An independent Safety Oversight Group (SOG) evaluated the safety data from the 40 of 250 patients to be enrolled on the 20/27 schedule and agreed that the trial should proceed without modification. No cases of TLS were observed. The most common adverse events were similar to the A0 portion of the study. A decrease in cases of renal impairment was observed from 47% all grades with 15% Grade 3/4 in A0 to 35% all grades and 2.2% Grade 3/4/ in A1. This is most likely due to the implementation of guidelines for hydration. Treatment-emergent peripheral neuropathy remains low on this portion of the study with 15% Grade 1/2 and no Grade 3 or 4 reported to date on PX-171-003-A1. In addition, anemia rates in the PX-171-003-A1 (higher dose) were lower than those reported in the PX-171-003–A0 portion of the study, possibly indicating that the higher dose of carfilzomib is achieving better clearing of neoplastic cells in the bone marrow. Rates of

thrombocytopenia and neutropenia were similar in the two cohorts, with Grade 3 neutropenia in ~5% without any Grade 4 neutropenia to date.[7]
In PX-171-004, the subset of patients (N=14) that had not seen bortezomib had an ORR of 57% (7% CR, 14% VGPR and 36% PR), while the bortezomib treated patients (N=17) had an ORR of 18% (18% PRs)[8]. The median TTP was 11.1 and 8.3 months in these two groups, respectively. Thus, carfilzomib can induce very high levels of response in patients who have not previously been treated with bortezomib and, even in bortezomib-treated patients, substantial anti-tumor activity is observed. Of note, disease control (PR + MR + SD) was achieved in ~65% of patients with progressive MM entering the study. Patients on these studies have been treated for >12 cycles with good tolerability, and cumulative toxicity (e.g., bone marrow, severe fatigue, or neuropathy) have not been observed.

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

1.3.5. Experience with Carfilzomib in Combination with Lenalidomide and Dexamethasone

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

As of 20 April 2009, 20 subjects have been enrolled in the first 3 cohorts, of whom 18 are evaluable for both response and toxicity[9]. Median number of prior lines of therapy was 2.5 (range: 1, 3) and included dexamethasone (18 subjects), bortezomib, lenalidomide, stem cell transplant (14 subjects each), alkylators (11 subjects), thalidomide (7 subjects), and anthracyclines (6 subjects); 12 subjects received both prior lenalidomide and bortezomib. No DLTs have been observed with doses of carfilzomib and lenalidomide up to 20 mg/m^2 and 20 mg, respectively. Two subjects had transient lenalidomide-induced rash. Cohort 5 (carfilzomib 20 mg/m^2 and lenalidomide 25 mg) is now enrolling. Responses were rapid and occurred within the first 28-day cycle. Responses to date with a median of 4 cycles (range: 1-9) for Cohorts 1 - 3 are shown in Table 1[9].

Table 1: Response to Carfilzomib to Date

Cohort	CFZ / LEN (mg/m^2 -mg)	N	VGPR	PR	MR	SD	PD
1	15 - 10	6	-	3	0	1	2
2	15 - 15	5	1	1	2	0	1
3	15 - 20	7	2	2	0	3	-

These results suggest that carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in combination are active and well tolerated at doses well below the single agent MTDs of either lenalidomide or carfilzomib. Importantly, lenalidomide-associated neutropenia and thrombocytopenia do not appear to be exacerbated by concurrent treatment with carfilzomib, suggesting that carfilzomib will combine nicely with other anti-cancer agents.

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

1.4. Dose Rationale

Preliminary data suggest that carfilzomib as a single agent can produce substantial response rates in myeloma subjects across a variety of dosing cohorts. Responses were seen over a wide therapeutic window, from 15 to 27 mg/m^2. Greater than 80% proteasome inhibition was seen at doses 11 mg/m^2 and higher in whole blood samples taken 1 hour after the first dose. The final analysis of the human pharmacokinetic (PK) data is ongoing but appears to be rapid and similar to the results from the animal studies. Carfilzomib is rapidly cleared from plasma with an elimination half life of < 60 minutes at the 20 mg/m^2 dose. Large, single arm studies of the 27 mg/m^2 dose are ongoing and suggest that this dose is very well tolerated with patients being treated for >10 cycles without cumulative toxicities.

As of July, 2009, over 200 subjects with relapsed and refractory multiple myeloma have been treated with the 20/27 mg/m^2 stepped-up dosing schedule (i.e., 20 mg/m^2 for Cycle 1 and 27 mg/m^2 for all subsequent cycles). Phase 1b/2 solid tumor study patients are also receiving a stepped up dosing schedule using 20/36 mg/m^2. In the solid tumor study and in this present study, the stepped up dose of carfilzomib 27 mg/m^2 is administered on Day 8 of Cycle 1 and for all subsequent doses.

Recent studies have shown that higher dosing with Carfilzomib has resulted in improved responses in patients; an acceptable safety profile has been retained [11,12].

1.5. Study Rationale

Thalidomide and bortezomib combined with dexamethasone and a third agent (alkylating agent or anthracycline) are now recognized as the most active drugs for remission induction in transplant candidates. In elderly patients they are combined with Melphalan/Prednisone (MP) in first line treatment. Both drugs share the disadvantage of inducing peripheral polyneuropathy which is dose limiting in 50% of patients and leads to premature termination of treatment in 25%.

Replacing bortezomib by carfilzomib would associate effective proteasome inhibition with lack of neuropathy, thereby improving the proportion of patients who are able to complete the planned treatment and reducing the rate of serious adverse events, in

particular polyneuropathy. In view of the recently reported high response rates with Bortezomib containing regimens (VD, VRD, VCD, VTD, PAD) prior and after high-dose therapy, a regimen with Carfilzomib combining less polyneuropathy with similar efficacy would be a likely candidate for standard induction in the future. Equally, such regimen could be used for short consolidation treatment after high-dose therapy.

2.0 OBJECTIVES

2.1. Primary Objective

To establish the response, in patients with Multiple Myeloma at first presentation, to carfilzomib in combination with thalidomide and dexamethasone.

2.2. Secondary Objectives

To investigate the clinical efficacy and toxicity of carfilzomib in combination with thalidomide and dexamethasone in remission induction of Multiple Myeloma at first presentation.

To investigate the clinical efficacy and toxicity of carfilzomib in combination with thalidomide and dexamethasone in consolidation treatment of Multiple Myeloma at first presentation.

To assess the stem cell harvest following carfilzomib in combination with thalidomide and dexamethasone.

To assess Progression-free survival (PFS).

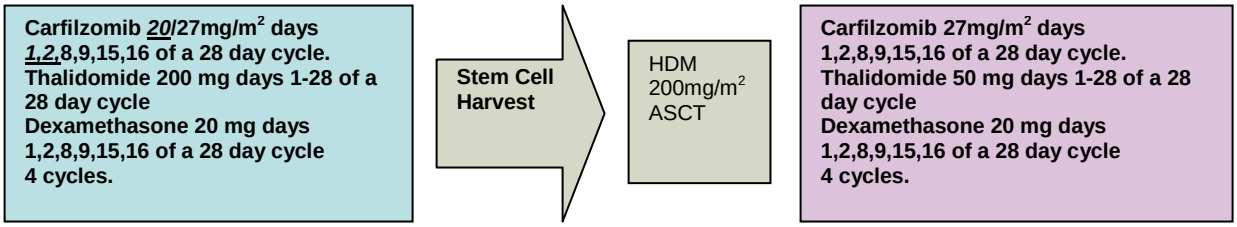
To assess Overall Survival (OS).

