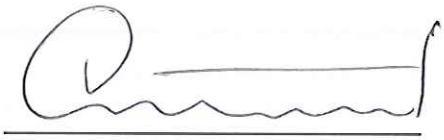
Pomalidomide combined with Carfilzomib and Dexamethasone (PCd) for induction and consolidation followed by Pomalidomide combined with Dexamethason vs Pomalidomide maintenance for patients with Multiple Myeloma in progression after prior 1st line treatment with Lenalidomide and Bortezomib.

The European Intergroup Trial of the European Myeloma Network EMN (EMN11/HO114)

Principal Investigator	**:**	**P. Sonneveld**
Sponsor	**:**	HOVON
EudraCT number	**:**	2013-003265-34

PRINCIPAL INVESTIGATOR SIGNATURE PAGE



25/03/2021

Signature of Principal Investigator

Date

PSonneveld

Printed Name of Principal Investigator

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

_____ _____

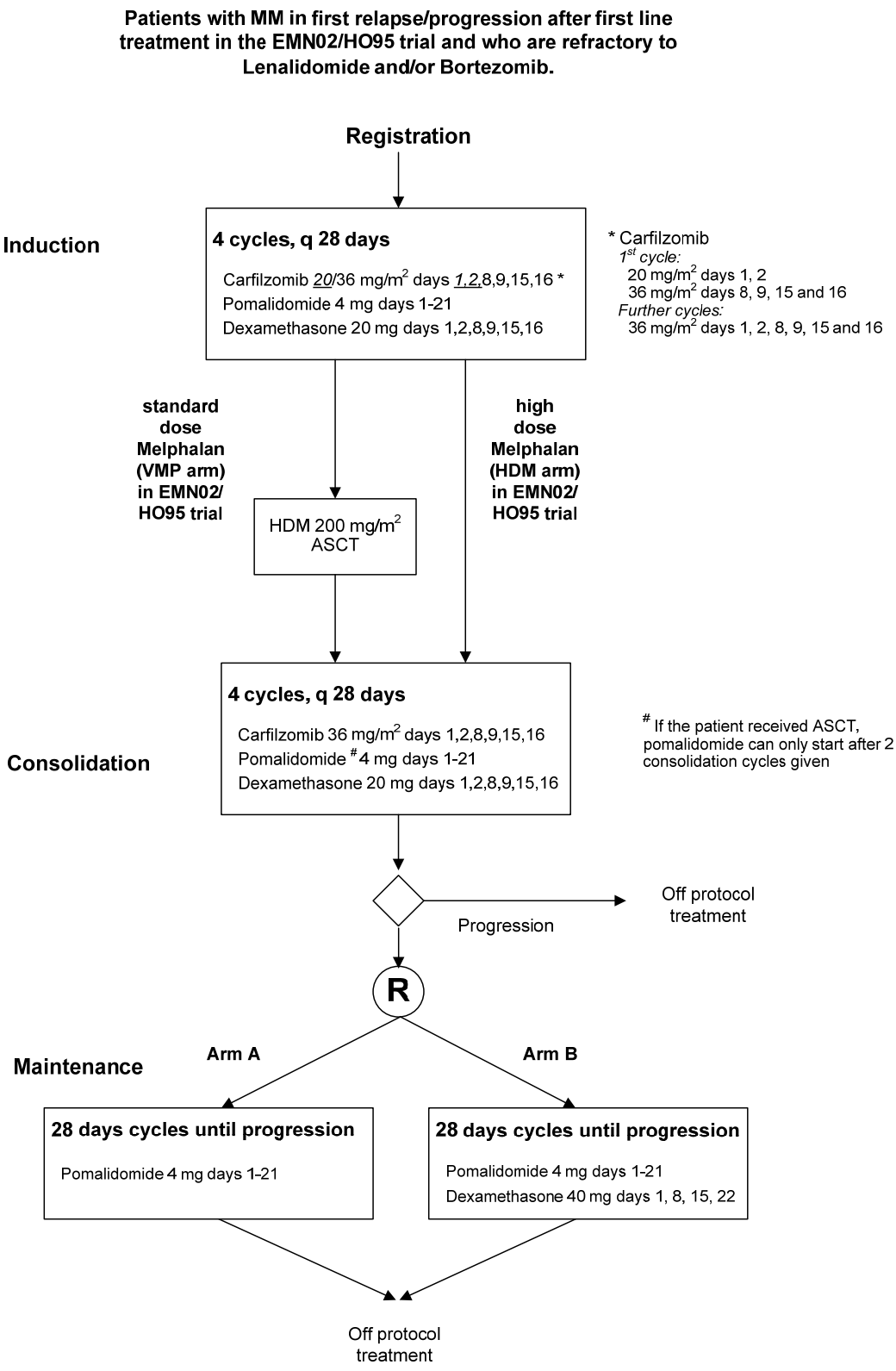
Signature of Local Investigator Date

_____

Printed Name of Local Investigator

By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.

1 Scheme of study



2 Table of contents

Page

3 Synopsis

Rationale	The treatment regimen is derived from the Carthadex (CTd) regimen which was presented at ASH 2012 (P. Sonneveld et al, ASH 2012). Four cycles of PCd are planned for induction and 4 cycles for consolidation. The number of induction and consolidation cycles is based on experiences in the Carthadex trial. The dosing rationale is based on the carfilzomib dose escalation in Carthadex and in the carfilzomib/lenalidomide/ dexamethason trial (AJ Jakubowiak et al, Blood 2012) where carfilzomib 20/36 mg/m^2 i.v. was proven safe, tolerable and effective. The dose and schedule of pomalidomide was based on the Celgene registration trial. Dexamethasone at low dose was based on the Carthadex trial. The maintenance regimen is derived from the experiences in the pomalidomide and low dose dexamethason trial (S. Jagannath et al, ASH 2012 abstract #450).
Study objectives	<u>Primary objectives</u> ♦ Evaluate the efficacy defined as PFS of pomalidomide maintenance plus dexamethasone versus pomalidomide maintenance in patients who responded (≥ PR) to the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation. ♦ Evaluate efficacy of the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation in subjects with relapsed or refractory multiple myeloma (MM) after prior first-line treatment in the EMN02/HO95 trial who are refractory to Lenalidomide and/or Bortezomib. This objective will be investigated in patients who have or have not received a prior autologous transplant.

	Secondary objectives ♦ Evaluate the response rate (after 8 cycles of PCd) before the start of maintenance. ♦ Evaluate the safety and tolerability of the combination of pomalidomide, carfilzomib and low dose dexamethasone in subjects with relapsed or refractory multiple myeloma. Exploratory ♦ Evaluation of biomarkers, including baseline markers predictive of response to pomalidomide combined with carfilzomib and dexamethasone. ♦ Evaluate the quality of life Evaluate the gene expression profiles and SNPs in relation to the treatment outcomes and side-effects
Study design	Phase II study
Patient population	Patients with symptomatic Multiple Myeloma who have a first progression on or after treatment in the EMN02/HO95 trial or who are refractory to lenalidomide and/or bortezomib.
Intervention	The following treatments will apply: Patients who progess from EMN02/HO95, who were treated with standard dose melphalan (VCD, followed by VMP, followed by yes/no VRD consolidation, followed by lenalidomide maintenance) will be treated with 4 cycles of PCd induction (Pomalidomide Carfilzomib dexamethasone). After induction they will receive HighDose Melphalan and autologous stem cell reinfusion (autoSCT) of cells already stored during initial treatment, if possible. Following hematologic recovery, these patients will receive 4 cycles of consolidation treatment with PCd. Patients who progress from EMN02/HO95, who were treated with High Dose Melphalan (VCD, followed by HDM+autoSCT followed by yes/no VRD consolidation, followed by lenalidomide maintenance) will be treated with 4 cycles of PCd induction, followed by 4 cycles of

	consolidation treatment with PCd. All patients who have completed the re-induction and consolidation treatment will be randomized for maintenance treatment with pomalidomide alone or pomalidomide plus dexamethasone until progression of disease.
Duration of treatment	Expected durations of therapies: - Induction therapy 4 months - Transplantation and recovery 2 – 4 months (if applicable) - Consolidation therapy 4 months - Maintenance therapy with pomalidomide or pomalidomide plus dexamethasone until disease progression. - All patients will be followed until a maximum of 8 years after registration.
Target number of patients	222 patients
Expected duration of accrual	24 months
Main study endpoints	♦ Response rate after induction and consolidation treatment ♦ Progression free survival (PFS) from randomization, defined as time from randomization to progression or death from any cause which ever occur first
Benefit and nature and extent of the burden and risks associated with participation	The combination of pomalidomide, carfilzomib and dexamethasone may be useful in the treatment of relapsed MM patients. In order to study the safety and efficacy of this combination it is required to include patients who have relapsed MM. The knowledge from this study may be of advantage to this group of patients in the future. The majority of the investigations performed in this study do not differ from the usual standard of care for this patient category. Exceptions are that at the beginning of the study patients will be requested to provide extra blood and bone marrow aspirate for analysis (this does not require extra punctures); patients will also be asked to complete Quality of Life Questionnaires at regular intervals and to protect unborn children women of childbearing potential will be

	asked to regularly perform a pregnancy test. There is a possibility that by taking part in the study patients will experience side effects from the medications under investigation. The treating physician will always safeguard the health and best interest of the patients.
Planned interim analysis and DSMB	One interim analysis is planned, primarily to describe adverse events observed during the carfilzomib + pomalidomide + dexamethasone re-induction chemotherapy. This will be done when data of the first 20 patients completing the 4 cycles of induction therapy are available. Results of the interim analysis will be presented to the principal investigators and to a DSMB.

4 Investigators and study administrative structure

IMPORTANT NOTE

This is an Intergroup study coordinated by the HOVON. The present protocol is written according to the HOVON procedures, and is fully applicable to all HOVON investigators. The scientific content is also fully applicable to investigators from all other collaborative groups. For administrative matters and logistic procedures, non HOVON investigators should refer to their Group specific addendum that will supersede the contents of applicable chapters in this protocol

.

Responsibility	Name	Affiliation/Address
Sponsor	HOVON	VU University Medical Center, P.O.Box 7057 1007 MB Amsterdam The Netherlands tel: +31 20 4443797
Co-sponsor	Fondazione Neoplasie Sangue Onlus (FO.NE.SA Onlus)	Via Genova 3 (registered office C.so Matteotti 44) 10126 Torino Italy Tel: +390116336107
Representative of Sponsor (HOVON)	J.J. Cornelissen, chairman N.M.A Blijlevens, treasurer	Erasmus MC Rotterdam Radboud University Nijmegen
Principal Investigator	P. Sonneveld Contact information for trial related medical decisions +31 10 703 3123	Erasmus MC Rotterdam
Co-investigators	A. Palumbo	Osp. G. Battista Le Molinette -V.Genova Torino, Italy
Coordinating investigator	H. Ludwig (CEMSG) H.Lokhorst (HOVON) A. Palumbo (GIMEMA) K. Wu (HOVON) M. Hanson M. Dimopoulos R. Hajek M. Beksac	Vienna, Austria Utrecht Medical Center University of Torino, Italy ZNA Stuivenberg, Antwerp, Belgium Skanes University Hospital Lund, Sweden General Hospital Alexandra, Athens, Greece University Hospital BRNO, Czech Republic Ankara University Hosp. Cebeci Hastanesi, Turkey
HOVON MM working group chair	H.M. Lokhorst	University Medical Center Utrecht

Writing Committee	G.M. Bos	Academic Hospital Maastricht
	P von dem Borne	Leiden University Medical Center
	M.J. Kersten	Academic Medical Center, Amsterdam
	S Zweegman	VU University Medical Center, Amsterdam
	E. Vellenga	University Medical Center Groningen
	A. Palumbo	Osp. G. Battista Le Molinette -V.Genova, Torino, Italy
	H. Ludwig	Wilhelminenspital, Vienna, Austria
	U.H. Mellqvist	Sahlgrenska sjukhuset, Goteborg,Sweden
Statistician	Kazem Nasserinejad	Erasmus MC – Cancer Institute Clinical Trial Center
Registration	EMN Data Center	University of Torino Via Genova 3 10126 Torino, Italy tel. +39 .011 6336107 fax. +39 011 6334301 fax +39 011 6963737
Monitoring (NL)	HOVON Data Center	Erasmus MC –Cancer Institute Clinical Trial Center
Central Laboratory	Erasmus MC, University Hospital Ostrava, University of Turin	
Trial management	HOVON Data Center	Erasmus MC – Cancer Institute Clinical Trial Center
Data management	EMN Data Center	University of Torino Via Genova 3 10126 Torino, Italy tel. +39 .011 6336107 fax. +39 011 6334301 fax +39 011 6963737
Serious Adverse Events (SAEs) notification	EMN Data Center	University of Torino Via Genova 3 10126 Torino, Italy tel. +39 .011 6336107 fax. +39 011 6334301 fax +39 011 6963737

5 Introduction and rationale

5.1 Description of disease and current treatment

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 more than 50 %. In the majority of subjects the disease follows a relapsing course, regardless of treatment regimen or initial response to treatment. Novel agents are urgently needed to improve the treatment results of this disease.

