Lenalidomide maintenance following tandem autologous stem cell and non-myeloablative allogeneic transplantation for patients with multiple myeloma ≤ 66 years who have been treated in or according to the HOVON 65 MM/GMMG-HD4 study.

PROTOCOL

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Date

Printed Name of Investigator
LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name:

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By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and local regulations governing the conduct of clinical studies.
1 Scheme of study

Treatment according to HOVON 65 MM/GMMG-HD4

3 x (V)AD +/- Bortezomib, CAD, HDM + Auto-SCT, and a NMA allo SCT (between 2 and 6 months after HDM)

Registration within 180 days following Allo-SCT

Maintenance

Lenalidomide 10 mg orally, days 1-21, 7 days rest for 24 months
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3 Synopsis

Study phase Phase II

Study objectives Efficacy and safety of lenalidomide treatment following non myeloablative Allo-SCT performed after intensive treatment including autologous stem cell transplantation

Patient population Patients with multiple myeloma, participating in or treated according to the HOVON 65/GMMG-HD4 MM trial, who have received 3 cycles of (V)AD ± Bortezomib, CAD, 1 cycle of HDM + Auto-SCT, and a NMA allogeneic stem cell transplantation which was applied between 2 and 6 months after HDM

Study design Prospective, multicenter, non-randomized

Duration of treatment Two years starting 1-6 months after non myeloablative Allo-SCT.

Number of patients 80 patients

Adverse events Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported

Planned start and end of recruitment Start of recruitment: II 2007
End of recruitment: IV 2009 – II 2010
## 4 Investigators and study administrative structure

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<tr>
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<td>H.M. Lokhorst</td>
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<td>Writing Committee</td>
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5 Introduction

5.1 Graft versus myeloma and allogeneic stem cell transplantation

Recently the existence of a Graft versus Myeloma (GVM) effect was proven by the induction of remissions by Donor Lymphocyte Infusions (DLI) in patients with relapsed MM after allogeneic stem cell transplantation (Allo-SCT). In a recent update of 54 patients, response to DLI was 53% and 17% of patients attained a CR. In 3 patients a molecular remission after DLI is now sustaining for more than 48 months, suggesting a curative potential of adoptive T-cell therapy in MM.

The necessity of performing Allo-SCT after myeloablative conditioning in MM however is disputed. Median OS in different reports varies from 18 to 28 months from transplantation. A survival advantage for patients receiving an Allo-SCT compared to patients with the same characteristics treated with Auto-SCT and no SCT at all has not been shown. In a retrospective case-matched analysis performed by the European Bone Marrow Transplantation (EBMT) registry the OS of patients receiving Auto-SCT was significantly better than of Allo-SCT patients. Only for patients alive at 1 year post-transplant OS and EFS were prolonged after Allo-SCT. A major reason for the poorer outcome of Allo-SCT is the high rate of Treatment Related Mortality (TRM) usually around 30-40%, which is not compensated for by a higher CR rate and lower relapse rate. An important factor responsible for the excessive toxicity of Allo-SCT in MM may be the high percentage of pretreated and refractory disease and the relatively high age of the patients included in published studies.

Since 1991 three intensive treatment protocols for MM were performed in the Netherlands and in Belgium under auspices of the Dutch-Belgian Haemato-Oncology Cooperative Group HOVON. In the phase III HOVON 24 MM trial with 453 patients, Interferon-α-2a (IFN) maintenance was compared to Auto-SCT and IFN maintenance following intensive induction therapy with Vincristine, Adriamycin, Dexamethasone (VAD) and Intermediate Dose Melphalan (Melphalan 70 mg/m², IDM). Patients under 56 years with an HLA-identical sibling could be allocated to Allo-SCT after induction therapy. This approach was chosen in order to evaluate the efficacy of early Allo-SCT on TRM and its possible favourable effect on long-term outcome in comparison with patients that received intensive treatment with or without Auto-SCT.