3.0 EXPERIMENTAL PLAN

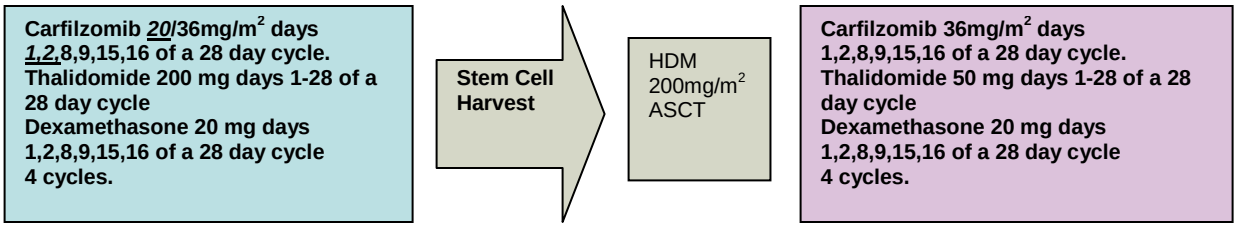
3.1. Study Design

This trial will try to establish the feasibility and efficacy of Carfilzomib, in combination with Thalidomide and Dexamethasone as an induction therapy prior to therapy with High Dose Melphalan (HDM) and Autologous Stem Cell Transplantation (ASCT) in previously untreated patients with Multiple Myeloma. In addition, the efficacy of a short consolidation schedule of Carfilzomib, in combination with Thalidomide and Dexamethasone will be investigated. The study will be conducted as a Phase II trial:

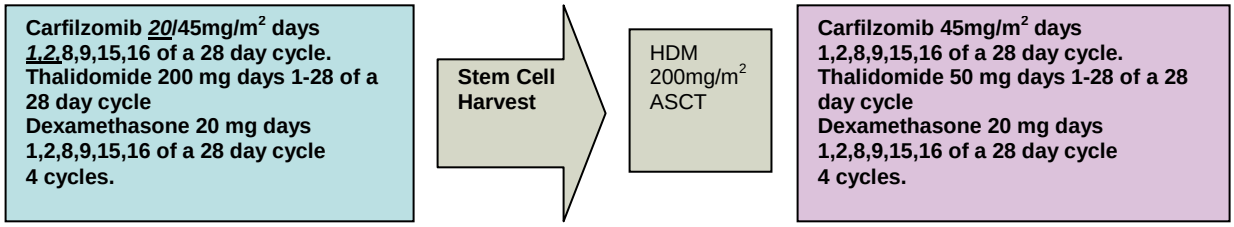
Patients number 1 to 50:



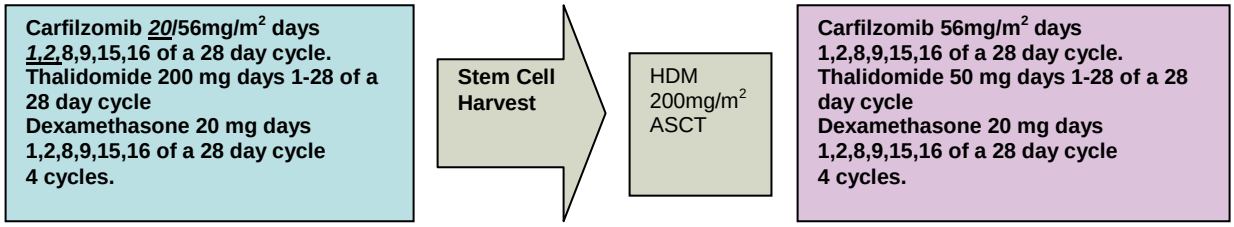
For 20 additional patients (numbers 51 to 70):



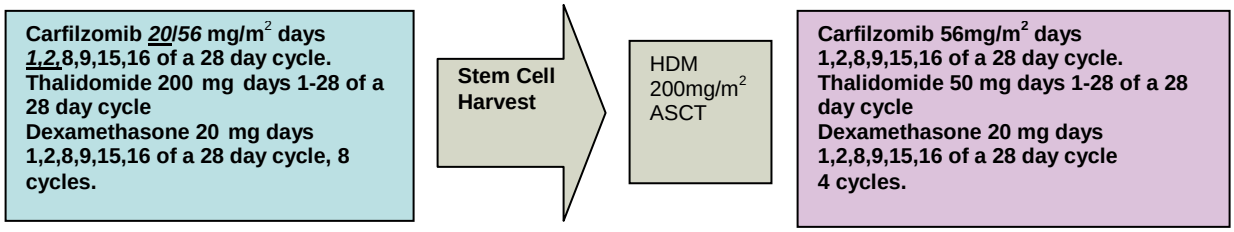
For 20 additional patients (numbers 71 to 90):



For 20 additional patients (numbers 91 to 110):



For 35 additional patients (numbers 111 to 145):



One hundred and forty five patients will be included in the study cohort. Extensive molecular (FISH) characterization and gene expression profiling of the myeloma tumor cells will be performed at inclusion, at remission for required confirmation and at relapse for diagnosis of relapse.
All patients will be followed closely for toxicities and response assessment, as indicated. After completion of treatment, all patients will be followed two-monthly until relapse or progression. Thereafter every 6 months until 5 years after registration.

3.2. Number of Centers

As of 14 June 2009, the following centers have agreed to participate:
Erasmus MC Rotterdam, The Netherlands
VUMC, Amsterdam, The Netherlands
UMCU Utrecht, The Netherlands
UMC Groningen, The Netherlands
AMC Amsterdam, The Netherlands
St. Antonius ZH Nieuwegein, The Netherlands
Isala, Zwolle, The Netherlands

3.3. Number of Subjects

145 patients will be enrolled.

3.4. Estimated Study Duration

Inclusion period: 12 months.
Treatment period: 11 months for patient 1 to 110 (4 months induction, 3 months HDM/ASCT, 4 months consolidation).
Treatment period: 15 months for patients 111 to 140 (8 months induction, 3 months HDM/ASCT, 4 months consolidation).

Follow up period: every 2 months until relapse or progression. Thereafter every 6 months until 5 years after registration.

3.5. Treatment Scheme

See section 3.1.

4.0 SUBJECT SELECTION

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

- Patients with a confirmed diagnosis of multiple myeloma stage I to III according to the ISS criteria (see appendix I);
- Age 18-65 years inclusive;
- WHO performance status 0-3 (WHO=3 is allowed only when caused by MM and not by co-morbid conditions) (see appendix II);
- Negative urine pregnancy test at inclusion if applicable;
- Written informed consent.

4.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to enroll in this study.

- Known intolerance of Thalidomide;
- Systemic AL amyloidosis;
- Non-secretory MM;
- Waldenstrom's macroglobulinemia or IgM MM;
- Previous chemotherapy or radiotherapy except 2 cycles of Melphalan/Prednisone or local radiotherapy in case of local myeloma progression;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix III);
- Severe pulmonary dysfunction;
- Significant hepatic dysfunction (serum bilirubin ≥ 30 μmol/l or transaminases ≥ 3.0 times normal level), unless related to myeloma;
- Creatinine clearance <15 cc/min;
- Alkaline Phosphatase >3x ULN;
- ANC < 1,0 $x10^9$/L, platelets < 75 $x10^9$/L, Hb < 4.9 mmol/L;
- Intolerance to thromboprophylaxis;
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- Patients with neuropathy, CTC grade 3 or higher or grade 2 painful peripheral neuropathy;
- Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;
- Patients (all males and all pre-menopausal women) who are not willing or capable to use adequate contraception during the therapy;
- Lactating women;
- WHO Performance status > 3.

5.0 SUBJECT ENROLLMENT

It is expected that 36 months will be required to recruit the 110 patients required for the study. 6 months is expected to be required the 35 patients for the 5th cohort.

6.0 TREATMENT PROCEDURES

6.1. Drug Preparation and Administration

Carfilzomib will be supplied on study. Carfilzomib for Injection is supplied as a lyophilized parenteral drug product in single-use vials. Prior to administration, the lyophilized product is reconstituted with Water for Injection (WFI), yielding 2 mg/mL solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

Please refer to the Pharmacy Manual for "Instructions for Handling of Lyophilized Carfilzomib for Injection."

Each dose will consist of Carfilzomib for Injection administered on an mg/m^2 basis and should be based on the subject's actual calculated BSA at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA. Carfilzomib for Injection will be given as an **IV infusion over approximately 30 minutes**. The dose will be administered at a facility capable of managing hypersensitivity reactions. Subjects will remain at the clinic for at least one hour following each dose of carfilzomib for clinical observation during all of Cycle 1 and Cycle 2, Day 1.