5.1.1 Treatment of Relapsed/Refractory Multiple Myeloma

The treatment options for subjects with primary resistant or relapsed MM are varied and include combination therapies with glucocorticoids and cytotoxic chemotherapeutic agents (1,2,3) more recently combined with autologous stem cell transplantation (AutoSCT) to allow higher doses that would otherwise destroy the bone marrow (4,5). Drugs targeting both myeloma and its microenvironment (6) have been approved for clinical use in newly diagnosed and relapsed and refractory MM subjects (7). These include bortezomib (Velcade®), a proteasome inhibitor, and the compounds thalidomide (Thalomid®) and lenalidomide (Revlimid®). Determination of an appropriate salvage regimen is dependent on a number of factors, including initial therapy regimen used and duration of response to that therapy. Treatment options for relapsed disease include AutoSCT, a re-challenge of a previous chemotherapy regimen, or a study of a new chemotherapy regimen.

Many of the same chemotherapy regimens that are used as initial therapy may be used as salvage therapy, providing that sufficient time has passed since prior therapy before relapse or progression. The current goals in relapsed MM are to optimize the efficacy of Velcade®, Thalomid® and Revlimid® through their most appropriate combinations, to determine the optimal sequences of treatment, and to promote active clinical research into new experimental agents (8).

The main considerations for choosing an appropriate treatment for relapsed MM are: risk level, prior therapy, duration of response to prior therapy, residual toxicity, age, physical condition,including degree of renal insufficiency, and whether or not the subject is a candidate for AutoSCT(9,10).

While MM subjects with relapsed disease may achieve responses to subsequent anti-myeloma therapies, the duration of response decreases with successive relapses until resistant disease develops. Until recently, the median overall survival following relapse after induction therapy was approximately one year (11).

5.1.2 Treatment Options for Relapsed and/or Refractory MM

The treatment options approved for use in relapsed and/or refractory MM currently include:
Lenalidomide plus Dexamethasone. Lenalidomide in combination with dexamethasone (DEX) is approved in the US, Canada, the EU and many other countries around the world for the treatment of subjects with MM who have received at least one prior therapy (12,13,14).
Bortezomib. Bortezomib monotherapy is approved in the US and Canada for the treatment of subjects with relapsed MM (15).
Pegylated Doxorubicin-Liposomal Plus Bortezomib. Pegylated liposomal doxorubicin in combination with bortezomib is approved in the US for the treatment of subjects with MM who have not previously received bortezomib and have received at least one prior therapy (16).
Other options that may be considered as salvage therapy in MM subjects include thalidomide alone or in combination with DEX or other agents, lenalidomide monotherapy, lenalidomide in combination with bortezomib and DEX, or lenalidomide or bortezomib in combination with cyclophosphamide and DEX (9).
Despite advances in new therapies, MM subjects do progress and the disease remains incurable (17;4,5). More recent studies show a poor survival outcome (median overall survival is 9 months) in MM subjects who experience disease progression following treatments that have included proteasome inhibitors and immunomodulatory agents (18). It is evident that there is an unmet medical need for additional novel therapeutic options for MM.

5.1.3 Consolidation and maintenance

Post-transplant consolidation and maintenance has been studied for several years. Two trials showed a superior effect of Thalidomide when given in this setting, particularly in patients failing at least VGPR after AutoSCT(s) (19,20). The results of other trials have been presented as abstract only (ASH 2008 # 157,656).

Bortezomib has also been investigated in the maintenance and consolidation setting in two small studies. Data from the Nordic Myeloma Study Group show that consolidation with Bortezomib may induce a significantly higher CR rate (Mellquist et al, ASH 2009, abstract #530). In addition, consolidation treatment with Bortezomib plus Thalidomide and Dexamethasone (VTD) induces molecular remissions in newly diagnosed patients (Ladetto et al,ASH 2008 abstract 3683). Ongoing randomized studies by several European study groups are further investigating Bortezomib as consolidation and maintenance therapy (Sonneveld et al. J Clin Oncol. 2012; 30: 2946-2955; Rosinol et al, ASH 2009, abstract # 120).

Lenalidomide was used as maintenance in an Italian trial (ASH 2008 # 159) as well as in a large prospective phase III trials by the French IFM group and by Celgene (MM015). Safety data indicate that Lenalidomide maintenance is well tolerated. Two recent presentations of large prospective randomized trials demonstrated a significant superior response and progression-free survival of Lenalidomide maintenance over placebo in elderly patients treated with MP-based regimens (Palumbo et al, NEJM. 2012; 366: 1759-1769) and as maintenance therapy after HDM/AutoSCT for MM (Attal et al, IFM 2005-02 ASCO 2010). These trials have established Lenalidomide as the best candidate to date for maintenance treatment because of good tolerability and high efficacy.

5.2 Investigational Medicinal Product Carfilzomib

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 (21,22)

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/m2, the severely toxic dose in 10% of animals (STD10) caused > 90% proteasome inhibition in red blood cells one hour after dosing. Overall, stronger inhibition of the proteasome and longer duration of inhibition was tolerated with carfilzomib compared with bortezomib. Daily administration of bortezomib at anti-tumor doses is not tolerated in animals, and therefore daily bortezomib has not been given in the clinic. A dose-dependent decrease in proteasome activity was demonstrated in animals, and equivalent levels of proteasome inhibition were achieved with administration of carfilzomib as either an intravenous (IV) push or an IV infusion. The 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 contrast to that observed with bortezomib. (23, 24).

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.

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. (21). 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 (25).

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.

Clinical experience with Carfilzomib

Carfilzomib entered clinical studies in September 2005.

On 20 July 2012, Kyprolis (Carfilzomib for Injection) was approved under the United States Food and Drug Administration's (US FDA's) accelerated approval program for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory drug (IMiD), and have demonstrated disease progression on or within 60 days of

completion of the last therapy. The approval was based on the results of the Phase 2 PX-171-003-A1 study.

Data are available from nine Phase 1 or Phase 2 clinical studies (PX-171-001, PX-171-002, PX-171-003, PX-171-004, PX 171-005, PX-171-006, PX-171-007, PX-171-008, and PX-171-010). Additional data are available from two Phase 3 studies (PX-171-011 [FOCUS], and PX-171-009 [ASPIRE]). A third Phase 3 study was initiated in June 2012 (2011-003, ENDEAVOR).

As of October 2011, 857 unique subjects had been enrolled to the Phase 1 or 2 studies, including 681 subjects with multiple myeloma and 176 subjects with solid tumors or hematologic malignancies other than multiple myeloma. Of the 681 with multiple myeloma, 336 subjects have been treated with single-agent carfilzomib. As of 01 November 2012, an additional 519 subjects have been enrolled in Phase 3 studies and randomized to a carfilzomib treatment arm.

Carfilzomib development in multiple myeloma initially involved single agent testing at various doses to assess tolerability, safety and efficacy (26). This series of investigations was the foundation for understanding the safety, tolerability and efficacy of carfilzomib (27,28,29,30). The treatment cycle was 4 weeks, and carfilzomib was administered as a 2 to 10 minute IV infusion on Days 1, 2, 8, 9, 15, and 16. The carfilzomib dose was 20 mg/m^2 on Days 1 and 2 of Cycle 1, followed by 27 mg/m^2 for all subsequent administrations (31,32).

Study PX-171-007 explored the single-agent safety and efficacy characteristics of carfilzomib at higher doses, and determined that for single-agent carfilzomib administered twice weekly the maximal tolerated dose (MTD) is 20/56 mg/m^2 when using an infusion time of 30 minutes. The same study explored a combination of dexamethasone (20 mg on Days 1, 2, 8, 9, 15, and 16, and 40 mg on Day 22) with carfilzomib at 20/45 mg/m^2 and 20/56 mg/m^2 and found it to be tolerable and safe. The 20/56 mg/m^2 carfilzomib dose plus dexamethasone is being examined in the ongoing ENDEAVOR study.

Subsequently, exploration of the combination of carfilzomib and lenalidomide provided insight into possible synergistic activity with the IMiD most recently added to the multiple myeloma treatment armamentarium.

The carfilzomib/lenalidomide/dexamethasone study, Study PX-171-006, was the first study to explore the option of combination therapy for subjects with multiple myeloma treated with carfilzomib. This study was the model for a study of the carfilzomib, lenalidomide, dexamethasone combination conducted by the Multiple Myeloma Research Consortium, which defined the carfilzomib MTD to be 36 mg/m^2 in patients with newly diagnosed multiple myeloma (33). The lowering of the carfilzomib MTD from 56 mg/m^2 seen with single-agent carfilzomib is consistent with the known lowering of MTD for individual chemotherapy agents that are used in combination with other drugs.

Recently data from the ASPIRE trial were published, showing that in patients with relapsed multiple myeloma, the addition of carfilzomib to lenalidomide and dexamethasone resulted in significantly improved progression-free survival at the interim analysis (median, 26.3 months, vs. 17.6 months) (34)

5.3 Investigational Medicinal Product Pomalidomide

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

Preclinical Pharmacology

Pomalidomide (CC-4047, 4-amino-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione) is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide (POM) shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide. An in vitro model of anti-tumor necrosis factor activity has shown that POM has an IC50 (inhibitory concentration 50%) of approximately 0.013 μM (13 nM) against TNF produced by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells. Thalidomide and lenalidomide, by comparison, have an IC50 of ~194 μM and 0.10 μM (100 nM), respectively (35,36). In LPS-stimulated human whole blood, the IC50 for TNF inhibition by POM is 0.025 μM (25 nM) (36). In addition, POM has demonstrated a 10-fold higher potency for T cell co-stimulation than lenalidomide (35;37).

POM also augmented the activity of natural killer cells and enhanced antibody-dependent cellmediated cytotoxicity (ADCC) of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens (38;39). Moreover, POM is also a potent inhibitor of the proliferation of MM cell lines in vitro. Concentrations of 2.73 to 27.3 ng/mL (0.01 to 0.1 μM) achieved a 50% inhibition of MM. 1S and Hs Sultan cell proliferation. In contrast, at concentrations of 25.8 μg/mL (100 μM), thalidomide inhibited the proliferation of MM.1S and Hs Sultan cells by only 15% and 20%, respectively. POM is also more potent than thalidomide or lenalidomide in inducing G1 growth arrest and apoptosis in MM cell lines and in subject MM cells that are resistant to melphalan, doxorubicin and DEX, as well as enhancing the anti-MM activity of DEX (6). Of potential relevance to the refractory MM setting, POM appears to retain anti-proliferative activity against H929 and KMS-12-BM MM cells that have increased resistance to acute lenalidomide treatment following chronic exposure to lenalidomide (40;41). Preliminary results from in vitro experiments performed at Celgene demonstrate that MM cell lines treated long-term with lenalidomide and which have become resistant to lenalidomide, are still sensitive to POM (41). Importantly, the combination of POM and DEX was strongly synergistic in both lenalidomide-sensitive and lenalidomide-resistant cell lines, inhibiting cell proliferation and inducing apoptosis. This suggests that the combination of POM plus DEX may be useful in the treatment of MM that is refractory to lenalidomide plus DEX.