Evaluation of the HOVON 24 study showed that 56 patients who were allocated to Allo-SCT had a significantly inferior outcome as compared to an age-matched group of 73 patients who were eligible after induction therapy for further treatment (IFN or Auto-SCT). Median OS after Allo-SCT was 25 months versus 47 months in the Auto-SCT/IFN group. A major reason for the inferior outcome of Allo-SCT was the high treatment related mortality of 32% which was not compensated for by a favourable graft versus myeloma effect. These results indicate that there is no indication for standard Allo-SCT as part of front-line therapy for myeloma.
The study objective of the recently closed HOVON 50/GMMG-HD3 study was to evaluate the effect of thalidomide combined with adriamycin and dexamethasone during induction and as maintenance following intensive treatment for patients with multiple myeloma ≤ 65 years. Patients from this study with an HLA-identical sibling donor could be allocated to non myeloablative Allo-SCT, 2-6 months after intensive treatment (HOVON 54 study: see below).

5.2 Non myeloablative allogeneic hematopoietic stem cell transplantation

In multiple myeloma several studies with NMA Allo-SCT have been performed. The Seattle group has used the following strategy in MM patients. Patients are treated with high dose Melphalan 200 mg/m² and autologous stem cell rescue followed after 60-90 days by an Allo-SCT from HLA-identical sibs after minimal conditioning with low dose TBI, 200 cGy alone or combined with Fludarabine and post-transplant immunosuppression with cyclosporin A and mycophenolate mofetil. By separating the high-dose conditioning regimen from the immunotherapeutic effect of the allograft, they hoped to decrease the TRM, yet provide the allogeneic effect of graft versus myeloma. Fifty-four patients, 52 years of age (median; range, 29-71 years), with previously treated stage II or III MM (52% refractory or relapsed disease) were given melphalan 200 mg/m² and autologous SCT. Regimen-related toxicities after autologous SCT were moderate with a median of 6 days of neutropenia, 7 days of hospitalization, and 1 death from infection. Forty to 229 days later (median, 62 days), 52 patients received a single fraction dose of 2 Gy total body irradiation and CS transplants from HLA-identical siblings with postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP). Patients experienced medians of 0 days of hospitalization, neutropenia, and thrombocytopenia. Sustained engraftment was uniform. With a median follow-up of 552 days after allografting, overall survival is 78%. One patient (2%) died before day 100 from disease progression. Thirty-eight percent of patients developed acute graft-versus-host disease (aGVHD; grade II in all but 4 cases) and 46% chronic GVHD requiring therapy. Tumor responses occurred slowly. Thus far, 57% of patients have achieved complete remissions and 26% have achieved partial remissions for an overall response of 83%. Despite being evaluated in elderly patients with MM, this 2-step approach has reduced the acute toxicities of allogeneic SCT while achieving potent antitumor activities.

Other groups have confirmed these encouraging results of non myeloablative transplants using HLA matched sibling and unrelated donors. Between July 2003 and April 2006 the HOVON 54 study was open for patients included in the HOVON 50 study with an HLA-identical sibling donor. Between 2 and 6 months following High Dose Melphalan 200 mg/m² and autologous stem cell transplantation, non myeloablative allogeneic stem cell transplantation is performed using a single dose fraction of 2 Gy total body irradiation with postgrafting immunosuppression with MMF and CSP according to the Seattle scheme. A total of 93 patients have been included. As of December 12, 2006, data of 79 NMA-
transplants are available. Sofar, 6 patients have died from TRM, which compares favorable with myelo-ablative conditioning regimens. Progression free survival at 12 months following NMA Allo-SCT was 73% (95% CI, 61-82%). Toxicity was mainly due to chronic GvHD, which was reported in 51% of patients. Sofar 20 patients relapsed or progressed, which indicates the necessity for effective post-transplant treatment.