Before and after drug administration, the line must be flushed with 20 mL of normal saline.

Subjects should be well hydrated prior to dosing with carfilzomib. Subjects may receive rasburicase prophylaxis at the discretion of the Investigator. See Section 6.4.1.6.

Procedures for dose reductions, adjustments and delays are summarized in 6.2.

6.2. Dose Reductions/Adjustments

The following sections and tables summarize dosing modifications of carfilzomib, thalidomide, and dexamethasone to manage possible toxicity. Dose reduction levels of carfilzomib, thalidomide, and dexamethasone for toxicity management of individual subjects are provided in Table 2-3, respectively.
In case of major dose reductions/adjustments the study coordinator should be consulted.

Table 2: Dose Decrements for Carfilzomib

Nominal Dose	Reduced Carfilzomib Doses	
	Dose –1	Dose –2
20 mg/m^2	15 mg/m^2	11 mg/m^2
27 mg/m^2	20 mg/m^2	15 mg/m^2
36 mg/m^2	27 mg/m^2	20 mg/m^2
45 mg/m^2	36 mg/m^2	27 mg/m^2
56 mg/m^2	45 mg/m^2	36 mg/m^2

Table 3: Dose Decrements for Thalidomide

It is advised that thalidomide is not prescribed to patients with known poor tolerance to thalidomide during the consolidation phase of the trial.

	Reduced Thalidomide Doses		
Nominal Dose	Dose –1	Dose –2	Dose –3
200 mg	100 mg	50 mg	50 mg every other day

Table 4: Dose Decrements for Dexamethasone

Nominal Dexamethasone Dose	**Reduced Dexamethasone Doses**	
	Dose –1	**Dose –2**
20 mg	10 mg	0 mg

Treatment guidelines for hematologic and nonhematologic toxicities are outlined in Sections 6.2.1 and 6.2.2, respectively.

Guidelines for dexamethasone dose modifications for are summarized in Table 7.

6.2.1. Dose Reductions for Hematologic Toxicities

Guidelines for the management of hematologic toxicities (thrombocytopenia and neutropenia) are summarized in Table 5.

6.2.2. Dose Reductions for Non-Hematologic Toxicities

Guidelines for the management of non-hematologic toxicities are summarized in Table 6.

Table 5: Treatment Guidelines for Hematologic Toxicity

Thrombocytopenia

	Recommended Action	
When Platelets:	**Thalidomide**	**Carfilzomib**
Fall to < 20 × 10^9/L for > 7 days or <10 x 10^9/L for any duration	Interrupt both thalidomide and carfilzomib, follow CBC weekly	
Return to ≥ 20 × 10^9/L	Resume at full dose	Resume at 1 dose decrement
Return to ≥ 30 × 10^9/L	Resume at full dose	Resume at full dose

Neutropenia

	Recommended Action	
When ANC	**Thalidomide**	**Carfilzomib**
Falls to < 0.5 × 10^9/L	Interrupt both thalidomide and carfilzomib, add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly	
Returns to > 1.0 × 10^9/L	Resume at full dose	Resume at full dose
Subsequently drops to < 0.5 × 10^9/L	Interrupt both thalidomide and carfilzomib	
Returns to > 1.0 × 10^9/L	Resume at full dose	Resume at full dose

Table 6: Treatment Guidelines for Nonhematologic Toxicity

Symptom	Recommended Action	
	Thalidomide	**Carfilzomib**
Grade 2 treatment-emergent neuropathy with pain or Grade 3 neuropathy	Hold until ≤ Grade 2 without pain. Then restart at 1 dose decrement	Continue to dose. If neuropathy persists for more than 2 weeks after holding thalidomide, hold carfilzomib until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement
Grade 4 neuropathy	Discontinue	Hold carfilzomib until resolved to ≤ Grade 2 without pain. Then restart at 1 dose decrement.
Non-Blistering Rash		
Grade 3	Hold (interrupt) dose; follow weekly If toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement. Discontinue medications that may cause rash (allopurinol, sulphonylureas, etc.).	Continue to dose; if Grade 3 rash persists for > 2 weeks after holding thalidomide, hold carfilzomib until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue thalidomide	Hold until ≤ Grade 1, reinstitute at full dose.
Desquamating (blistering) rash – Any Grade	Discontinue thalidomide	Hold until ≤ Grade 1, reinstitute at full dose.
Erythema multiforme ≥ Grade 3	Discontinue thalidomide	Continue to dose; if Grade 3 rash persists for > 2 weeks after holding thalidomide, hold carfilzomib until ≤ Grade 1, reinstitute at full dose.
Sinus bradycardia/ other cardiac arrhythmia	Hold (interrupt) dose. Follow at least weekly.	Hold until ≤ Grade 1, reinstitute at full dose.
≤ Grade 2	If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	
≥ Grade 3	Discontinue thalidomide	Hold until ≤ Grade 1, reinstitute at full dose.

Symptom	Recommended Action	
	Thalidomide	**Carfilzomib**
Allergic reaction/hypersensitivity		
Grade 2 – 3	Hold (interrupt) dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	Hold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue	Discontinue
Tumor lysis syndrome (≥ 3 of following: ≥ 50% increase in creatinine, uric acid, or phosphate; ≥ 30% increase in potassium; ≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold both thalidomide and carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	
Infection Grade 3 or 4	Hold both thalidomide and carfilzomib until systemic treatment for infection complete. If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.	
Herpes zoster or simplex of any grade	Hold both thalidomide and carfilzomib until lesions are dry. Reinstitute at full doses	
Renal Dysfunction		Renal Dysfunction
CrCl > 15 mL/min	Full dose	Full dose
CrCl ≤ 15 mL/min	Full dose	Hold until CrCl > 15 mL/min; restart at 1 dose decrement

Table 6: Treatment Guidelines for Nonhematologic Toxicity (continued)

Symptom	Recommended Action	
	Thalidomide	**Carfilzomib**
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) thalidomide dose and adjust anticoagulation regimen; re-start at Investigator's discretion at full dose	Full dose
Hyperthyroidism or hypothyroidism	Omit thalidomide for remainder of cycle, evaluate, and initiate appropriate therapy. Restart thalidomide next cycle at 1 dose decrement	Full dose
Congestive heart failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose or the subject may be withdrawn from the study. If no resolution after 2 weeks, the subject will be withdrawn from the study.	
Other non-hematologic toxicity assessed as thalidomide-related ≥ Grade 3	Hold thalidomide dose. Follow at least weekly. If the toxicity ≤ Grade 1 before Day 21, restart at 1 dose decrement and continue until Day 21	Full dose
Other non-hematologic toxicity assessed as carfilzomib-related ≥ Grade 3	Full dose	Hold dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement
Other nonhematologic toxicity assessed as drug-related ≥ Grade 3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Hold dose and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline

Table 7:Treatment Guidelines for Dexamethasone-related Toxicity

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone permanently.
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone at one dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Neurology	Confusion or mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists discontinue dexamethasone permanently.
Metabolic	Hyperglycemia ≥ Grade 3	Treatment with insulin or PO hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.

6.2.3. Missed Doses

Missed doses of carfilzomib will be given after the last administration of a given cycle following the same weekly scheduling.

6.2.4. Changes in Body Surface Area (BSA)

Dose adjustments for carfilzomib do not need to be made for weight gains/losses of ≤ 20%. Subjects with a BSA of 2.2 m^2 or higher receive a dose based upon 2.2 m^2 BSA.

6.3. Autologous Stem cell transplantation

In all eligible patients (see section 4.0) stem cell collection will be performed 4-6 weeks after last Carfilzomib administration, after priming with Cyclophosphamide and G-CSF, according to local protocols. Stem cells will be harvested at a minimum of ≥ 4 x 10^6 $CD34^+$ cells/kg and cryopreserved.

6.3.1. Eligibility criteria for Cyclophosphamide and stem cell collection

- WHO performance 0-2;
- Absence of severe pulmonary, neurologic, or psychiatric disease;
- Bilirubin and transaminases of less than 2.5 times the upper limit of normal values.