Clinical Studies of Pomalidomide in Relapsed and/or Refractory Multiple Myeloma

There are six Celgene clinical studies and two investigator-initiated studies that have beencompleted or ongoing.

Celgene Phase Ib Study (CDC-407-00-001 / CC-4047-MM-001; Completed). This was a Phase Ib single-center, ascending dose (1, 2, 5, and 10 mg), open-label study to identify the maximum tolerated dose (MTD) and evaluate the safety and efficacy of POM given continuously (cohort 1) (42) or on alternate days (cohort 2) (43) in 45 subjects with MM who were considered refractory to treatment after at least two cycles of treatment or who relapsed after previous treatment. The MTD was 2 mg continuously and 5 mg on alternate days; the most common dose limiting toxicity (DLT) was grade 4 neutropenia. The most common AEs were neutropenia, thrombocytopenia, pharyngitis, cough, dyspnea, and hypoesthesia. Overall, 23 of 45 (51%) subjects had partial response (PR) or better, including 6 complete responses (CR) and 12 very good partial responses (VGPR). In cohort 1, the median progression free survival (PFS) was 9.75 months and the median overall survival (OS) was 22.5 months; in cohort 2, the median PFS was 10.5 months and the median OS was 35.9 months.

Celgene Phase Ib/2 Study (CC-4047-MM-002; Enrollment Completed). This was a Phase Ib/2 multicenter, randomized, open-label, dose escalation (2, 3, 4, and 5 mg) study to evaluate the MTD of POM alone (Phase I) and the safety and efficacy of POM alone using a cyclic regimen (21 of 28 days) and in combination with low-dose DEX (LD-DEX) (Phase 2) using a cyclic regimen (21 of 28 days) in subjects with relapsed and refractory MM who had received ≥ 2 prior anti-MM regimens. All subjects must have received prior treatment that included lenalidomide and bortezomib. Subjects with serum creatinine ≥ 3.0 mg/dL were not eligible. In the Phase Ib segment of the study, 38 subjects were enrolled. The MTD was 4 mg which was the dose selected for the phase II part of the study. The safety profile was similar across cohorts except for grade 4 neutropenia, which was the DLT and was experienced at the highest rate in the 5 mg cohort. A total of 221 subjects were enrolled in phase II (POM+LD-DEX n = 113; POM n = 108); 219 received ≥ 1 dose of study treatment and 191 subjects were evaluable for response. Baseline characteristics were comparable between the two arms with a median of 5 (range 2–13) prior therapies in both arms. Among subjects who were randomized to receive POM alone, 61 (56%) subsequently went on to receive POM+LD-DEX due to progressive disease (PD) per protocol. Response of ≥ PR was seen in 30% of subjects in the POM+LD-DEX arm and 9% in the POM alone arm, including 1% and 0% CR, respectively, in each arm. Response of ≥ minor response (MR) was achieved with POM+LD-DEX in 45% and with POM alone in 25%; median PFS was 3.8 and 2.5 months, respectively. Grade 3/4 AEs in POM+LDDEX vs. POM alone, respectively, were: neutropenia 38% and 47%; febrile neutropenia 2% and 2%; thrombocytopenia 19% and 21%; anemia 21% and 17%; pneumonia 19% and 8%; and fatigue 10% and 8%. All grades of peripheral neuropathy, deep vein thrombosis, and renal failure occurred in 7% and 10%, 2% and 1%, and 2% and 1% of subjects for POM+LD-DEX vs. POM alone, respectively (44).

Celgene Phase III Study (CC-4047-MM-003; Ongoing). This is a phase III multicenter, randomized, open-label study to compare the efficacy and safety of POM in combination with LD-DEX (Treatment Arm A) versus high-dose DEX (Treatment Arm B) in subjects with refractory MM or relapsed and refractory MM. There is 2:1 randomization, Arm A vs. Arm B, respectively. Study sites are located in the EU, Russia, Canada, and Australia. The study is currently ongoing.

Celgene Phase III Study (CC-4047-MM-003/C; Ongoing). This is an open-label, multicenter, single-arm companion study for clinical study CC-4047-MM-003. The study is to evaluate the safety and efficacy of POM monotherapy for subjects who have discontinued study treatment with DEX alone (Treatment Arm B) in the CC-4047-MM-003 study due to PD. Study sites are located in the EU, Switzerland, Russia, Canada, and Australia. The study is currently ongoing.

Celgene Phase I Study (CC-4047-MM-005; Ongoing). This is a phase I multicenter, openlabel study to determine the MTD for the combination of POM, bortezomib and LD-DEX in subjects with relapsed or refractory MM. Study sites are located in US. The study is currently ongoing.
Celgene Phase I Study (CC-4047-MM-008; Ongoing). This is a phase I multicenter, openlabel, dose-escalation study to determine the pharmacokinetics (PK) and safety of POM when given in combination with LD-DEX in subjects with relapsed or refractory MM and impaired renal function. Study sites are located in US. The study is currently starting.

Investigator Initiated Phase II Study at the Mayo Clinic (PO-MM-PI-0010; Enrollment Completed). This is a phase II open-label study of POM (2 mg continuous) plus LD-DEX (40 mg/day on Days 1, 8, 15, and 22) in subjects with relapsed or refractory MM who had received 1-3 prior regimens (45). Subjects with serum creatinine > 2.5 mg/dL were not eligible. A total of 60 subjects were initially enrolled into this study. Thirty-eight (63%) of the 60 subjects had confirmed response including 3 CR and 17 VGPR. Responses were seen in 8 of 12 (66.7%) lenalidomide-refractory subjects, 6 of 16 (37%) thalidomide-refractory subjects, and 6 of 10 (60%) bortezomib refractory subjects. The most common Grade 3/4 hematological toxicity was neutropenia, and the most common non-hematological Grade 3/4 toxicities were fatigue and pneumonia.
Since responses were observed in some subjects who were refractory to lenalidomide in the initial cohort of 60 subjects, an additional cohort of 34 subjects, who were refractory to prior lenalidomide therapy, were enrolled from November 2008 to April 2009. The overall response rate (≥ PR) was 32% for this cohort of 34 subjects. The most common Grade 3/4 hematologic toxicity was neutropenia (29%) and the most common Grade 3/4 non-hematologic toxicity was fatigue (9%), which was consistent with that observed in the initial cohort of 60 subjects (46).
Based on experience of Richardson, et al. (47) where the MTD of POM was determined to be 4 mg, a phase II study was initiated by Lacy, et al. to compare the two different dosing regimens in MM

subjects who were refractory to both lenalidomide and bortezomib. POM was given orally 2 mg/day or 4 mg/day, on Days 1 to 28 of a 28-day cycle, with DEX 40 mg daily on Days 1, 8, 15 and 22. A total of 70 subjects were enrolled (35 in the 2 mg cohort and 35 in the 4 mg cohort). The most common grade 3/4 hematologic toxicity was neutropenia, and the most common non-hematologic toxicity was fatigue. The overall response rate (≥ PR) was 25% and 29% for the 2 mg and 4 mg cohorts, respectively (48).

Investigator Initiated Phase II Study (PO-MM-PI-0024; Enrollment Completed). This is a phase II, multicenter, randomized, open-label study of POM plus DEX in subjects with relapsed and refractory MM who have received bortezomib and lenalidomide, conducted by the Intergroupe Francais du Myelome (IFM). Subjects with creatinine clearance (CrCl) < 50 mL/min were not eligible. Subjects received a 4 mg dose of POM, given either in a continuous (28-day) or a cyclic (21-day out of 28-day cycles) regimen in combination with LD-DEX. The primary endpoint is the response rate, and the secondary endpoints are safety, time to response, time to progression, and OS. Eighty-four subjects were enrolled into this study, 43 in the 4 mg 21/28 days arm (Cohort A) and 41 in the 4 mg 28/28 days arm (Cohort B). At the cut-off of 01 Mar 2011, overall response rate (ORR) was 34.9% in Cohort A and 34.1% in Cohort B, including 4.7% and 7.3% VGPR, respectively. Overall, 40 (47.6%) subjects had stable disease (including minor response) and 3 subjects reached CR. The median PFS was 6.3 (4.1-9.1) months in either arm or the median duration of response was 11.4 (3.7-13.6) months and 7.9 (4.0- not reached) months in Cohort A and in Cohort B, respectively. The median PFS was 4.2 (3.3-6.9) months for subjects with stable disease (SD) as compared to 12.6 (9.9-14.8) months in subjects that had a response. The primary toxicity was myelosuppression and was similar in both treatment arms (49).

A Phase I/II of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with relapsed/refractory multiple myeloma showed that the Car-Pom-d regimen is a well-tolerated regimen and achieves a high response rate (ORR of 64%; ≥MR rate of 81%) in a heavily pre-treated Lenalidomide-refractory population with prior bortezomib exposure, with a median of 6 lines of prior therapy. Importantly, responses were seen in patients with poor risk cytogenetics, specifically del (17p) with prolonged disease control(50).

Overall Clinical Experience

The results of studies conducted thus far indicate that POM has activity in subjects with relapsed and/or refractory MM. Confirmed response rates range between 30% and 60% at POM doses between 2 mg and 4 mg/day. Notably, POM produces responses in subjects who are refractory to lenalidomide or thalidomide, aligning with the non-clinical results observed in lenalidomideresistant cells (40). Response rates in this range are consistently seen in subjects who are refractory to both lenalidomide and bortezomib. The most common hematological toxicity experienced by these

subjects is neutropenia (non-febrile), which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are fatigue and pneumonia.
Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IP.

5.4 Rationale of the study

The treatment regimen is derived from the Carthadex (CTd) regimen which was presented at ASH 2012 (P. Sonneveld et al, ASH 2012 abstract #333).
Four cycles of PCd are planned for induction and 4 cycles for consolidation. The number of induction and consolidation cycles is based on experiences in the Carthadex trial. The dosing rationale is based on the Carfilzomib dose escalation in Carthadex and in the Carfilzomib/Lenalidomide/Dexamethason trial (33) where Carfilzomib 20/36 mg/m^2 i.v. was proven safe, tolerable and effective. The dose and schedule of Pomalidomide was based on the Celgene registration trial. Dexamethasone at low dose was based on the Carthadex trial. The maintenance regimen is derived from the experiences in the Pomalidomide and low dose Dexamethason trial (S. Jagannath et al, ASH 2012 abstract #450).

6 Study objectives

Primary objectives

- Evaluate the efficacy, defined as PFS, of pomalidomide maintenance plus dexamethasone versus pomalidomide maintenance in patients who responded (≥ PR) to the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation .
- Evaluate efficacy defined as response rate (sCR, CR, VGPR, PR) of the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation in subjects with relapsed or refractory multiple myeloma (MM) after prior first-line treatment in the EMN02/HO95 trial who are refractory to Lenalidomide and/or Bortezomib. This objective will be investigated in patients who have or have not received a prior autologous transplant.

Secondary objectives

- Evaluate the response rate after 8 cycles of PCd before the start of maintenance.
- Evaluate the safety and tolerability of the combination of pomalidomide, carfilzomib and low dose dexamethasone in subjects with relapsed or refractory multiple myeloma.

Exploratory

- Evaluation of biomarkers, including baseline markers predictive of response to pomalidomide combined with carfilzomib and dexamethasone

- Evaluate the quality of life
- Evaluate the gene expression profiles and SNPs related to treatment outcome and side effects

7 Study design

This trial will try to evaluate the efficacy of the combination of Pomalidomide, Carfilzomib and low dose Dexamethasone for induction and consolidation in subjects with relapsed or refractory multiple myeloma after prior first-line treatment in the EMN02/HO95 trial and who are refractory to Lenalidomide and/or Bortezomib. This trial will be conducted in patients who have or have not received a prior Autologous Stem Cell Transplantation (AutoSCT). The study will be conducted as a Phase II trial:

Patients will be treated with 4 cycles of PCd induction (Pomalidomide Carfilzomib Dexamethasone). After induction patients who did not receive a prior autoSCT will receive high-dose Melphalan and autoSCT of cells already stored during initial treatment, if possible. Following hematologic recovery, these patients will receive 4 cycles of consolidation treatment with PCd.
Patients who already received autoSCT will continue from induction to consolidation treatment with PCd.