Two prospective studies comparing non myeloablative Allo-SCT with autologous transplantation have been reported. In the first study performed by French IFM, patients with unfavourable de novo myeloma (high β-2-microglobulin and deletion of chromosome 13) received an autologous transplant followed by NMA or double autologous transplantation depending on availability of an HLA-identical sibling donor. The interim analysis presented at ASH 2003 and updated at ASH 2004 showed comparable EFS and importantly comparable low TRM below 10%. At ASH 2005 a multicenter trial performed in Italian transplantation centers and Seattle was presented of de novo patients that received a double autologous transplant (n=54) or an autologous transplant followed by NMA after conditioning with low dose TBI (n=54) depending on availability of an HLA-identical sibling donor irrespective of risk features. CR rate (54 vs 26%), progression free (52 vs 24 months) and overall survival (not reached vs 48 months) were significantly improved in patients receiving NMA. TRM in the first 24 months was 8% and chronic GvHD was present in 65% of patients including 44% with extensive GvHD. Although prolonged, no plateau in the PFS and OS was observed in the NMA arm again indicating the necessity for effective post-transplant treatment.

5.3 Maintenance therapy and potential effect of thalidomide (analogs) on Graft versus Myeloma

Several prospective fase 3 trials are currently investigating the effect of maintenance treatment with thalidomide following high dose and conventional treatment. Low dose Thalidomide (100 mg daily) given as maintenance after standard melphalan/prednisone significantly improved PFS with 16 months. Low dose Thalidomide (100 mg) given as maintenance following autologous stem cell transplantation improved both EFS (50 versus 38 months) and overall survival (p=0.01 both arms 50% survival not reached).

Maintenance treatment with thalidomide following NMA has not been explored yet. However there are strong indications that thalidomide and analogs may enhance graft versus myeloma. In a phase 1/2 study the effect of low-dose thalidomide (100 mg) followed by DLI in 18 patients with progressive disease or residual disease and prior ineffective DLI after allografting was evaluated. The overall response rate was 67%, including 22% complete remission. Only 2 patients experienced mild grade I aGvHD of the skin, while no grades II to IV aGvHD was seen. De novo
limited cGvHD was seen in 2 patients (11%). The 2-year estimated overall and progression-free survival were 100% and 84%, respectively.

A second indication that novel agents including thalidomide may enhance Graft versus Myeloma comes from a retrospective study in patients receiving DLI for relapsed myeloma following NMA-Allo-SCT. Fifteen of 18 patients (83%) not responding to DLI were sensitive to treatment with novel agents thalidomide or bortezomib. In 2 responding patients a flare-up of GvHD was accompanying the GvM effect suggesting that immune modulation contributed to the response.21

In another study 24 relapsed or refractory myeloma patients were treated with a dose-escalating regimen of the thalidomide analog CC-4047 (Actimid).22 Treatment resulted in a greater than 25% reduction in M-protein in 67% of patients, 13 patients (54%) experienced a greater than 50% reduction in M-protein, and four (17%) of 24 patients entered complete remission. Importantly all patients showed increased CD45RO expression on CD4+ and CD8+ cells, with a concomitant decrease in CD45RA+ cells. Increased CD45RO expression indicates that T-cells are activated. CC-4047 treatment was associated with significantly increased serum interleukin (IL)-2 receptor and IL-12 levels, which is also consistent with activation of T cells and monocytes and macrophages. These studies clearly demonstrate in vivo T-cell costimulation by thalidomide and analogs, supporting a potential role for these agents as an immunostimulatory adjuvant treatment.

Recently, it was demonstrated in vitro that the thalidomide analog CC-5013, lenalidomide, enhances antigen-specific expansion of Natural Killer T-cells in response to NKT ligand α-galactosyl-ceramide in PBMC of both healthy donors and myeloma patients.23 This expansion was also demonstrated in vivo in 2 MM patients treated with thalidomide and in 5 MDS patients treated with lenalidomide treatment.
5.4 Lenalidomide

5.4.1 Introduction

Lenalidomide belongs to a proprietary class of Celgene compounds called IMiDs®. IMiDs®, of which thalidomide is the parent compound, have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production. Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide’s activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-γ secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis. In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.