6.3.2. Stem cell mobilization with Cyclophosphamide and G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	up to 4000 mg/m^2	i.v.	1
G-CSF (filgrastim)	10 μg/kg (divided in 2 gifts daily, according to local rules)	s.c.	day 5 until last pheresis*

6.3.3. Special management orders in conjunction with Cyclophosphamide

Selective gut decontamination may be performed according to local protocols.

6.3.4. Stem cell collection

Stem cell collection will be performed as soon as $CD34^+$ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. In case double intensification is planned (immediately or a second course at relapse) a minimum of 5 x 10^6 $CD34^+$ cells/kg is required. Otherwise 2.5 x 10^6 $CD34^+$ cells/kg are sufficient. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed.
Patients who do not meet the eligibility criteria for intensification will go off protocol treatment.

It should be noted that no response or progressive disease by itself is not a reason to go off protocol treatment.

6.3.5. High Dose Melphalan

All patients who meet the eligibility criteria for intensification will be treated with High Dose Melphalan 200 mg/m² total (given in two days) followed by autologous stem cell reinfusion. All eligible patients will start intensification with High Dose Melphalan between 4 and 6 weeks after stem cell collection.

6.3.6. Eligibility criteria for intensification

- WHO performance 0-2;
- Absence of severe pulmonary, neurologic, or psychiatric disease;
- Bilirubin and transaminases of less than 2.5 times the upper limit of normal values;
- A suitable stem cell graft containing at least 2.5 x 10^6 $CD34^+$ cells/kg.

6.3.7. High Dose Melphalan followed by stem cell reinfusion

Agent	Dose/day	Route	Days
Melphalan	100 mg/m²	i.v. rapid infusion	-3, -2*
Stem cell infusion	2.5 x 10^6 $CD34^+$ cells/kg		0

* Patients with renal insufficiency 100 mg/m² only at day –3.
Although Melphalan pharmacokinetics are not adversely affected by impaired renal function, the general toxicity of Melphalan 200 mg/m^2 total may be increased in patients with a creatinine clearance ≤ 40 ml/min. For patients with a creatinine clearance ≤ 40 ml/min, Melphalan dose should be reduced to 100 mg/m^2 total, given only at day -3.

6.3.8. Special management orders with Melphalan 200 mg/m² total and stem cell reinfusion

A hydration regimen will be started 30 minutes before administration of Melphalan and consists of 500 ml NaCl 0.9 % and 40 mmol KCl over 1 hour. Diuretics must be administered when needed. On day 0 the stem cells are thawed at the bedside and infused without washing steps. The procedure will be performed according to the local standard protocols.

6.3.9. Supportive care during Melphalan 200 mg/m² induced aplasia

- Placement of an indwelling central venous catheter;
- Anovulatory drugs for menstruating females;
- Antibacterial and antifungal prophylaxis;
- Antistreptococcus prophylaxis is recommended from day +4 until day +14.

6.4. Safety Considerations

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

- A "first-dose" effect has been seen, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis *and/or* cytokine release.

- Should a "first-dose" effect occur at any point during Cycle 1 or 2, treatment with high dose glucocorticoids (e.g. methylprednisolone 50-100 mg) is recommended. In addition, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted as medically indicated.

- All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. Renal function must be monitored closely during treatment with carfilzomib. **Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib during Cycles 1 and 2.** Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.

- Subjects with active or suspected infections of any kind should not be dosed with carfilzomib until infection has resolved and if being treated with an anti-infective, the course of antibiotics has been completed.

- Subjects with grade 4 neutropenia should not be treated until ANC resolves to $>0.5 \times 10^9$/L..

- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts < 20,000/mm^3 lasting > 7 days or < 10,000/ mm^3 for any duration carfilzomib dosing must be held. If platelet counts do not recover, the dose of carfilzomib may be reduced or held according to the Dose Reductions/ Adjustments rules outlined in Section 6.2.1.

- Subjects should have anemia corrected in accordance with the Institutional guidelines.

- Drug should be withheld for all ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline, with exceptions, as noted in Section 6.2. After resolution of the ≥ Grade 3

non-hematological toxic effects, treatment with carfilzomib will resume, according to the guidelines as summarized in Section 6.2.2.

- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

6.4.1. Guidelines for Monitoring, Prophylaxis, and Treatment of Tumor Lysis Syndrome (TLS)

TLS, which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some patients with MM who have been treated with carfilzomib.

The following safety measures are mandatory for all subjects. In addition, MM subjects with high tumor burden (e.g., ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk.

6.4.1.1. Hydration and Fluid Monitoring

1. Oral hydration

For subjects thought to be at particularly high risk for the development of TLS, based on high tumor burden, PO hydration up to 48 hours before starting carfilzomib may be given.

2. Intravenous Fluids

Intravenous hydration will be given immediately prior to carfilzomib during Cycle 1 and at the investigator's discretion in Cycle 2 and higher. This will consist of 250 to 500 mL IV normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload (refer to the current carfilzomib IB).

Post-dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) may be given immediately after carfilzomib during Cycle 1 as needed and at the investigator's discretion in Cycle 2 and higher. Subjects should be monitored periodically during this period for evidence of fluid overload.

6.4.1.2. Laboratory Monitoring

Obtain *and* review serum electrolytes and chemistries ***prior*** to each administration of carfilzomib on Days 1, 2, 8, 9, 15, and 16 during Cycles 1 and 2 *and* on Days 3, 10, and 17 of Cycle 1. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with

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

If risk factors for TLS persist after Day 17 of Cycle 1, monitoring of serum chemistries on Days 3, 10, and 17 should be continued through Cycle 2.

6.4.1.3. Clinical Monitoring

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

6.4.1.4. Management of Tumor Lysis Syndrome

A "first-dose effect" has been seen, which is notable for fever, chills, and/or rigors occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a "first dose" effect occur at any point during Cycle 1 or 2, treatment with glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted, as medically indicated.

If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

All cases of TLS must be reported to Onyx as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

6.4.1.5. Dosing carfilzomib in Subjects with Acute or Chronic Renal Insufficiency

Carfilzomib has not been fully characterized in subjects with creatinine clearance < 15 mL/min. It is critical that the subject's renal function is known at the time of dosing. See Section 6.2 for guidance regarding dose reduction in subjects with compromised renal function.

6.4.1.6. Urate Lowering Prophylaxis

At the discretion of the investigator, uric acid levels may be corrected to within normal range prior to carfilzomib doses during Cycles 1 and 2. For subjects judged to be at increased risk for Tumor Lysis Syndrome by the investigator, initiate rasburicase 3 mg iv prior to the

planned first dose of carfilzomib (Day 1 and Day 8, Cycle 1). If risk factors for TLS no longer exist, rasburicase may then be discontinued. Other uric acid lowering agents such as febuxostat may be substituted for raburicase.
The use of allopurinol is not advised because of possible medication interaction with Carfilzomib.

In patients considered to be still at risk for TLS at completion of Cycle 1, rasburicase may be continued into Cycle 2, if clinically indicated.

The dose of rasburicase should be adjusted based on renal function, if indicated, according to its package insert.

6.5. Concomitant Medications

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

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential.

Approved bisphosphonates and erythropoietic agents are allowed. Subjects may receive antiemetics and antidiarrheals as necessary, but these should not be administered unless indicated. Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

Subjects may receive RBC or platelet transfusions, if clinically indicated, per institutional guidelines. Subjects who require repeated platelet transfusion support should be discussed. Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines.

Subjects should receive antibiotic prophylaxis with ciprofloxacin or other fluoroquinolone. In addition, subjects should receive acyclovir or similar (famiciclovir, valacyclovir) anti-varicella (anti-herpes) agent prophylaxis.
The use of trimethroprim/sulfamethoxazole (co-trimoxazol) is not advised because of possible medication interaction with Carfilzomib.

Palliative radiation therapy is permitted if clinically indicated.

Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

All subjects must receive prophylaxis with hydration and patients at high risk for TLS should receive allopurinol or rasburicase (see Section 6.4.1).

6.5.1. Excluded Concomitant Medications

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

7.0 STUDY TESTS AND OBSERVATIONS

See appendix VII for study flow sheet of procedures

7.1. Required investigations at entry, during treatment and during follow up

Prior to treatment at entry

- Medical history;
- Prior history of multiple myeloma, diagnostic results, prognostic factors (cytogenetics / FISH), prior treatment, prior response to treatment and toxicities;
- Physical examination including body weight, height, signs of extramedullary myeloma;
- WHO performance status;
- Urine pregnancy test;
- Hematology;
- Blood chemistry;
- Serum b2-microglobulin;
- Serum and urine M-component type (immune-electropheresis and immune fixation) and M-component quantification ;
- Chest X-ray (at entry or within the last month) and skeletal radiography (at entry or within the last 3 months);
- Cardiac ejection fraction, measured by MUGA or echocardiogram (at entry or within the last month);
- ECG (at entry or within the last 48 hours);
- Coagulation studies including fibrinogen, fibrin degradation products;
- Bone marrow aspiration for:
    - Cytology and cytochemistry to establish the number of plasma cells (%)
    - Cytogenetics (cell culture and banding analysis) and FISH
    - Molecular analysis (see Appendix VI).

- Bone marrow biopsy for histopathology;
- Peripheral blood for Molecular analysis (see Appendix VI).

Prior to each induction treatment cycle

- History and physical examination;
- WHO performance status;
- Hematology;
- Blood chemistry;
- Qualitative and quantitative serum and urine M-component (immune electrophoresis and immune fixation);
- Bone marrow examination for % plasma cells at the moment of complete disappearance or reappearance of serum/urine M-component and/or at 4 weeks after last treatment;
- Skeletal radiography at the moment of complete disappearance of serum/urine M-component and/or at 4 weeks after last treatment.

Prior to High-dose Melphalan and autologous stem cell transplantation

- Stem cell harvest evaluation;
- History and physical examination;
- WHO performance status;
- Hematology;
- Blood chemistry;
- Serum b2-microglobulin;
- Qualitative and quantitative serum and urine M-component (immune electropheresis and immune fixation);
- Cardiac ejection fraction, measured by MUGA or echocardiogram (on indication);
- Bone marrow examination for % plasma cells at the moment of complete disappearance or reappearance of serum/urine M-component and/or at 4 weeks after last treatment;
- Skeletal radiography at the moment of complete disappearance of serum/urine M-component and/or at 4 weeks after last treatment.

After High-dose Melphalan and autologous stem cell transplantation and prior to each consolidation cycle

- History and physical examination;
- WHO performance status;
- Hematology;
- Blood chemistry;
- Qualitative and quantitative serum and urine M-component (immune electropheresis and immune fixation) once monthly;

- Bone marrow examination for % plasma cells at the moment of complete disappearance or reappearance of serum/urine M-component and/or at 4 weeks after last treatment;
- Skeletal radiography at the moment of complete disappearance of serum/urine M-component and/or at 4 weeks after last treatment.

At every 2 monthly follow up visit

- History and physical examination;
- WHO performance status;
- Hematology;
- Blood chemistry;
- Qualitative and quantitative serum and urine M-component (immune electropheresis and immune fixation);
- Bone marrow examination for % plasma cells at the moment of complete disappearance or reappearance of serum/urine M-component and/or at 4 weeks after last treatment;
- Skeletal radiography at the moment of complete disappearance of serum/urine M-component and/or at 4 weeks after last treatment.

If patient discontinues for any reason

- History and physical examination;
- WHO performance status;
- Hematology;
- Blood chemistry;
- Qualitative and quantitative serum and urine M-component (immune electropheresis and immune fixation);
- Bone marrow examination for % plasma cells at the moment of complete disappearance or reappearance of serum/urine M-component and/or at 4 weeks after last treatment;
- Skeletal radiography at the moment of complete disappearance of serum/urine M-component and/or at 4 weeks after last treatment.

Medical history
Standard medical history, with special attention for:
- WHO performance status;
- Bone pain;
- Infections;
- Bleeding tendency;
- Constipation;
- Polyneuropathy.

Only at entry:
- Occupational history;
- Prior and present other diseases;
- Antecedent hematological or oncological diseases;

- Previous chemotherapy or radiotherapy.

Physical examination

Standard physical examination including body weight and height, with special attention for:

- Macroglossia;
- Kyphoscoliosis;
- Orthostatic hypotension;
- Carpal tunnel syndrome;
- Polyneuropathy or other neurologic symptoms;
- Edema;
- Infections;
- Bleeding tendency.

Hematology

- Hemoglobin;
- Hematocrit;
- Reticulocytes;
- WBC count, differential count;
- Platelets;
- At entry: PB for molecular analysis (see appendix VI);
- At relapse/progression: PB for molecular analysis (see appendix VI).

Blood chemistry

- BUN;
- Serum creatinine;
- Liver enzymes (AST & ALT);
- Bilirubin (direct & indirect);
- Alkaline phosphatase;
- Total proteins;
- Albumin;
- LDH;
- Glucose;
- Gamma GT;
- CRP;
- Calcium;
- Phosphate;
- Sodium;
- Potassium;
- Uric acid.

Immunochemistry

- Qualitative and Quantitative serum M-protein, including immunofixation to confirm CR;
- Qualitative and Quantitative urine M-protein in 24 hrs urine, including immunofixation to confirm CR.

Bone marrow

- Bone marrow biopsy;

Bone marrow aspirate at entry for:

- Morphology;
- Cytogenetic analysis (see 11.2.9);
- Molecular analysis (Appendix VI);

Bone marrow aspirate at response evaluation for confirmation of response (CR):

- Morphology including immunofixation to confirm CR.
- Flowcytometric MRD analysis

Bone marrow aspirate at progression for:

- Morphology;
- Cytogenetic analysis (see 11.2.9);
- Molecular analysis (Appendix VI).

Specific investigations

- Serum b2-microglobulin;
- Creatinin clearance if increased serum creatinin;
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones;
- X-Thorax;
- ECG;
- Cardiac ejection by scintigraphy or cardiac echo; a Left Ventricular Ejection Fraction (LVEF) should be performed in all patients before start of treatment. In addition it is recommended to repeat the LVEF during pre-transplantation screening prior to HDM.

Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis;
- Bleeding time;
- Cryoglobulins, cold agglutinins;
- Serum viscosity, fundoscopy;
- Spirometry.

Cytogenetic analysis

Conventional cytogenetic analysis should have been already performed in all patients at diagnosis. For this study additional FISH analysis is required for chromosome 13q deletions and for numerical aberrations for chromosome 9 or 11 (to detect hyperdiploidy) and for 14q32 abnormalities. The following cytogenetic abnormalities will be evaluated as prognostic variables: 1p/q, t(4;14)(p16;q32), t(14;16)(q32;q23), del(13q), 13q-, numerical

abnormalities 9 or 11 (i.e. hyperdiploidy), complex cytogenetic abnormalities. Conditions for FISH will be used as standardized by the HOVON Cytogenetic Working Party.

Molecular analysis
Gene expression profiling, miRNA profiling, paired-end whole exome sequencing and SNP analysis will be performed to further characterize MM subgroups at the molecular level, to find new biomarkers with prognostic value, to elucidate mechanisms of drug resistance & disease progression and identify SNPs related to treatment outcome and side-effects. Bone marrow samples and peripheral blood will be drawn before start of treatment, at time of confirmation of response and at progression. Samples will be sent to the Erasmus MC as per instructions in Appendix VI. Since there are inter-ethnic differences in frequency of SNPs, it is necessary to document the ethnicity of patients included in the trial. This will allow us to perform multivariate analysis to find whether a certain SNP is an independent prognostic factor.

7.2. Response evaluation

The response to induction treatment will be evaluated after each cycle and at 2 months intervals during consolidation treatment. Response will be evaluated according to International Myeloma Working Group (IMWG) criteria, see appendix IV. Progression-free survival will be calculated from the start of therapy until progression or death.