All patients who have completed the re-induction and consolidation treatment and who have responded (≥ SD) to the above combination will be randomized for maintenance treatment with Pomalidomide 4 mg orally days 1-21 of a 28 days cycle or Pomalidomide 4 mg orally days 1-21 of a 28 days cycle plus Dexamethasone 40 mg orally days 1, 8, 15, 22, of a 28 days cycle until disease progression.

Two hundred and twenty two 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. All patients will be followed until a maximum of 8 years after registration.

Details of all treatments (dose and schedule) are given in paragraph 9.

8 Study population

8.1 Eligibility for registration

All patients must be registered before start of treatment and must meet all of the following eligibility criteria.

8.1.1 Inclusion criteria

- Included in EMN02/HO95 trial. Induction therapy followed by autologous stem cell transplant (AutoSCT) and consolidation/ maintenance will be considered as one regimen.
- The subject must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures.
- Age ≥ 18 years at the time of signing the informed consent form.
- Able to adhere to the study visit schedule and other protocol requirements.
- Documented diagnosis of multiple myeloma and measurable disease (serum M-protein ≥ 10 g/L or urine M-protein ≥ 200 mg/24 hours or abnormal FLC ratio with involved free light chain (FLC) > 100 mg/L) or proven plasmacytoma by biopsy).
- Documented progression or refractory multiple myeloma as per the IMWG uniform response criteria (Durie, 2006) during or after the EMN02/HO95 trial. Normal renal function with a Creatinine Clearance > 45mL/min according to the Modification of Diet in Renal Disease (MDRD) equation for estimation of Glomerular Filtration Rate (GFR)
- WHO performance status score of 0, 1 or 2.
- Patients must be willing and capable to use adequate contraception during the therapy (all men, all pre-menopausal women).
- Patients must be able to adhere to the requirements of the Pregnancy Prevention Risk Management Plan.
- Patients must be eligible for autologous stem cell transplantation when not previously given in first line treatment.
- All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment.
- All subjects must agree not to share medication.

8.1.2 Exclusion criteria

- Patient received more than 1 regimen (EMN02/HO95), except local radiotherapy.
- Absolute neutrophil count (ANC) <1.0 x 10^9/L, unless related to MM.

- Platelet count < 75 x 10^9/L, unless related to MM.
- Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L).
- Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted).
- Significant hepatic dysfunction (Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN) or serum total bilirubin > 3.0 x ULN)
- Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
  - Basal or squamous cell carcinoma of the skin.
  - Carcinoma in situ of the cervix or breast.
  - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
- Previous therapy with pomalidomide or carfilzomib.
- Hypersensitivity to thalidomide, lenalidomide, bortezomib or dexamethasone (this includes ≥ Grade 3 rash during prior thalidomide or lenalidomide or bortezomib therapy).
- Peripheral neuropathy ≥ Grade 2.
- Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment.
- LVEF ≤ 40%.
- QTc > 450 msec.
- History of torsade de pointes.
- History of ventricular tachycardia, ventricular fibrillation.
- Uncontrolled atrial fibrillation/flatter.
- Congestive heart failure (NY Heart Association Class III or IV).
- Myocardial infarction within 12 months prior to starting study treatment
- Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris.
- History of pulmonary hypertension.
- Uncontrolled infection.
- Subjects who received any of the following within the last 14 days of initiation of study treatment:
  - Major surgery (kyphoplasty is not considered major surgery).
  - Use of any anti-myeloma drug therapy.
- Use of any investigational agents (with the exception of lenalidomide) within 28 days or five half-lives (whichever is longer) of treatment.
- Incidence of gastrointestinal disease that may significantly alter the absorption of pomalidomide.

- Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the informed consent form.
- Pregnant or breastfeeding females.
- Known human immunodeficiency virus (HIV) positivity, active infectious hepatitis A, B or C or chronic hepatitis B or C.
- Pre-existing pulmonary, cardiac or renal impairement that prevents hydration measures as described at section 9.5.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

8.2 Eligibility criteria for randomization

After completion of induction and consolidation treatment patients can be randomized for maintenance treatment if they meet the following criteria

- Patient has responded (at least SD).
- No toxicity suspected to be related to Pomalidomide ≥ Grade 2.

9 Treatment

9.1 Induction / consolidiation treatment

Patients who progress from EMN02/HO95, who were treated with standard dose Melphalan (VCD, followed by VMP, followed by yes/no VRD consolidation, followed by Lenalidomide maintenance) will be treated with 4 cycles of PCd **induction treatment**. Every next cycle will start at day 29.

Agent	Dose/day	Route of administration	Days
Pomalidomide	4 mg	orally	1-21
Carfilzomib*	20/36 mg/m^2	i.v.	1,2, 8, 9,15,16
Dexamethasone	20 mg	orally	1, 2, 8, 9, 15, 16,

***** **Induction treatment**: Carfilzomib 20 mg/ m^2 for days 1, 2, then 36 mg/m^2 days 8, 9, 15 and 16 of cycle 1, then 36 mg/ m^2 throughout next cycles.
Consolidation treatment: Carfilzomib 36mg/ m^2 days 1, 2, 8, 9, 15 and 16 of a 28 day cycle.

After induction they will receive high-dose Melphalan and autologous stem cell reinfusion of cells already stored during EMN02/HO95 if possible. Following hematologic recovery, these patients will receive 4 cycles of **consolidation treatment** with PCd according to the same schedule as above.

Consolidation treatment will start after at least 124 days following autoSCT. Pomalidomide can only start at the 3rd consolidation cycle (after 180 days following autoSCT).

Patients who progress from EMN02/HO95, who were treated with High Dose Melphalan (VCD, followed by HDM+autoSCT, followed by yes/no VRD consolidation, followed by Lenalidomide maintenance) will be treated with 4 cycles of PCd **induction treatment** according to the above schedule followed by another 4 cycles of **consolidation treatment** with PCd according to the same schedule. Each cycle starts on day 29.

9.2 High dose Melphalan and Autologous stem cell transplantation

Autologous stem cell transplantation for patients who received standard dose melphalan in EMN02 /HO95 trial

Stem cells have already been collected and stored during treatment in the EMN02/HO95 trial.
High Dose Melphalan. A stem cell harvest of 2.5x10 ^{6} CD34 + cells/kg is required. If insufficient stem cell harvest is acquired or in case of failure to qualify for autologous stem cell transplantation patients may continue with consolidation treatment.
Patients will be treated with High Dose Melphalan 200 mg/m² total (given in two days) followed by autologous stem cell reinfusion. HDM will start 4-6 weeks after completion of induction cycle 4.

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.

If 2 HDM is standard policy a second course of High Dose Melphalan may be administered between 2 and 3 months after the first course when the patient achieved at least PR.
Patients will be evaluated for response after the 2nd course of High Dose Melphalan. Patients with progressive disease will go off protocol treatment.

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.

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.

9.3 Maintenance treatment

All patients who have completed the re-induction and consolidation treatment and who have responded (≥ SD) to the above combination will be randomized for maintenance treatment with pomalidomide or pomalidomide and dexamethasone according to the schedule below. Maintenance treatment should start on day 29 after start of the 4th consolidation cycle.
Each next cycle starts at day 29. Patients will be treated until disease progression.
It is advised that pomalidomide is not prescribed to patients with known poor tolerance to pomalidomide during the trial.

Arm A

Agent	Dose/day	Route of administration	Days
Pomalidomide	4 mg	orally	1-21

Arm B

Agent	Dose/day	Route of administration	Days
Pomalidomide	4 mg	orally	1-21
Dexamethasone	40 mg	orally	1,8,15,22

9.4 Dose adjustments

The following sections and tables summarize dosing modifications of carfilzomib, pomalidomide, and dexamethasone to manage possible toxicity.
In case of major dose reductions/adjustments the study coordinator should be consulted.

9.4.1 Dose levels

Dose reduction levels of carfilzomib, pomalidomide, and dexamethasone for toxicity management of individual subjects are provided in table 1-3, respectively.

Table 1: 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
36 mg/m^2	27 mg/m^2	20 mg/m^2

Table 2: Dose Decrements for Pomalidomide

Nominal Dose	Reduced Pomalidomide Doses		
	Dose –1	Dose –2	Dose –3
4 mg	3 mg	2 mg	1 mg

Table 3: Dose Decrements for Dexamethasone

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

Guidelines for dexamethasone dose modifications are summarized in Table 6.

9.4.2 Dose Reductions for Hematologic Toxicities

Guidelines for the management of hematologic toxicities (thrombocytopenia and neutropenia) are summarized in Table 4.

Table 4: Treatment Guidelines for Hematologic Toxicity

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

Return to ≥ 30 × 10^9/L	Resume at 1 dose decrement	Resume at full dose
Neutropenia		
	Recommended Action	
When ANC	**Pomalidomide**	**Carfilzomib**
Falls to < 0.5 × 10^9/L	Interrupt both pomalidomide 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 pomalidomide and carfilzomib	
Returns to > 1.0 × 10^9/L	Resume at full dose	Resume at full dose

9.4.3 Dose Reductions for Non-Hematologic Toxicities

Guidelines for the management of non-hematologic toxicities are summarized in Table 5 and 6.

Table 5: Treatment Guidelines for Nonhematologic Toxicity for Pomalidomide and Carfilzomib

Symptom	**Recommended Action**	
	Pomalidomide	**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 pomalidomide, 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 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 pomalidomide, hold carfilzomib until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue pomalidomide	Hold until ≤ Grade 1, reinstitute at full dose.
Desquamating (blistering) rash – Any Grade	Discontinue pomalidomide	Hold until ≤ Grade 1, reinstitute at full dose.
Erythema multiforme ≥ Grade 3	Discontinue pomalidomide	Continue to dose; if Grade 3 rash persists for > 2 weeks after holding

		pomalidomide, hold carfilzomib until ≤ Grade 1, reinstitute at full dose.
Sinus bradycardia/ other cardiac arrhythmia		
≤ Grade 2	Hold (interrupt) dose. If the toxicity resolves to ≤ Grade 1 restart at full dose.	Hold until ≤ Grade 1, reinstitute at full dose.
≥ Grade 3	Discontinue pomalidomide	Hold until ≤ Grade 1, reinstitute at full dose.
Allergic reaction/hypersensitivity		
Grade 2 – 3	Hold (interrupt) dose. If the toxicity resolves to ≤ Grade 1 restart at 1 dose decrement.	Hold until ≤ Grade 1, reinstitute at full dose.
Grade 4	Discontinue	Discontinue

Symptom	**Recommended Action**	
	Pomalidomide	**Carfilzomib**
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 pomalidomide and carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	
Infection Grade 3 or 4	Hold both pomalidomide 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 pomalidomide and carfilzomib until lesions are dry. Reinstitute at full doses	
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
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	Hold pomalidomide dose for remainder	Full dose

toxicity assessed as pomalidomide-related ≥ Grade 3	of cycle. If the toxicity ≤ Grade 2 restart at 1 dose decrement	
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 6: 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.

9.5 Management of carfilzomib induced toxicity

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.

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.

Hydration and Fluid Monitoring

Intravenous Fluids.
250–500 mL of IV normal saline (or other appropriate IV fluid formulation) must be given before each carfilzomib dose during Cycle 1. Hydration after carfilzomib is optional based on treating physician discretion and patients need and risk of fluid overload. If lactate dehydrogenase (LDH) or uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for Cycle 2. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

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

Laboratory Monitoring

Obtain and review serum electrolytes and chemistries prior to each administration of carfilzomib on Days 1, 2, 8 and 9 during Cycles 1 and 2 and on Days 3 and 10 of Cycle 1. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib 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 and 10 should be continued through Cycle 2.

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.

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

Urate Lowering Prophylaxis

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 rasburicase.
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.

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 Table 5 for guidance regarding dose reduction in subjects with compromised renal function.