5.4.2 Clinical experience in solid tumors with lenalidomide

Twenty patients with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in patient dose-escalation design, where patients started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy.

Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1.

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled.
Lenalidomide was administered in daily doses of 5 mg (3 patients), 10 mg (3 patients) and 20 mg (6 patients). Dose limiting toxicity was seen at 20 mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients.\(^{31}\)

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analyses of response rates are pending. The toxicity profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a lenalidomide dose of 25 mg daily orally for 21 days with a 7 day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favourable and similar to the previous phase III study.\(^{37}\)

### 5.4.3 Clinical experience in multiple myeloma with lenalidomide

In 2 phase I studies in multiple myeloma, a total of 42 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5 mg, 10 mg, 25 mg, and 50 mg (9). In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled.\(^{33}\)

Anti-myeloma activity was observed in each of these 2 phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25 mg and 50 mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5 mg, 10 mg, 25 mg, and 50 mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1
hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5 mg to 50 mg.\textsuperscript{34}

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15 mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30 mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone.\textsuperscript{35}

A recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently reported by the Mayo Clinic. Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, two had minor response (MR) and one stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Lenalidomide/Dexamethasone is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma.\textsuperscript{38}

A phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients is ongoing. The MTD of lenalidomide was 10 mg on Days 1-21 in combination with Doxil® 40 mg/m\textsuperscript{2} on Day 1, vincristine 2 mg on Day 1 and dexamethasone 40 mg on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81 mg prophylactically. The dose limiting toxicity with lenalidomide 15 mg on Days 1-21 in combination with DVd was sepsis/septic shock.\textsuperscript{36} Additional phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in patients with relapsed or refractory multiple myeloma.\textsuperscript{37} More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40 mg qd, Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone,
patients were randomized to lenalidomide 25 mg qd or placebo, Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40 mg qd, Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. A New Drug Application (NDA) is currently being prepared for the use of lenalidomide in Multiple Myeloma. Data continue to mature, but the preliminary interim analysis showed the following results.

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<td>61</td>
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<td>20.5</td>
<td>24</td>
</tr>
<tr>
<td>CR (%)</td>
<td>12.9</td>
<td>15.3</td>
<td>0.6</td>
<td>3.4</td>
</tr>
<tr>
<td>PR (%)</td>
<td>48.1</td>
<td>43.8</td>
<td>19.9</td>
<td>21.6</td>
</tr>
<tr>
<td>PD (%)</td>
<td>2.9</td>
<td>1.1</td>
<td>14.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Median TTP (mos)</td>
<td>11.1</td>
<td>11.3</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>29.6</td>
<td>Not estimable</td>
<td>20.5</td>
<td>20.6</td>
</tr>
</tbody>
</table>

**5.5 Rationale of the study**

This is a phase 2 trial to test the efficacy and safety of treatment with lenalidomide following non myeloablative Allo-SCT in patients initially included in the HOVON 65/GMMG-HD4 study. Patients treated according to the HOVON 65/GMMG-HD4 may be included as well. Although a considerable proportion of patients achieve CR following NMA Allo-SCT, patients do relapse including those with a CR. This urges the exploration of post transplant therapies i.e. especially strategies that enhance GVM without the stimulation of GVHD. This study will explore the feasibility of the thalidomide analog lenalidomide (CC-5013) as this drug has a low toxicity profile, is highly effective against myeloma and may have immunemodulating effects favouring GVM. A low dose of the thalidomide analog is chosen based on the efficacy of low dose thalidomide as maintenance following conventional and intensive treatment of myeloma (see paragraph 5.4) and the expectation that prolonged administration of “full therapeutic” lenalidomide 25 mg daily may be associated with increased (non) haematological toxicity.
6 Study objectives

Primary objective
♦ To estimate PFS after low dose lenalidomide maintenance treatment following non myeloablative Allo-SCT

Secondary objectives
♦ To estimate OS after low dose lenalidomide
♦ To estimate the CR rate after low dose lenalidomide for patients not in CR before start treatment with lenalidomide
♦ To estimate the ongoing response defined as the achievement of new VGPR and CR following start of lenalidomide treatment
♦ To estimate the incidence and severity of adverse events according to the CTC criteria (appendix C)
♦ To estimate the incidence and severity of acute and chronic GvHD (appendix F)
♦ To analyse relevant immunomodulating effects of lenalidomide in Multiple Myeloma in vivo.