8.0 STUDY DISCONTINUATION

8.1. Study termination

The study can be discontinued when 50 evaluable patients have been included. The principal investigator and/or company can decide on premature study discontinuation in case of unexpected or serious toxicity.

9.0 ADVERSE EVENTS

9.1. Adverse Events Definitions

An AE is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.0 should be used to describe the event and for assessing the severity of AEs (see Appendix V). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.
For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

9.2. Causality

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

- Yes: The event is suspected to be related if:
  - there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
  - there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or

- the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

- No:
  - the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
  - the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
  - the event is unlikely to be related to the investigational product(s)

9.3. Adverse Events Reporting Procedures

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate form.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.

AEs should be reported from the time the subject signs consent through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever occurs first. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject is randomized but discontinues study prior to receiving any study drug, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone, and documented in the subject's source. AEs continuing at 30 days post-last dose should have a comment in the source by the Investigator that the event has stabilized or is not expected to improve.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI-CTCAE grading scale v4.0.

All Grade 3 and 4 laboratory abnormalities must be recorded as AEs on the CRF. Grade 1 and 2 abnormalities should only be recorded if they require treatment or are otherwise considered clinically significant by the Investigator.

Expected AEs that occur during ASCT or in recovery period after ASCT do not have to be reported.

The Principal Investigator may delegate these duties to Subinvestigators and must ensure that these Subinvestigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572.

9.4. Serious Adverse Events Definitions

An SAE is one that meets the following criteria:

- Death
- Life threatening experience defined as any adverse experience that places the subject, in the view of the Investigator, at immediate risk of death at the time of occurrence; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject
- Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE, when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any death occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the Sponsor as an SAE.

9.5. Serious Adverse Event Reporting and Documentation Requirements

All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. All SAEs regardless of relationship to study drug must be followed to resolution or to stabilization if improvement or resolution is not expected.

If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The Investigator-sponsor must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The Investigator-sponsor is responsible for notifying the appropriate health authorities (HAs), ethics

committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations. Any safety report submission will cross reference the Onyx investigational new drug (IND) or clinical trial approval (CTA) number. The Investigator is also responsible for notifying the local ECs in accordance with local regulations. Additionally, the Investigator-sponsor is responsible for reporting SAEs to Onyx as described below:

SAE Reporting by Investigator-sponsor to Onyx
The Investigator-sponsor must inform Onyx in writing by e-mail or fax at the contact information listed below for all SUSARs that are judged as reasonably related to the Onyx study drug. Site will transmit the final CIOMS of that event to Onyx within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Onyx in English.

The Individual Case Safety Report (ICSR) may be referred to as an individual safety report or SAE Report, including Pregnancy Exposure Reports and Follow up Reports. The ICSR must be as complete as possible, at a minimum including event reference number, protocol name and number, investigator contact information, specific patient identifiers (e.g., initials, patient number, date of birth or age, or gender), the name of the suspect Study Drug, the date and dosage(s) of exposure, event, the date(s) of event, country of event, "Serious" Criteria, Relationship/causality of Study Drug, Hospitalization history for the event, Event status/outcome, Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment, and narrative summary.
Sponsor shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports and will exercise commercially reasonable due diligence to obtain follow-up information on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the Company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, Company will not contact non-party investigators directly, but will route all such inquiries through Site for forwarding to such investigator(s). Site will be responsible to ensure such inquiries are completed and timely provided to Company.

Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant laboratory values, scan data and autopsy reports) which are received after the initial report must be documented on a follow-up form, and submitted to Onyx in the same timelines as outlined above. Sponsor shall be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts.

Other aggregate analysis including reports containing safety data generated during the course of the study is to be submitted to Onyx at the time the sponsor ISS submits to anybody

governing research conduct i.e. RA, IRB etc. Final study report including unblinding data when applicable and reports of unauthorized use of a marketed product to be submitted to Onyx at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. but not later than one calendar year of study completion.

Sponsor will provide an annual IND report to Onyx. Reports containing safety data generated during the course of the study is to be submitted to Onyx at the time the sponsor submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. Sponsor will support reconciliation of all ICSRs at the end of the study at a minimum.

Onyx Drug Safety and Pharmacovigilance Contact Information:

- Drug Safety Reporting Fax
- Toll-free US 888-814-8653
- Toll US 805-480-9205

Drug Safety Reporting by secure e-mail can be established upon request.

9.6. Pregnancy

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of carfilzomib, Onyx Drug Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Onyx Drug Safety and Pharmacovigilance Contact information above). If the subject is pregnant, carfilzomib must be withheld.
Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to report the results to Onyx Drug Safety.
If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

10.0 STATISTICAL ANALYSIS

10.1. Study Design

This phase II study is designed to determine whether induction treatment with Carfilzomib and Thalidomide/Dexamethasone (CTD) warrants further investigation in clinical trials. The CR+VGPR rate after 4 cycles of CTD chemotherapy will be considered as primary endpoint for the sample size calculation.

- Let P_0 be the largest CR+VGPR rate which, if true, implies that the therapeutic activity is too low and therefore does not warrant further investigation. In the present trial, P_0 has been taken as 15% (25%).
- Let P_1 be the smallest CR+VGPR rate which, if true, implies that the therapeutic activity is sufficiently high and therefore this schedule warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 45%.

In order to reject the null hypothesis H_0: $P = P_0$ in favor of the alternative hypothesis H_1: $P = P_1$ with power $1 - \beta = 0.80$ (2-sided significance level $\alpha = 0.05$), 53 (41)* eligible patients are required. However, in order to overcome dropout, 60 (50)* patients will be included in the phase II trial.

For cohort 5, the primary endpoint will be the CR rate after 8 induction cycles. All patient who complete 8 induction cycles and are then in CR, will be considered a success. All other patients, including those who discontinue protocol treatment before cycle 8 and those with an early CR but with progression before or following cycle 8, will be considered a failure.

The aim of this cohort is to evaluate whether 8 cycles of induction treatment result in a sufficiently high CR rate to consider this regimen for further investigation in clinical trials.

10.1.1. Sample size and power considerations

For the sample size calculation, the optimal Simon two-stage design has been used[13]. This design shields patients from an ineffective regimen by requiring early termination of the trial if the results are not sufficiently promising.

The following parameters and decision rules are used:
- P0 is the highest CR rate after induction cycle 8, which, if true, implies that this regimen is not sufficiently active and does not warrant further investigation. In the present trial, P0 has been taken as 30%.
- P1 is the lowest CR rate after cycle 8, which, if true, implies that this regimen is active and does warrant further investigation of the current regimen. In the present trial, P1 has been taken as 55%.

Statistical errors will be:
- α is the accepted probability of recommending for further investigation a regimen with a true "success" rate equal to or smaller than P0. In the present trial, α has been taken as 0.10.
- β is the accepted probability of rejecting from further trials a regimen with a true "success" rate of at least P1. In the present trial, β has been taken as 0.10.

These design parameters imply that a maximum of 31 patients should be treated within cohort 5, with an interim analysis after the first 13 registered patients:

- If after the first 13 registered patients, ≤ 4 have a CR after induction cycle 8, the trial will be closed for further entry with the conclusion that the regimen is not sufficiently effective, and should not be further investigated. Otherwise entry will be extended to 31 patients.
- If after 31 registered patients ≤ 12 patients have a CR after induction cycle 8, the conclusion will be that the regimen is not sufficiently effective, and should not be further investigated.
- Otherwise, the trial will conclude that the induction regimen is effective, and warrants further investigation in this patient population.

Patients who have been registered but afterwards appear to be not eligible, based on data that should have been available at registration, will be excluded from all analysis. Therefore a total of 35 patients will be registered.

10.2. Statistical analysis

All analyses will be according the intention to treat principle, restricted to eligible patients. A safety analysis is planned after 20 evaluable patients have been included. This analysis will focus on hematologic and non-hematologic toxicities. The following stopping rule will be applied: if 5 or more patients have experienced grade ≥3 non-hematologic toxicity or grade 4 hematologic toxicity, the trial will be amended.