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 x 10^9/L.
- Thrombocytopenia has been transient and typically resolves during the week between treatments. For platelet counts < 20x10^9/L lasting > 7 days or 10x10^9/L 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 Table 4

- Subjects should have anemia corrected in accordance with the Institutional guidelines.
- Drug should be withheld for all ≥ Grade 3 non-hematologic events until resolved to ≤ Grade 1 or return to baseline, with exceptions, as noted in Table 5. After resolution of the ≥ Grade 3 non-hematological toxic effects, treatment with carfilzomib will resume, according to the guidelines as summarized in Table 5.
- 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.

9.6 Co-intervention

- 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.
- Low-dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects.
- 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.
- All subjects must receive prophylaxis with hydration and patients at high risk for TLS should receive rasburicase (see Section 9.5)

- Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed.
- Subsequent anti-myeloma treatment should not be initiated prior to PD or study treatment discontinuation.
- Chronic use of steroids (other than DEX) or any other immunosuppressive therapies is prohibited in this study.
- Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary.

9.7 Investigational Medicinal Products Carfilzomib & Pomalidomide

9.7.1 Summary of known and potential risks

Refer to Investigator's Brochure for the known risks of carfilzomib and for the known risks of pomalidomide to the SPC.

For Pomalidomide risks were indentified regarding serious hepatotoxicity, interstitial lung disease (ILD) and cardiac failure:

Hepatotoxicity

- Serious cases of acute hepatitis due to pomalidomide have occurred that led to hospitalization and discontinuation of treatment.
- Regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and thereafter as clinically indicated.

Interstitial lung disease (ILD)

- ILD and related events have been observed with pomalidomide.
- Patients with an acute onset or unexplained worsening of pulmonary symptoms should be carefully assessed to exclude ILD. Treatment with pomalidomide should be interrupted pending investigation of these symptoms.
- If ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and risks.

Cardiac failure

- Cardiac failure has been reported, mainly in patients with pre-existing cardiac disease or risk factors

- Pomalidomide should be used with caution in patients with cardiac disease or risk factors and if used, patients should be monitored for signs or symptoms of cardiac failure.

9.7.2 Preparation and labeling

Pomalidomide and carfilzomib will be shipped to trial sites in containers labeled as an Investigational Medicinal Product. Pomalidomide and carfilzomib will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

9.7.3 Storage and handling

Pomalidomide should be stored and handled in accordance with the instructions in the summary of product characteristics or package insert.

Carfilzomib should be stored and handled in accordance with the instructions in the Investigators Brochure or package insert.
The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented.

9.7.4 Study drug supply

The sponsor will arrange delivery of pomalidomide and carfilzomab to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.
Pomalidomide will be supplied as Investigational Product by Celgene Corporation as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. It will be packaged in containers containing a 21 day supply of POM.
Carfilzomib will be supplied as Investigational Product by Amgen Ltd as a lyophilized parenteral drug product in single-use vials. Each vial contains 60 mg of carfilzomib.

As soon as pomalidomide has obtained a marketing authorization for the indication under study, the investigator should start using commercially available pomalidomide if this is allowed by applicable national laws and regulations. The sponsor will notify the investigator when the delivery of investigational medicinal product will end.

9.7.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These

records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

9.7.6 Study drug return and destruction

The patient should return unused or partially used pomalidomide in their original packaging/blisters for drug accountability. The investigator should collect and count the remaining medication, empty boxes and blisters of medication to check that the patient has taken the assigned dose.Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned. Capsules and vials should be discarded in a safe manner.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
At the end of the trial or after expiry of the product unused investigational medicinal product should be destroyed by the trial site. Destruction should be documented.

9.8 Investigational Medicinal Product: Dexamethasone

9.8.1 Summary of known and potential risks

Refer to the summary of product characteristics for the known risks of carfilzomib and for the known risks of pomalidomide to the SPC.

9.8.2 Preparation and labeling

Dexamethasone with commercial labeling and packaging will be used.

9.8.3 Storage and handling

Dexamethsaone should be stored and handled in accordance with the instructions in the summary of product characteristics or package insert.

9.8.4 Study drug supply

The investigator should use commercially available dexamethasone.

9.8.5 Drug accountability

As dexamethasone will be used from commercial stock, no drug accountability is required other than regular pharmacy procedures.

10 Study procedures

10.1 Time of clinical evaluations

Patients will be evaluated:

- At entry
- After induction treatment cycle 2 and 4
- After High-dose Melphalan and autologous stem cell transplantation (if applicable)
- After consolidation treatment cycle 2 and 4
- After every 2nd maintenance cycle until progression
- During follow up every 2 months until progression. Thereafter every 6 months until 8 years after registration.

All patients will be followed until a maximum of 8 years after registration.

10.2 Required investigations

Required investigations at entry, during treatment, maintenance and during follow up

	At entry	After induction cycle 2 and 4	After HDM and SCT (if applicable)	After consolidation cycle 2 and 4	After every 2nd maintenance cycle	During follow up[8]
Medical history	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x
Hematology	x	x	x	x	x	x
Blood chemistry	x	x	x	x	x	x
Immunochemistry	x	x	x	x	x	x
Bone marrow aspirate	X[10, 11]	x[1]	x[1]	x[1]	x[1]	x[1]
Morphology	x	x	x	x	x	x
Immunophenotyping	x	x	x	x	x	x
FISH analysis	x					
BM cryopreservation[12]	x	x[9]	x[9]	x[9]	x[9]	x[9]
PB cryopreservation[12]	x	x[9]	x[9]	x[9]	x[9]	x[9]
Specific investigations						
X-thorax	x[3]					
Skeletal survey or CT [2,]	x[4]	x[2]	x[2]	x[2]	x[2]	x[2]
ECG	x[5]					
Cardiac ejection (MUGA or ECHO) fraction	x[6]					
ß2-microglobulin	x					
Creatinin clearance or GFR	x	oi	oi	oi	oi	
Response evaluation		x	x	x	x	x
Quality of Life [7]	x	x		x	x	
Pregnancy test	x	x	x	x	x	x
Pregnancy counselling	x	x	x	x	x	x
Survival status						x

o.i. on indication

1) At disappearance or reappearance of serum/urine M-component
2) In case of extramedullary plasmacytoma, the skeletal surveys or CT scans should be repeated at all evaluation moments plus at
   disappearance of serum/urine M-component
3) Within last month before entry
4) Within last 3 months before entry
5) Within 48 hours before entry
6) On indication
7) QoL frequency: at entry, after 4 induction cycles, after 4 consolidation cycles & every 6 months during maintenance
8) Every 2 months until progression of disease , thereafter every 6 months until 8 years after registration
9) Only at progressive disease
10) Within 1 month before entry. The EMN02/HO95 relapse sample may be used if all required tests are performed and the timelines are met.
11) Sampling of blood and bone marrow for central lab is mandatory for enrolment.

12) To be sent to central laboratory.

Medical history

Standard medical history, with special attention for:
Multiple myeloma history & previous treatment
WHO performance status; Bone pain; Infections; Bleeding tendency; Constipation; Polyneuropathy.

Only at entry:

Ethnicity
ISS stage
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; Absolute Neutrophil Count; Platelets;
At entry: PB cryopreservation for SNP analysis and protein analysis: 2 x 6 mL EDTA tubes, 1x 6 mL heparin, 1x6ml Citrate and 1x5ml Serum tubes (see 10.5).
At progressive disease: PB cryopreservation for SNP analysis and protein analysis: 2 x 6 mL EDTA tubes, 1x 6 mL heparin, 1x6ml Citrate and 1x5ml Serum tubes (see 10.5).

Blood chemistry

Serum creatinine; Creatinine clearance or GFR; Liver enzymes (AST & ALT); Total Bilirubin; Alkaline phosphatase; Albumin; LDH; Calcium; Uric acid.

Pregnancy counselling

Pregnancy counselling using Pomalidomide Pregnancy Risk Minimization Plan

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 aspirate at entry for:
  - Morphology,
  - immunophenotyping (see10.3)
  - FISH analysis (see 10.4)
  - BM cryopreservation: 2 x 10 mL heparine tubes (see10.5 and appendix F)
- Bone marrow aspirate during treatment, maintenance and follow up (when needed to confirm CR) for:
  - Morphology
  - Immunophenotyping (see 10.3)
- Bone marrow aspirate at time of progressive disease:
  - BM cryopreservation (see10.5 and appendix F)

10.3 Immunophenotyping

Each physician responsible for the immunophenotyping analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study.
Special investigations are required in patients that achieve a CR. At the time that patients have obtained normal free light chain ratio, and are expected to be in CR, CR has to be confirmed on bone marrow morphology and additional immunophenotyping is needed to confirm stringent CR (sCR=polyclonal plasmacell phenotype). Bone marrow aspirate will be processed using a 4-color direct immunofluorescence technique. CD138/CD38/CD45 and light scatter characteristics will be assessed simultaneously in at least one tube. Sample quality, number of events and clonality assessment will be performed according to EMN Consensus (Rawstron AC et al. Haematologica 2008; 93(3) 431-438).
For the assessment of stringent CR (sCR) bone marrow samples can be collected and analysed in the coordinating center or in case this technique is not locally available, the samples will be sent to central laboratories in each participating country.

10.4 Cytogenetic analysis

Each cytogeneticist responsible for the cytogenetic analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study.

FISH analysis is required in all patients at start of study. The following cytogenetic abnormalities will be evaluated as prognostic variables del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p. Conditions for FISH will be according to the EMN consensus.

10.5 Gene expression profiling, miRNA profiling, paired-end whole exome sequencing & single nucleotide polymorphism (SNP) 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, and in the event of progression. Samples will be sent to the central laboratory as per instructions in Appendix F. 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. Material collected at progression will allow us to track subclonal development.

10.6 Response evaluation

The response will be evaluated after induction cycle 2 and 4, after autoSCT (if applicable), after consolidation cycle 2 and 4, after every 2nd maintenance cycle and at 2 months intervals during follow up. Response will be evaluated according to International Myeloma Working Group (IMWG) criteria, see appendix B. Progression-free survival will be calculated from the start of therapy until progression or death.

10.7 Quality of Life assessment

The EORTC QLQ-C30 questionnaire will be used supplemented by the myeloma module MY-20.

- The QLQ-C30 is a multidimensional, cancer-specific quality-of-life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) Study Group on Quality of Life for use in international clinical trial settings.The QLQ-C30 includes 5 functional scales (physical, role, emotional, social and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale and a number of single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation and diarrhea) and perceived financial impact. For the majority of the QLQ-C30 items a 4-point Likert-type response scale is used. Exceptions are the items for the global quality of life scale (where a 7-point scale is used). All subscale and individual item

responses are linearly converted to 0 to 100 scales. For the functional and global quality of life scales, a higher score represents a better level of functioning. For the symptom scales and items, a higher score reflects a greater degree of symptomatology.

- The QLQ-MY20 questionnaire contains 20 items, and is a reliable and valid instrument recommended for use in myeloma patients. The questionnaire contains the following scales: pain, side effects of treatment, social support, body image, and future prospectives.

QoL will be measured:

- prior to treatment at entry,
- after 4 induction cycles,
- after 4 consolidation cycles
- every 6 months during maintenance.

The quality of life measurements will be stopped when patient goes off protocol treatment.
At entry the patient should be given an explanation of the objective of the questionnaire and instructions for filling out the questionnaires. The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self-administered questionnaire that should be filled out preferably by the patient him/herself.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions.
- All questions should be answered.

The collection of the QoL questionnaires will be performed in the following manner:
A QoL coordinator will be assigned in each participating center. As soon as a patient is registered, the baseline questionnaire will be handed over to the patient by the QoL coordinator/local investigator. The next QoL questionnaires will be presented to the patient by the QoL coordinator/local investigator at the appropriate time points (see above).
The completed questionnaires should be entered in the EMN database. In the EMN database an English version of the questionnaire is available. The original questionnaires will be kept on site.