7 Study design

Details of treatment (dose and schedule) are given in chapter 9.
The study is designed as a Phase 2 study for oral administration of lenalidomide following non myeloablative Allo-SCT.

7.1 Maintenance therapy with lenalidomide

Patients included in or treated according to the HOVON 65/GMMG-HD4 study who have received 1 course of HDM and Auto-SCT and a subsequent non myeloablative Allo-SCT (according to the criteria described in 8.2), and who are meeting all eligibility criteria will be included.
Lenalidomide treatment will start at day +28 following Allo-SCT, unless hematological repopulation following NMA is delayed or other inclusion criteria as defined in chapter 8 are not met.
Lenalidomide treatment may be delayed until 180 days following Allo-SCT, with a preference of registration within the first 90 days after Allo-SCT.
Patients will continue lenalidomide treatment for a maximum of 24 months unless relapse occurs.
8 Study population

8.1 Eligibility for registration

All eligible patients have to be registered within 180 days following Allo-SCT before start of treatment and have to meet all of the following inclusion criteria.

8.1.1 Inclusion criteria

- Age 18-66 years;
- Patients with, before start (V)AD, a confirmed diagnosis of multiple myeloma stage II or III according to the Salmon & Durie criteria (see appendix A), included in or treated according to the HOVON 65/GMMG-HD4 study;
- Patient has received 3 cycles of (V)AD induction therapy with or without bortezomib, CAD and 1 cycle of high dose Melphalan with autologous stem cell reinfusion;
- Patient has received a NMA allogeneic transplantation between 2 and 6 months after autologous stem cell reinfusion according to the criteria described in paragraph 8.2;
- The allogeneic transplantation has been administered between 28 and 180 days ago;
- WHO performance status 0-2 (see appendix D);
- Laboratory test results within these ranges:
  - Absolute neutrophil count ≥ 1.0 x 10^9/L
  - Platelet count ≥ 75 x 10^9/L
  - Serum creatinine clearance ≥ 50 ml/min
  - Total bilirubin ≤ 30 µmol/l
  - AST (SGOT) and ALT (SGPT) ≤ 3 x Upper Limit of Normal (ULN);
- Negative pregnancy test before inclusion if female of child bearing potential;
- Sexually active women of child bearing potential must agree to use 1 adequate contraceptive method while on study drug (and 4 weeks before and after study drug) (for detailed information see section 9.2.2);
- Men must agree not to father a child and to use a condom if his partner is of childbearing potential;
- Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast;
- Written informed consent, preferably signed in the presence of both patient and investigator and signed on the same date.
8.1.2 Exclusion criteria

- Progressive myeloma (see appendix B)(within 3 weeks before start therapy, response must be checked and patients who developed progressive myeloma must be excluded);
- Acute Graft versus host Disease ≥ grade 2 (at time of registration);
- Pregnant or lactating females;
- Concurrent use since NMA Allo SCT of other anti-cancer agents or treatments or use of any other experimental drug or therapy within 28 days of planned start lenalidomide;
- Known hypersensitivity to thalidomide;
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs;
- Any prior use of lenalidomide;
- Patients with brain disease with the exception of those patients whose brain disease has been treated with either radiotherapy or surgery and remains asymptomatic, with no active brain disease, as shown by CT scan or MRI, for at least 6 months;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E);
- Known positive for HIV or infectious hepatitis, type B or C.