10.3. Efficacy analysis

The main endpoint of the phase II part is the proportion of patients who obtain a CR or VGPR during induction chemotherapy. A 95% confidence interval (CI) will be constructed, and the null hypothesis H_0: $P = P_0$ will be rejected in favor of the alternative hypothesis H_1: $P = P_1$ if the lower bound of the 95% CI is larger than 0.15 (0.25).

Secondary efficacy endpoints concern (improvement of) response, progression free survival and overall survival.
Response rates will be described as percentages with 95% CI. Actuarial survival curves for all time-to-event endpoints will be computed using the Kaplan-Meier method, and 95% CI will be constructed.

11.0 INVESTIGATIONAL PRODUCT

11.1. Carfilzomib Description

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

11.2. Formulation

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

11.3. Storage

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

11.4. Accountability

Onyx, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Onyx and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Onyx and by regulatory authorities.

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

12.0 REGULATORY OBLIGATIONS

12.1. Informed Consent

The Investigator at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the trial. Patients must also be notified that they are free to discontinue from the trial at any time. The patient should be given the opportunity to ask questions and be allowed as much time as they require to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the trial. The original signed and dated informed consent forms will be stored by the Investigator. A copy of the signed written Informed Consent Form must be given to the patient.

12.2. Compliance with Laws and Regulations

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

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Onyx with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Onyx as follows:

Onyx Inc.
Regulatory Department
2100 Powell St.
Emeryville, CA 94608

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

Onyx will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study.

Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee and Onyx with a summary of the trial's outcome.

12.3. Pre-study Documentation Requirements

The local investigator for each investigational site must provide the following documents to the Erasmus Data Center before shipment of study drug to the investigational site and before enrollment of the first patient:

- Name and address of the (central) Ethical Committee including a current list of the members and their function;

- Hospital Registration Form, signed and dated by the local investigator;
- Investigator Agreement, signed and dated by the local investigator;
- A copy of the dated and signed (central) Ethical Committee approval of the protocol, any amendments and informed consent form for the investigational site. (This approval must clearly identify the specific protocol by title, number and version date and must be signed by the chairman or authorized designee. The approval must also clearly identify the site(s) the approval applies to);
- A copy of the approved local version of the Patient Information and Informed Consent form;
- Approval of participation by site's Board of Directors, if required by local regulations;
- CV of local investigator;
- Any other documentation required by local regulations.

12.4. Subject Confidentiality

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Onyx, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

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

13.0 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1. Protocol Amendments and Study Termination

The Sponsor (the Terminating Party) may terminate the participation of a local investigational site in the trial with immediate effect at any time if the local investigational site is in breach of any of it's obligations (including a failure without just cause to meet a Timeline, adhere to the Protocol or if data recording is chronically inaccurate or incomplete) and fails to remedy such breach where it is capable of remedy within 28 days of a written notice from the Terminating Party specifying the breach and requiring its remedy.

The Sponsor may terminate this trial if overall trial enrolment has been met, even if the enrolment at an individual investigational site has not been completed.

The Sponsor may terminate this trial on notice to a local investigational site if the local investigator is no longer able (for whatever reason) to act as local investigator and no mutually acceptable replacement can be found.

A Party may terminate participation in this trial on notice to the other Party with immediate effect if it is reasonably of the opinion that the Clinical Trial should cease in the interests of the health of Clinical Trial Subjects involved in the Clinical Trial.

It is clearly understood by the Parties, that it would be unethical to stop the treatment of enrolled patients for other than medical or safety reasons. Therefore, the Parties expressly agree that any termination may not affect the treatment or interest of enrolled patients. In view hereof the manufacturer of the investigational product (Carfilzomib) undertakes to ensure that in any case of termination of this trial, the continuation of the treatment of the enrolled patients is secured at no cost to the investigational sites.

13.2. Study Documentation and Archive

All study documents will be archived at the end of the trial and retained for at least 15 years after the trial is complete.

14.0 REGISTRATION AND DOCUMENTATION

14.1.Registration

When a patient has been established as eligible for the study by the local investigator a completed registration form must be sent to the Clinical Trial Centre, Erasmus MC. Once the registration form has been controlled & patient eligibility checked, the patient will be assigned a unique study subject number which will be communicated in writing to the responsible centre.

14.2.Regulatory Documentation

Before, during and after the study all documents required according to ICH-GCP guidelines will be collected and stored at each investigational site.

15.0 DATA COLLECTION

15.1.CRFs

Electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the SAE form. Paper forms must be completed legibly in ink. Subjects are to be identified by birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor. Electronic data transfer is acceptable.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

15.2. Study Monitoring and Data Collection

The completed paper SAE/pregnancy forms, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub investigator. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool.

The sponsor will perform on-site monitoring visits. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. At a minimum, source documentation must be available to substantiate: subject identification, eligibility and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of adverse events; administration of concomitant medication; drug receipt/dispensing/return records; study drug administration information; date of subject completion, discontinuation from treatment, or withdrawal from the study, and the reason if appropriate. Specific items required as source documents will be reviewed with the investigator before the study.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

16.0 ETHICS

16.1. Independent ethics committee or Institutional review board

The appropriate ethics committee at each investigational site must approve the protocol, patient information sheet and informed consent document plus any amendments to the protocol or patient information sheet and informed consent document that are required during the course of the study.

16.2. Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000) and the ICH-GCP Guidelines of 17 January 1997 and the European Clinical Trial Directive as implemented in Dutch law (WMO). The local

investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

16.3. Patient information and consent

Written Informed consent of patients is required before randomization. The procedure and the risks and the opinions for induction therapy in multiple myeloma will be explained to the patient.

17.0 TRIAL INSURANCE

The Principal Investigator has organized insurance to cover all patients from participating centers in the Netherlands according to Dutch law (WMO). The WMO insurance statement will be provided to participating centers.

18.0 PUBLICATION POLICY

The final publication of the trial results will be written by the Principal Investigator on the basis of the statistical analysis performed at the Erasmus Data Center. A draft manuscript will be submitted to the Data Center and all co-authors and Onyx for review. After revision by the Data Center, the other co-authors and Onyx, the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the Principal Investigator, investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the data manager in charge of the trial, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses.

Any publication, abstract or presentation based on patients included in this study must be approved by the Principal Investigator. This is applicable to any individual patient or any subgroup of the trial patients. Such a publication cannot include any of the study end-points unless the final results of the trial have already been published.

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Appendix I ISS Criteria

Stage	ISS Criteria
I	ß2-M <3.5 mg/l and Albumin ≥3.5 g/dl
II	Neither stage I nor stage III
III	ß2-M >5.5 mg/l

Appendix II WHO performance status

- 0 - Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
- 1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
- 2 - Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
- 3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
- 4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
- 5 - Death

Appendix III The Stages of Heart Failure – NYHA Classification

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

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 IV Response Criteria for Multiple Myeloma (based on IMWG criteria)

RESPONSE CRITERIA

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus ▪ Normal serum FLC ratio and ▪ Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	▪ Negative immunofixation on the serum and urine and ▪ Disappearance of any soft tissue plasmacytomas and ▪ ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
PR	▪ ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h ▪ If the serum and urine M-protein are unmeasurable,[d] 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-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% ▪ In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD[e]	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; nCR, near complete response; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[d] Refer to Table 4 for definitions of measurable disease.

[e] not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates

NOTE: Once (s)CR is established, response remains (s)CR until relapse is documented.