11 Withdrawal of patients or premature termination of the study

11.1 Withdrawal of individual patients from protocol treatment

Patients should be withdrawn from protocol treatment if any of the following criteria for withdrawal are met:

- Death
- Patient not eligible in hindsight
- Progression during treatment
- Pregnancy of a female subject

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a patient from protocol treatment for other reasons than the criteria described above. Examples of such reasons for withdrawal from protocol treatment are:

- Excessive toxicity
- Refusal of patient to continue protocol treatment
- No compliance of the patient: patient is unable or unwilling to adhere to the treatment schedule and/or procedures required by the protocol

Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

11.2 Follow up of patients withdrawn from treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in 10.2 for follow up. SAE information will be collected as described in 12.3.
However, for patients who are withdrawn from treatment because in hindsight they did not fulfill the eligibility criteria (see 8.1) at time of enrolment, data will be collected until 30 days after the last protocol treatment given.

11.3 Withdrawal of informed consent

If a patient states that he or she withdraws his/her consent to participate in the trial, the investigator should attempt to verify the patients intent and record this in the patients medical file:

- The patient can refuse further treatment and/or procedures according to protocol, while still consenting with further follow up data collection.
- The patient can refuse further treatment and/or procedures according to protocol, and withdraw consent for further follow up data collection.
- The patient can refuse further treatment and procedures according to protocol, withdraw consent for further follow up data collection and withdraw consent to use any data in the trial.

If the patients intent is to withdraw consent for further data collection or to withdraw consent to use his or her data in the trial, the investigator should inform the HOVON Data Center so appropriate actions can be taken.
If the patient's intent can not be verified, further follow up data will be collected for this patient as described in <10.2> for follow up.

11.4 Premature termination of the study

The sponsor may decide to terminate the study prematurely based on the following criteria:

- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that continuation of the study cannot serve a scientific purpose following confirmation of the DSMB.
- The DSMB recommends to end the trial based on viable arguments other than described above

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

12 Safety

12.1 Definitions

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

Serious adverse event (SAE)
A serious adverse event is defined as any untoward medical occurrence or effect that at any dose :

- Results in death
- Is a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)

- Requires hospitalization or prolongation of an existing hospitalization
- Results in significant or persistent disability
- Is a congenital anomaly or birth defect
- Is an important medical event (i.e. important adverse events that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the above characteristics/consequences, including suspected transmission of infectious agents by a medicinal product).

Suspected unexpected serious adverse reaction (SUSAR)

All **suspected** Adverse Reactions which occur in the trial and that are both **unexpected** and **serious**. Suspected adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorized medicinal product).

12.2 Adverse event

12.2.1 Reporting of adverse events

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.

Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

Adverse Events have to be reported on the Adverse Events CRF. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 (see appendix D).

Pre-existing conditions will be collected on the baseline concomitant diseases CRF, i.e. active (symptomatic) diseases of CTCAE grade ≥ 2, diseases under treatment, chronic diseases and long term effects of past events as present at the time of baseline assessment.

All Adverse Events have to be reported, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AEs of CTCAE grade 1

- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Alopecia
- Nausea/vomiting
- Relapse/Progression of the disease under study; complications as a result of disease progression remain reportable Adverse Events

12.2.2 Follow up of adverse events

All adverse events will be followed clinically until they have been resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
On the AE CRF only the incidence of adverse events is recorded. Any ongoing adverse event that increases in severity is to be reported as a new adverse event on the CRF. Other follow up information is not collected on the CRF.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Serious Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

SAEs must be reported to the EMN Data Center by fax **within 24 hours** after the event was known to the investigator, using the SAE report form provided. This initial report should contain a minimum amount of information regarding the event, associated treatment and patient identification, as described in the detail in the instructions for the SAE report form. Complete detailed information should be provided in a follow-up report within a further 2 business days, if necessary.
The following events do not require to be reported as a Serious Adverse Event:

- Relapse/Progression of the disease under study; **death or complications as a result of disease progression remain reportable Serious Adverse Events**
- Hospitalization for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.

- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an adverse event. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Hospitalization for a procedure that was planned prior to study participation (i.e. prior to registration or randomization). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.2 Causality assessment of Serious Adverse Events

The investigator will decide whether the serious adverse event is related to trial medication, i.e. any of the products from the protocol treatment schedule. The decision will be recorded on the serious adverse event report. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

12.3.3 Follow up of Serious Adverse Events

All serious adverse events will be followed clinically until they are resolved or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information on SAE's should be reported monthly until recovery or until a stable situation has been reached. The final outcome of the SAE should be reported on a final SAE report.

12.3.4 Processing of serious adverse event reports

The EMN Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator and the manufacturer of the investigational medicinal products. The EMN Data Center will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR)
The Carfilzomib IB and Pomalidomide IB will be used as a reference document for expectedness assessment.
Where reporting of SAE's to the Dutch Ethics Committee is required by national laws or regulations or by the procedures of the Ethics Committee, the HOVON Data Center will report those SAE's by means of a six-monthly SAE line listing

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

The EMN Data Center, on behalf of the sponsor, will ensure the reporting of any SUSARs to the Ethics Committees (EC), the Competent Authorities (CA), the manufacturer of the investigational medicinal products and the investigators within the timelines required by the EU Clinical Trial Directive.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

Expedited reporting of SUSARs will occur no later than 15 days after the EMN Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

12.5 Pregnancies

Pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject, occurring while the subject

is on protocol treatment or within 30 days following the last dose of any drug from the protocol treatment schedule, should be reported to the sponsor. Pregnancies must be reported to the EMN Data Center by fax as soon as possible after the event was known to the investigator, using the pregnancy report form provided.

The investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor of the outcome of the pregnancy within 5 days or as specified below. The investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for classification as a SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly - including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live “normal” birth, the sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects is related to the in utero exposure to the investigational medicinal product(s) should also be reported.
The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission.

12.6 Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to any study drug, occurring at any time for the duration of the study, from the time of signing informed consent until 5 years after registration in the trial or until completion of maintenance therapy for patients who are still on maintenance at 5 years after registration.
Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g. pathology report).
The incidence of second primary malignancies is also monitored via a separate form (Second Primary Malignancy Report Form). This form should be filled out, dated and signed by the responsible investigator and returned to the EMN Data Center by fax within 24 hours after establishment of a second primary malignancy. SPM must also be documented in the other appropriate page(s) of the CRF (e.g. Adverse Event Form and Follow up Form).

12.7 Reporting of safety issues

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of findings that could affect adversely the safety of patients, impact the conduct of the trial, increase the risk of participation or otherwise alter the EC's approval to continue the trial. In the occurrence of such an event the sponsor and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The local investigator will inform the patients and local ethics or review committees according to hospital policy. The sponsor will inform any other parties that are involved in the trial.

12.8 Annual safety report

The sponsor will submit once a year a safety report to the Ethics Committees and Competent Authorities of the concerned Member States. The first report is sent one year after the first approval date of the trial. The last report is sent one year after the last patient has completed protocol treatment. The content of the annual safety report will be according to the EU guidance document '*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'.*

12.9 Data Safety and Monitoring Board

The DSMB will advise the Principal Investigator, co-investigators and the chair of the working group in writing about the continuation of the trial. The DSMB will review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events and safety, and differences in results between the arms of a randomized trial. The DSMB will consider if there is any concern regarding the safety and well-being of trial subjects or regarding the scientific validity of the trial results. The DSMB will base its advice on the reports provided by the statistician. The DSMB is free to take into consideration external information, such as the (interim) results of other trials or literature reports.

The DSMB consists of at least three members, with at least one statistician and two physicians. Details of the DSMB constitution and tasks are documented in the trial specific DSMB charter.

The DSMB will receive at least the following reports from the trial statistician for review:

- Interim analysis report (as described in 14.3)
- Annual safety data listing the incidence of (serious) adverse events, (serious) adverse reactions and SUSARs
- Annual progress data listing the number of enrolled patients and the status of data collection

12.10 Product complaints

Please also inform the HOVON Data Center of your complaint by fax (+31 (0)10 704 1028) or email (hdc@erasmusmc.nl). Note that product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to EMN Data Center see section 12.3

13 Endpoints

13.1 Primary endpoints

- Progression free survival (PFS) from randomization, defined as time from randomization to progression or death from any cause which ever occur first. Patient still alive at the date of last contact will be censored.
- Response rate (sCR, CR, VGPR, PR) after induction and consolidation treatment

13.2 Secondary endpoints

- Response rate after 8 cycles of PCD before start of maintenance
- Toxicity
- Improvement of response during/after maintenance
- Progression free survival calculated registration
- Overall survival calculated from time of registration or from start of maintenance treatment, until death from any cause. Patients still alive at the date of last contact will be censored.
- Quality of life as defined by the EORTC QLQ-C30 and QlQ-MY20.

14 Statistical considerations

14.1 Patient numbers and power considerations

The primary endpoint for this trial is PFS from randomization.
There are no data yet on PFS after 8 cycles of carfilzomib + pomalidomide + dexamethasone re-induction plus consolidation chemotherapy. However, in the phase I/II pomalidomide-dexamethasone trial, median PFS was 6.3 months. In a trial with patients refractory to bortezomib and lenalidomide the response to pomalidomide plus dexamethasone was 25 % and median OS 17 months. In a comparable group of patients treated with carfilzomib/dexamethasone median PFS after randomization was 8 months

Median PFS for lenalidomide maintenance in the IFM trial after HDM/AutoSCT was 42 months. Based on these data it is expected that the relapse rate in EMN02 will be 100/yr starting 2013 increasing to 150 yr starting 2014.

For the current sample size calculation the following assumptions have been made:

- uniform accrual for 24 months;
- additional follow up of 24 months after the last patient has been randomized;
- two-sided significance level $\alpha = 0.05$;
- power $1 - \beta = 0.80$;
- median PFS in the pomalidomide maintenance arm = 9 months;
- median PFS in the pomalidomide maintenance plus dexamethasone arm = 15 months, which corresponds to a HR = 0.60

This results in a total number of patients to be randomized of 146 (= 73 per arm), and the final analysis will be performed when 126 events have been reported.

If we assume that 66% (based on the 34% discontinuation rate in the VISTA trial) of the patients will be randomized, then 146/0.66 = 222 patients have to be registered (= 9-10 per month).

This maximum number of 222 patients enable to estimate the response rate after 8 cycles Pom-Car-Dex with a standard error of about 3% in the whole group, and in the subgroups of transplanted (within EMN02/HO95 trial) and non-transplanted patients, the standard error will be about 5%.

14.2 Statistical analysis

All main analyses will be according the intention to treat principle, i.e. patients will be analyzed according to the treatment arms they were assigned to. However, patients initially randomized but considered ineligible afterwards based on information that should have been available before randomization, will be excluded from the respective analyses.

14.2.1 Efficacy analysis

The main endpoint efficacy analysis will be on PFS from randomization. The PFS will be formally compared between the two randomization arms based on hazard ratio (with 95% confidence interval) estimated applying a multivariate Cox regression analysis with adjustment for stratification factors. The actuarial Kaplan-Meier method will be used to estimate PFS probabilities at appropriate time points, while the Greenwood estimate will be used to construct corresponding 95% CIs. Competing

risk analysis will be used to calculate cumulative incidences of PFS, progression/relapse, and death without progression (which add up to 100% at every time point). A Kaplan-Meier curve will be generated to illustrate PFS in each arm.

Other efficacy endpoints include response rates and overall survival rate. The response rates along with the 95% confidence intervals will be estimated. Cox regression, will be used to estimate and compare the hazard rates between the arms
In case the accrual will be 24 months, randomization will take place 9 months after registration of a patient, and if 24 months of follow up after the last patient is required, then the final analysis may be performed after 24 + 9 + 24 = 57 months after start of the trial, if the complete data including 126 events are available.

14.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events CTCAE grade 2 or more by induction cycle, and also for maintenance and placebo. Data from all subjects who receive any study drug will be included in the safety analyses. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE grade.

14.2.3 Additional analyses

Additional analyses may involve the analysis of prognostic factors, e.g. ISS stage, FISH analysis, molecular analysis, with respect to PFS, response rate and OS. Logistic and Cox regression could be used for this purpose. To include all patients in (multivariate) analyses, a multiple imputation algorithm will be used to impute missing covariate values if applicable. Before any additional analysis will be performed, a separate analysis plan will be discussed with the PI. Any such analysis should, however, be considered as exploratory, i.e. hypothesis generating, and not confirmatory

14.2.4 Statistical analysis plan

Before the final analysis, a SAP will be prepared by the trial statistician and approved by the principal investigator. It will describe in detail the analyses to be performed. Deviations from the analyses as specified in par. 14.2.1-14.2.3 will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary (confirmatory) analysis on which the sample size is based. All analyses except the primary analysis should be considered as hypothesis-generating only.