RELAPSE CRITERIA

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ≥ 25% from baseline/**nadir** in ▪ Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[b] ▪ Urine M-component and/or (the absolute increase must be≥ 200 mg/24 h) ▪ Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dl. ▪ Bone marrow plasma cell percentage: the absolute % must be ≥10%[c] ▪ 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 or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 2.65 mmol/l) [11.5 mg/dl] 4. Decrease in hemoglobin of ≥ 1.25 mmol/l [2 g/dl] 5. Rise in serum creatinine by 177 μmol/l or more [2 mg/dl or more]
Relapse from CR[a] (To be used only if the end point studied is DFS)[d]	Any one or more of the following: ▪ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ▪ Development of ≥ 5% plasma cells in the bone marrow[c] ▪ Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a] All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b] For progressive disease, serum M-component increases of ≥ 1 gm/dl are sufficient to define relapse if starting M-component is ≥ 5 g/dl.
[c] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

PRACTICAL DETAILS OF RESPONSE EVALUATION

Laboratory tests for measurement of M-protein

- Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If SPEP is not available or felt to be unreliable (e.g., in some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response and SPEP and nephelometric values cannot be used interchangeably.
- Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended

Definitions of measurable disease

- Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements:
  - Serum M-protein ≥ 1 g/dl (≥ 10 mg/l)[10 g/l]
  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) provided serum FLC ratio is abnormal
- Response criteria for CR are applicable for patients who have abnormalities on one of the three measurements. Note that patients who do not meet any of the criteria for measurable disease as listed above can only be assessed for stringent CR, and cannot be assessed for any of the other response categories

Follow-up to meet criteria for PR or SD

- It is recommended that patients undergoing therapy be tracked monthly for the first year of new therapy and every other month thereafter
- Patients with 'measurable disease' as defined above need to be followed by both SPEP and UPEP for response assessment and categorization
- Except for assessment of CR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP[a]
- Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR
- To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; patients with negative UPEP values pretreatment still require UPEP testing to confirm CR and exclude light chain or Bence–Jones escape
- Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice; bone marrow is required only for categorization of CR, and for patients with non-secretory disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; SPEP, serum protein electro-phoresis; UPEP, urine protein electrophoresis.

[a] For good clinical practice patients should be periodically screened for light chain escape with UPEP or serum FLC assay.

Appendix V Common Toxicity Criteria

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse events, CTCAE version 4.0, May 28, 2009. A complete document may be downloaded from the following sites:

http://ctep.cancer.gov/reporting/ctc.html
http://www.eortc.be/Services/Doc/CTC

Appendix VI Molecular analysis

Molecular analysis consists of the following parts: genotyping for genome wide association studies, gene expression analysis (mRNA and miRNA), sequencing analysis and protein marker analysis. Minimal residual disease assessment is performed only in patients with complete response.

a) For these analyses, it is essential to obtain high quality bone marrow aspirates. The most important sampling point for molecular analyses is at the start of the trial prior to any treatment being given (i.e. at entry). We also require peripheral blood at entry. Bone marrow aspirates should be collected in heparin tubes with more than 10ml collected and divided over two 10ml heparin tubes to promote efficient anticoagulation. To obtain sufficient DNA from peripheral blood, we require 2 x 6ml EDTA tubes as well as one 6ml heparin tube. To perform protein marker analysis, we require in addition one citrate tube and one serum tube. Material should be collected and shipped at room temperature. The material should be sent to the central laboratory on the day of collection by overnight mail according to specific shipment guidelines, allowing material to reach the central laboratory in time the next day to be processed (using either a 9AM or 10AM service). Please consult the current laboratory manual for shipment guidelines.

At entry

Central laboratory

Erasmus Medical Centre	Jasper Koenders	**Bone marrow**
Department of Hematology	Michael Vermeulen	>10ml (in 2 x 10 ml heparin tubes)
Room Ee 1330 (faculty building)	Martijn Schoester	**Peripheral blood**
Dr. Molewaterplein 50	Phone: 0031 107 043 609	2 x 6ml EDTA
3015 GE Rotterdam	Fax: 0031 107 044 745	1 x 6ml heparin
The Netherlands	e-mail:	1 x 6ml citrate
	myeloma.hematology@erasmusmc.nl	1 x serum (3.5ml gel)

b) In addition to material obtained at entry of the clinical trial, we require a bone marrow aspirate to be obtained at complete response for minimal residual disease assessment. For this purpose, patients with both M-protein negativity and immunofixation negative in serum and urine, i.e. complete response, will undergo an additional bone marrow aspirate (>5ml bone marrow aspirate in a heparin tube). In the laboratory this material will be stored for molecular analysis by sequencing analysis. Please note that CR samples are only required for patients with complete response. For patients with very good partial response or worse, no CR sample is required.

At CR

Central laboratory

Erasmus Medical Centre	Jasper Koenders	**Bone marrow**
Department of Hematology	Michael Vermeulen	>5ml (in 1 x 10 ml heparin tube)
Room Ee 1330 (faculty building)	Martijn Schoester	
Dr. Molewaterplein 50	Phone: 0031 107 043 609	
3015 GE Rotterdam	Fax: 0031 107 044 745	
The Netherlands	e-mail:	
	myeloma.hematology@erasmusmc.nl	

c) Finally, we would like to request bone marrow aspirate of patients at relapse/progression. When the patient demonstrates relapse/progression, please send in a high-quality bone marrow aspirate (> 10ml in 2 x 10ml heparin tubes). At this point, the full set of peripheral blood should also be sent in.

At relapse

Central laboratory

Erasmus Medical Centre	Jasper Koenders	**Bone marrow**
Department of Hematology	Michael Vermeulen	>10ml (in 2 x 10 ml heparin tubes)
Room Ee 1330 (faculty building)	Martijn Schoester	**Peripheral blood**
Dr. Molewaterplein 50	Phone: 0031 107 043 609	2 x 6ml EDTA
3015 GE Rotterdam	Fax: 0031 107 044 745	1 x 6ml heparin
The Netherlands	e-mail:	1 x 6ml citrate
	myeloma.hematology@erasmusmc.nl	1 x serum (3.5ml gel)

For all shipments please notify laboratory staff clearly what type of material is being sent, when the material is being sent, and what the tracking number is, if applicable. For this purpose a dedicated sample collection form is made. All shipments should be kept at room temperature, and shipped by expedited mail, so samples will arrive at the central laboratory at 9 or 10 o'clock the next morning. Participating centers will be provided with special enveloped for the sending of all samples. Red enveloped will be used for entry samples (i.e. prior to any therapy within this trial) and for relapse samples; blue envelopes are dedicated to CR samples.

Appendix VII

	At entry	prior to each dose of Carfilzomib during cycle 1 and 2		Prior to each induction cycle (Car/Thal/Dex)	Prior HDM	After HDM & prior to consolidation cycles	Discontinuation	During follow up[4]
		cycle 1 day 1,2,3,8,9,10,15,16&17	cycle 2 day 1,2,8,9,15&16					
Informed consent	X							
Medical history	X			X	X	X	X	X
Stem cell harvest evaluation					X			
Myeloma history	X							
Physical examination	X			X	X	X	X	X
Concomitant medication / Adverse Event check	X			X	X	X	X	X
WHO performance status	X			X	X	X	X	X
ECG	X							
Urine Pregnancy test	X							
Hematology	X			X	X	X	X	X
Blood chemistry	X			X	X	X	X	X
Blood chemistry review		X	X					
Serum/Urine M-component	X			X	X	X	X	X
Blood for central lab (see appendix VI)	X			X[2)]	X[2)]	X[2)]	X[2)]	X[2)]
Bone marrow:								
Bone marrow aspirate	X			X[1)]	X[1)]	X[1)]	X	X[1)]
Bone marrow biopsy	X							
BM aspirate for central lab (see appendix VI)	X			X[1)]	X[1)]	X[1)]	X[1)]	X[1)]
Cytogenetic analysis	X							
Specific investigations:								
b_2-microglobulin	X				X		X	
Creatinin clearance	o.i.			o.i.	o.i.			
Skeletal survey	X			X[3)]	X[3)]	X[3)]	X	X[3)]
X-thorax	X							
Cardiac ejection (MUGA or echocardiogram)	X				o.i.			
Additional investigations	o.i.			o.i.	o.i.	o.i.	o.i.	o.i.

o.i. on indication

1) at disappearance or reappearance of serum/urine M-component

2) at reappearance of serum/urine M-component

3) in case of extramedullary plasmacytoma, the skeletal surveys should be repeated at all evaluation moments plus at disappearance of serum/urine M-component

4) every 2 months until progression of disease, thereafter every 6 months until 5 years after registration