14.3 Interim analysis

One interim analysis is planned, primarily to describe adverse events observed during the carfilzomib + pomalidomide + dexamethasone re-induction chemotherapy. This will be done when data of the first 20 patients completing the 4 cycles of induction therapy are available. The accrual will not be discontinued while waiting for these data. Results of the interim analysis will be presented to the principal investigators and to an independent data and safety monitoring board (DSMB). The DSMB is free in its public recommendations to the study coordinators and the confidential recommendations to the study statistician. For the interim analysis a detailed report will be generated and presented to the DSMB. It will include the number of entered patients and at that time evaluable patients, treatment given, and incidence of SAE's and other adverse events and infections by grade. Adverse events will be described by summary table broken by site, CTCAE grade and relation to trial treatment. The study will be closely and sequentially monitored before the interim analysis. Monitoring will be based on the reported SAE's, which are not subjected to data delay. In addition, a separate report on the incidence of SAE's and other adverse events and infections, as described before, will be sent to the DSMB once a year.

14.4 Statistical analysis of the quality of life assessement

All patients with the baseline and at least one follow-up QoL questionnaire, separately for QLQ-C30 and QLQ-MY20, will be included in the analysis, The main purpose will be to describe QoL during induction and consolidation chemotherapy and during the maintenance treatments. QoL after randomization will also be summarized separately for both randomized groups. For randomized patients, the QoL after the last induction chemotherapy will then be considered as baseline. To evaluate the difference in QoL between the two randomization arms with respect to the multi-item scales of the QLQ-C30 and QLQ-MY20, the repeated measures may be analyzed separately using mixed ANOVA models, and the single items using (ordinal) logistic regression with random effects. However, the limited number of randomized patients implies limited power, which might hamper firm conclusions.

15 Registration and Randomization

15.1 Regulatory Documentation

Required regulatory and administrative documents must be provided to the HOVON Data Center before shipment of study drug and before enrolment of the first patient. This will always include an Ethics Committee approval for the investigational site. The HOVON Data Center will provide each

investigator with an overview of the required documents. Each investigational site will be notified when all requirements are met and enrolment can start

15.2 Registration and Randomization

15.2.1 Registration

Eligible patients should be registered before start of treatment. Patients will be registered at the EMN Data Center by web http://www.emntg.org. Investigators who do not have an account yet should register at this website to obtain an account after consultation of HDC.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Sex
- Date of birth
- Date written informed consent
- Specific items patient gives consent for (see ICF)
- Eligibility criteria
- Criteria for measurable disease and CRAB criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number

15.2.2 Randomization

All patients eligible for randomization can be randomized at the EMN Data Center (as described above)
The following information will be required:

- Protocol number
- Patient's study number
- Eligibility criteria

Patients will be randomized, stratified by center and current response (sCR/CRvs other). with a minimization procedure, ensuring balance within each stratum and overall balance.

16 Data collection and quality assurance

16.1 Case Report Forms

Data will be reported on electronic Case Report Forms (CRF) which will be completed and submitted using Remote Data capture (RDC). Guidelines on how to use RDC will be provided to all centers. All RDC forms (CRF forms) will be specifically designed by the EMN Data center for this study. These electronic forms will be used by all participants.

Data will be collected to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- Inclusion and exclusion criteria;
- Baseline status of patient including medical history and stage of disease;
- Timing and dosage of protocol treatment;
- Baseline concomitant diseases and adverse events;
- Parameters for response evaluation;
- Any other parameters necessary to evaluate the study endpoints;
- Survival status of patient;
- Reason for end of protocol treatment.

The forms must be electronically completed according to the schedule defined in the CRF guidelines through the EMN web based Remote Data Capture (RDC) system that can be accessed at http://www.emntg.org. The list of staff members authorized to enter forms (with a sample of their signature) must be identified on the signature log and sent to the HOVON Data Center by the responsible investigator before the start of the study.
In all cases, it remains the responsibility of the investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

Each page can be changed and saved whenever necessary until it is submitted; once the CRF is submitted, the center that wants to change the data can unlock the CRF. All changes will be tracked: the database of the web site will keep track of the first version with the date of validation, and of the second version with the date of correction.

All CRF entries must be based on source documents.
SAE, SPM and Pregnancy Notification forms will be sent by fax to EMN Data Center, where they will be entered in the database.

16.2 Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study, and site visits by the sponsor.
Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data on the CRF. The investigator should answer data queries within the specified time line.

16.3 Monitoring

This trial is part of the HOVON Site Evaluation Visit program. Site evaluation visits will be performed for HOVON trials to review the quality of the site and not specifically the quality of a certain trial. It will enable HOVON to collect quality data and facilitate improvement of the participating sites. Data cleaning or monitoring of the performance of specific trials is not the goal of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan.
The HOVON site evaluation visit plan applies to sites in the Netherlands and Belgium only. Monitoring of the quality of trial conduct in participating sites from other countries will be organized by the coordinating investigator or co-sponsor. The frequency and content of the site visits in other countries will be at least equal to the specifications of the site evaluation visit plan, and are described in a monitoring plan provided by HOVON.
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 site 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.

16.4 Audits and inspections

In accordance with regulatory guidelines, audits may be carried out for this study. The investigator is required to facilitate an audit by means of a site visit.
. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected.
Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17 Ethics

17.1 Accredited ethics committee

An accredited Ethics Committee will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. The investigator should take into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.
There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee in advance of use.
The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any substantially revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

17.4 Benefits and risks assessment.

The combination of pomalidomide, carfilzomib and dexamethason may be useful in the treatment of relapsed MM patients. In order to study the safety and efficacy of this combination it is required to include patients who have relapsed MM. The knowledge from this study may be of advantage to this group of patients in the future.
The majority of the investigations performed in this study do not differ from the usual standard of care for this patient category. Exceptions are that at the beginning of the study patients will be requested to provide extra blood and bone marrow aspirate for analysis (this does not require extra punctures); patients will also be asked to complete Quality of Life Questionnaires at regular intervals and to protect unborn children women of childbearing potential will be asked to regularly perform a pregnancy test.
There is a possibility that by taking part in the study patients will experience side effects from the medications under investigation.
The treating physician will always safeguard the health and best interest of the patients and furthermore an independent physician is available to provide independent advice to the patients.

17.5 Trial insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. The sponsor will take out an insurance policy or delegate this responsibility to a national co-sponsor. Proof of insurance will be submitted to the Ethics Committee.
In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial.

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. In some cases date of birth is also listed.

The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting hospital staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies)
The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents should be retained for 15 years after the end of the trial. They should be destroyed after this time, unless a longer record retention period is required by site specific regulations.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial, described in section 18.4. . Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.1.4 Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures.
Storage of biological samples on site is subject to the site's guidelines; samples may be labeled with the patients identifying information (e.g. name, hospital record number)
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research, should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

18.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the Ethics Committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the Ethics Committee and to the Competent Authority.

Non-substantial amendments will not be submitted, but will be recorded and filed by the sponsor.

18.3 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. The first report is sent one year after the first approval date of the trial. The last report is sent one year after the last patient has completed protocol treatment. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

18.4 End of trial report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the trial within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the primary endpoint analysis of the trial, the sponsor will submit an end of study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority. Upon request of the accredited Ethics Committee or the Competent Authority the sponsor will submit an updated version of the end of study report within one year after the last patient's last visit.

18.5 Publication policy

Final publication of trial results

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.

The final publication of the trial results will be written by the Principal Investigator, the Co-investigators and the trial statistician on the basis of the statistical analysis performed by the trial statistician. A draft manuscript will be submitted for review to:

- All co-authors
- The chair of the relevant HOVON working group, who is entitled to share and discuss the manuscript with working group members
- An industry partner if so agreed in the contract between HOVON and company

After revision the final manuscript is submitted to the HOVON secretary for review of compliance with this policy. After approval by the HOVON board the manuscript will be sent to a peer reviewed scientific journal.

Authorship

Authors of the main manuscript will include the Principal Investigator, the Co-investigators, investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion rate), the trial statistician and the trial manager. If a substantial part of the publication is based on centrally reviewed data (e.g. cytogenetics or pathology), the central reviewer will be included as author. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement.

Authors of correlative manuscripts (e.g. results of side studies) will include the Principal Investigator, the Co-investigators, and those persons who have made a significant contribution to the published results.

The Principal Investigator should discuss and decide on the matter of authorship of the main manuscript prior to the start of the trial – with the exception of authors included on account of inclusion rate. The Principal Investigator is urged to use the maximum number of authors allowed by the journal to the full extent.

Interim and partial publications

Interim publications, abstracts or presentations of the study may include demographic data, overall results and prognostic factor analyses, results for secondary endpoints, but no comparisons between randomized treatment arms for the primary endpoint may be made publicly available before the recruitment is discontinued.

Investigators participating in the trial have a right to publish results from data they collected for the study. The Principal Investigator, the Co-investigator(s) and the trial statistician must approve any such publication, abstract or presentation based on patients included in this study. This is applicable to any individual patient or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study endpoints unless the final results of the trial have already been published.

Abstracts and presentations

Abstracts and presentations at public meetings will represent the trial as a project under HOVON affiliation. The abstract or presentation should not be represented under affiliation of the working group or a specific hospital.

Slides will be designed using the HOVON style template and any other presentation materials will show the HOVON logo.

If the trial is conducted in partnership with a co-sponsor (e.g. intergroup trial), the abstract and presentation should represent the co-sponsor contribution and slides may show the co-sponsor logo in addition to the HOVON logo.

Prior to its public use, the abstract or presentation is submitted to the HOVON secretary for review of compliance with this policy.

Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
Ca	Calcium
CA	Competent Authority
CAR	Carfilzomib
CR	Complete Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease Free Survival
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EFS	Event Free Survival
EMN	European Myeloma Networtk
FCBP	Female of Child Bearing Potential
FFS	Failure Free Survival
FISH	Fluorescence In Situ Hybridisation
FLC	Free Light Chain
GCP	Good Clinical Practice
Hb	Hemoglobin
HDM	High Dose Melphalan
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFM	Intergroup Français de Myelome
IMP	Investigational Medicinal Product
ISS	International Staging System
ITT	Intention To Treat

IU	International Units
KCl	Potassium chloride
LD-DEX	Low Dose Dexamethasone
LDH	Lactate Dehydrogenase
METC	Medical Ethical Review Committee
MM	Multiple Myeloma
NaCl	Sodium Chloride
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PCD	Pomalidomide, Carfilzomib, Dexamehtasone
PD	Progressive Disease
PET	Positron Emission Tomografy
PFS	Progression Free Survival
PO	Per Os
POM	Pomalidomide
PR	Partial Response
QoL	Quality of Life
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SPEP	Serum protein electro-phoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal
UPEP	Urine protein electro-phoresis
VCD	Bortezomib, Cyclophosphamide, Dexamethasone
VGPR	Very Good Partial Response
VMP	Bortezomib, Melphalan, Prednisone
VRD	Bortezomib, Lenalidomide, Dexamethasone
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

19 References

1. Alexanian R, Yap BS, Bodey GP. Prednisone pulse therapy for refractory myeloma. Blood1983; 62: 572-7.
2. Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. Ann Int Med 1986; 105: 8-11.
3. Anderson KC, Hamblin TJ, Traynor A. Management of multiple myeloma today. Sem Hematol 1999; 36 (Suppl 3): 3-8.
4. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized, trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996; 335: 91-97.
5. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. New Engl J Med 2003; 348: 1875-83.
6. Hideshima T, Anderson KC. Molecular mechanisms of novel therapeutic approaches formultiple myeloma. Nature reviews 2002; 2: 927-937.
7. Richardson PG, Mitsiades C, Schlossman R, Munshi N, Anderson K. New drugs for myeloma. Oncologist 2007; 12:664-89.
8. San-Miguel J, Harousseau JL, Joshua D, Anderson KC. Individualizing treatment of patients with myeloma in the era of novel agents. J Clin Oncol 2008; 26: 2761-2766.
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma (V.1.2012), 2012 [www.nccn.org].
10. Kastritis E, Charidimou A, Varkaris A, Dimopoulos MA. Targeted therapies in multiple myeloma. Target Oncol 2009; 4: 23-36.
11. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplant. Br J Haematol 1998; 102: 1115-1123.
12. Dimopoulos MA, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007; 357: 2123-32.
13. Munshi NC, Anderson KC. Cancer: Principles & Practice of Oncology, 8th Edition: Chapter 54 -Plasma Cell Neoplasm: 2008.
14. Palumbo A, Anderson KC. Medical Progress –Multiple Myeloma: N Engl J Med 2011; 364:1046-60.
15. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352: 2487-98.
16. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized Phase III Study of Pegylated Liposomal Doxorubicin Plus Bortezomib Compared With Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression. J Clin Oncol 2007; 25: 3892-3901.
17. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. N Engl J Med 1994; 330:484-489.
18. Kumar S, Lee JH, Lahuerta J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. Leukemia 2012; 26:149-157.

19. Spencer, A., et al., Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol, 2009. 27(11): p. 1788-93.
20. Attal, M., et al., Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood, 2006. 108(10): p. 3289-94.
21. Demo SD, Kirk CJ, Aujay MA, et al. Anti-tumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007; 67(13):6383-91.
22. Arastu-Kapur S, Shenk K, Parlati F and Bennett M Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib Blood (ASH Annual Meeting Abstracts), Nov 2008; 112: 2657
23. Bortezomib Summary Basis of Approval (www.fda.gov/cder/foi/nda/2003/21602_Velcade.htm)
24. Bross PF, Kane R, Farrell AT, Abraham S, Benson K, Brower ME, Bradley S, Gobburu JV, Goheer A, Lee SL, Leighton J, Liang CY, Lostritto RT, McGuinn WD, Morse DE, Rahman A, Rosario LA, Verbois SL, Williams G, Wang YC, Pazdur R Approval summary for bortezomib for injection in the treatment of multiple myeloma. Clin Cancer Res. 2004 10(12 Pt 1):3954-64.
25. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk, KD, Sun CM, Demo SD, Bennett, SD, van Leeuwen, F, Chanan-Khan, A and Orlowski, RZ. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007 Nov 1;110(9):3281-90
26. Alsina M, Trudel S, Furman R, et al. A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed orrefractory multiple myeloma or lymphoma. Clin Cancer Res. 012;18:4830-4840.
27. Hajek R, Bryce R, Ro S, et al. Design and rationale of FOCUS (PX-171-011): A randomized, open-label, phase 3 study of carfilzomib versus best supportive care regimen in patients with relapsed and refractory multiple myeloma (R/R MM). BMC Cancer. 2012;12:415.
28. Jagannath S, Vij R, Stewart AK, et al. An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. Clinical Lymphoma, Myeloma & Leukemia. 2012:12(5):310-318.
29. O'Connor OA, Stewart AK, Vallone M, et al. A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res. 2009;15(22): 7085-7091.
30. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120: 2817-2825.
31. Vij R, Wang M, Kaufman J, et al. An open-label, single arm, phase 2 (PX-171-004) study of single agent carfilzomib in bortezomib naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012a;119:5661-5670.
32. Vij R, Siegel SS, Jagannath S, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. British Journal of Haematology, 2012b;158:739-748.
33. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A Phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012;120:1801-1809.
34. Stewart K, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52.

35. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol 1999; 163: 380-6.

36. Muller GW, Chen R, Huang SY, Corral LG, et al. Amino-substituted thalidomide analogs: potent inhibitors of TNF-α production. Bioorg Med Chem Lett 1999; 9:1625-1630.

37. Teo ST, Stirling DI, Zeldis JB. Thalidomide as a novel therapeutic agent: new uses for an old product. Drug Discovery Today 2005; 10:107-14.

38. Hayashi T, Hideshima T, Akiyama M, Podar K, et al. Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. Br J Haematol 2005; 128: 192–203.

39. Hernandez-Ilizaturri FJ, Reddy N, Holkova B, et al. Immunomodulatory Drug CC-5013 or POMALIDOMIDE and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res 2005; 11: 5984-5992.

40. Adams M, Schafer P, and Bartlett JB. The anti-proliferative effect of lenalidomide on MM cells in vitro is ameliorated by prior exposure to pomalidomide, an agent with activity against lenalidomide resistant MM cells. ASH Annual Meeting 2009; 114: 4926.

41. Rychak E, Mendy D, Adams M, et al. Overcoming resistance; the use of pomalidomide and dexamethasone (DEX) in re□sensitizing lenalidomide-resistant multiple myeloma (MM) cells. 13th International Myeloma Workshop (IMW) 2011; Poster # 328.

42. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, pomalidomide, in relapsed or refractory multiple myeloma. J Clin Oncol 2004; 22: 3269-3276.

43. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced AEs and evidence of in vivo immunomodulation. Br J Haematol 2008; 141: 41-51.

44. Richardson PG, Siegel D, Baz R, et al. A Phase 1/2 multicenter, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. ASH Annual Meeting 2011; Abstract # 0634.

45. Lacy M, Hayman S, Gertz M, Dispenzieri A, et al. Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma. J Clin Oncol 2009; 27:5008-5014.

46. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). Leukemia 2010; 24:1934–1939.

47. Richardson PG, Siegel D, Baz R, et al. A Phase 1/2 multicenter, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. ASH Annual Meeting 2010; Abstract # 0864.

48. Lacy M, Mandrekar S, Abraham M et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease [abstract]. Proceedings of the 52nd Annual Meeting of the American Society of Hematology (ASH) 2010a; December 4-7; Orlando, FL; USA: Abstract #863.

49. Leleu X, Attal M, Arnulf B, et al. Phase 2 Multicenter, Randomized, Open Label study of 2 Modalities of Pomalidomide plus low dose-dexamethasone in Patients with Multiple Myeloma,

Refractory to both Lenalidomide and Bortezomib. IFM 2009-02. ASH Annual Meeting 2011; Abstract # 0812.

50. Jatin J. Shah JJ, Stadtmauer EA, Abonour R, et al.Phase I/II Dose Expansion Of a Multi-Center Trial Of Carfilzomib and Pomalidomide With Dexamethasone (Car-Pom-d) In Patients With Relapsed/Refractory Multiple Myeloma. Blood. 2013; 122(21): 690-690

A. Criteria for symptomatic MM and measurable disease

B.G.M. Durie et al. (Leukemia, 2006: 20; 1467-1473

Criteria for symptomatic MM

Presence of a M-protein and/or abnormal free light chain ratio in serum

In case no M-protein or free light chain in serum urine parameter might be used

AND

Clonal plasma cells in bone marrow or soft tissue plasmocytoma

AND

At least 1 myeloma-related dysfunction*:

- Corrected calcium > 2.65 mmol/l
- renal insufficiency (creatinine > 177µmol/l)
- anemia (Hb < 6.2 mmol/l or > 1.25 mmol/l below normal limit)
  (Hb < 10.0 g/dl or > 2.1 g/dl below normal limit)
- bone disease (lytic lesions or osteopenia)

* must be attributable to the underlying plasma cell disorder

Criteria for measurable disease

Serum M-protein ≥ 10 g/l **or**

Urine M-protein ≥ 200 mg/24 hours **or**

Abnormal FLC ratio with involved free light chain (FLC) > 100 mg/l **or**

Proven plasmacytoma by biopsy

ISS criteria

International Staging System for Multiple Myeloma of the International Myeloma Working Group (J Clin Oncol 2005: 23; 3412-3420).

Stage	Criteria
I	Serum β_2-microglobulin < 3.5 mg/L
	Serum albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III*
III	Serum β_2-microglobulin ≥ 5.5 mg/L

* There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

..

B. Response criteria for Multiple Myeloma

Based on International Myeloma Working Group uniform response criteria. B.G.M. Durie et al. (Leukemia, 2006: 20; 1467-1473)

RESPONSE CRITERIA

Response subcategory	*Response criteria*[a]
sCR*	CR as defined below plus ▪ Normal FLC ratio and ▪ Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunophenotyping[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 ▪ 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[d]	Not meeting criteria for CR, VGPR, PR or progressive disease

* will only be determined in case the FLC assay is available in the participating hospitals

Abbreviations: CR, complete response; FLC, free light chain; 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.

[b] Confirmation with repeat bone marrow examination 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] 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 lowest response level in serum M-component (the absolute increase must be ≥ 0.5 g/dl)[b] and/or ▪ Increase of ≥ 25% from lowest response level in urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or ▪ Increase of ≥ 25% from lowest response level in 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 hypercalcaemia (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. Hypercalcaemia (> 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 hypocalcaemia 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 initiation of any new therapy.

[b] For progressive disease, serum M-component increases of ≥ 10 g/l are sufficient to define relapse if M-component is ≥ 50 g/l.

[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

Follow-up to meet criteria for PR or SD

- It is recommended that patients undergoing therapy will be tracked monthly for the first year of new therapy and every other month thereafter
- 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.

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

5 Death

D. Common Terminology Criteria for Adverse Events

The grading of adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.0. A complete document may be downloaded from the HOVON website:

http://www.hovon.nl (under Trials > General information about studies)

E. NYHA scoring list

The New York Heart Association functional and therapeutic classification applied to dyspnoea

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

F. Molecular analysis

Analyses will be performed on material collected prior to HOVON 114 treatment, i.e. at the onset of the trial and in case of progression.

Transcriptome analysis and mutation profiling

Gene expression patterns will be investigated in this trial using a combination of microarray and RNA-seq. Mutation analysis will be performed using DNA-seq analyses, making use of either custom capture or whole exome sequencing protocols. Gene expression profiles and mutation patterns will be correlated with response, progression-free survival and overall survival. The performance of our gene expression signature for high-risk MM will be assessed in this setting. At least 10ml bone marrow aspirate is required for this analysis, containing good quality bone marrow to allow for purification of sufficient myeloma cells. Aspirated bone marrow should be collected in 2 to 3 heparin tubes. Aspirations should take place prior to the onset of HOVON 114 treatment, and in case of progression.

Genome wide association studies

The involvement of inherited genetic polymorphisms will be investigated prospectively in this trial, using a Genome-wide analysis of SNPs (GWAS). The patterns of inherited genotype polymorphisms will be correlated with response, progression-free survival and toxicity. 12 ml of EDTA blood is needed to obtain a reasonable amount of DNA, necessary for the analyses. Blood samples should be collected prior to the onset of HOVON 114 treatment, and in case of progression.

Proteomics

The presence of known and unknown proteins will be assessed using blood obtained at the onset of this study. For this purpose both ELISA and mass spectrometry will be used. Heparin blood, citrate blood and serum will be collected for this purpose. Protein markers will be correlated with response, and survival, as well as with bone disease.

To maintain a good quality of DNA, RNA and protein, blood and bone marrow samples should be sent on the day of collection to the central laboratory at room temperature by overnight mail (to arrive before 10AM the next morning; overnight shipment, please follow instructions from your central laboratory. The centers will be provided with special envelopes for the shipment of these samples. Please fill in the sampling form completely and label the samples sufficiently (please mark clearly whether the sample is taken prior to the onset of HOVON 114 treatment or at progression).

Overview of material:

Biological material		Type of collection tube	Biobanking
Bone marrow*	≥5 mL	Heparin tube 1 (10 mL tube)	Tumour RNA, DNA & miRNA
	≥5 mL	Heparin tube 2 (10 mL tube)	
Peripheral blood*	6 mL	EDTA tube 1 (6 mL)	Genomic DNA
	6 mL	EDTA tube 2 (6 mL)	
	6 mL	Heparin tube 3 (6 mL)	Protein
	6 mL	Citrate tube 1 (6 mL)	
	5 mL	Serum tube 1 (5 mL)	

*, Please mix bone marrow and blood tubes well to avoid coagulation. Please aspirate carefully to obtain bone marrow containing sufficient myeloma cells.