8.2 Criteria of NMA allogeneic transplantation

To be eligible for this study the patient has to have received a NMA allogeneic transplantation according to the following criteria:

- The allogeneic transplantation was administered between 2 and 6 months after autologous stem cell reinfusion.
- The allogeneic transplantation was done after conditioning with low dose TBI (2 Gy) (it is allowed to combine TBI with medications such as Fludarabin or ATG).
- Immunosuppression after NMA is given according to the following scheme:

  Day 0: Mycophenolate mofetil (MMF) has been started at 15 mg/kg, orally twice daily to day +84.
  The first dose was given 5-10 hours after the allogeneic stem cell infusion. If no GvHD is present at day +84 MMF is tapered and stopped in 2 weeks.

  Day -3: Cyclosporin A was started at 4.5 mg/kg orally, twice daily to day +120. If no GvHD has occurred Cyclosporin A is tapered and stopped in 2 weeks. If the patient has (experienced) GvHD Cyclosporin A is continued to day +180. Thereafter (if no GvHD is present) Cyclosporin A is tapered with a ~10% dose reduction per week. In case of excessive (nephro) toxicity due to cyclosporin-A alternatively sirolimus 4 mg daily may be used.

If the NMA allogeneic transplantation was performed according to a different scheme, the patient is not eligible for this study.
9 Treatments

9.1 Lenalidomide

The planned dose of lenalidomide for investigation is 10 mg/day, orally for 21 days with 7 days rest (28 day cycle). Dosing will be in the morning at approximately the same time each day. The drug can be taken with food. Subjects experiencing adverse events may need study treatment modifications (see section 9.4.1).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/day</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>10 mg</td>
<td>Orally</td>
<td>Day 1-21 followed by 7 days rest for 24 months</td>
</tr>
</tbody>
</table>

9.1.1 Supplier(s)

Celgene Corporation will supply Revlimid®, lenalidomide (CC-5013).

9.1.2 Dosage form

Lenalidomide will be supplied as 5 mg capsules for oral administration.

9.1.3 Packaging

Drug will be shipped to the pharmacy at the study site in individual bottles with tear-off labels. Two bottles will contain a sufficient number of capsules to last for 21 days of dosing.

9.1.4 Special Handling Instructions

Women of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

9.1.5 Labeling

Lenalidomide investigational supplies are dispensed to the patient in individual bottles of capsules that are labeled in accordance with the appropriate regulatory requirements. Each bottle will identify the contents as study medication and bear the patient number and protocol number. In
addition, the label will bear the Investigator’s name and telephone number, quantity contained (21 capsules of 5 mg) and message use according to instructions of treating physician.

9.1.6 Receipt of study drug

The Investigator is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

9.1.7 Storage

At the study site, all investigational study drugs will be stored in a double locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

9.1.8 Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules.

9.1.9 Record of administration

Accurate records will be kept and stored of all study drug administration (including dispensing and dosing).

9.2 Concomitant therapy

9.2.1 Prohibited concomitant therapy

Concomitant use of haematopoietic growth factors, with the exception of G-CSF and erythropoietin, other anti-cancer therapies, including radiation, thalidomide, or other investigational
agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

9.2.2 Obligatory contraception

Effective contraception must be used by patients for at least 4 weeks before beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions and for 4 weeks following discontinuation of lenalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. One reliable form of contraception must be used unless continuous abstinence from heterosexual sexual contact is the chosen method. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential.

Male Patients: It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

9.3 Treatment compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit.

9.4 Dose interruption

9.4.1 Dose modification or interruption

<table>
<thead>
<tr>
<th>Table 1: Lenalidomide Dose Reduction Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Dose:</strong> 10 mg daily for 21 days every 28 days</td>
</tr>
<tr>
<td><strong>Dose Level 1:</strong> 5 mg daily for 21 days every 28 days</td>
</tr>
</tbody>
</table>
### Table 2: Dose Modification for lenalidomide (Based on CC-5013-Related Toxicity Observed on Days 2-28)

<table>
<thead>
<tr>
<th>CTC AE Grade</th>
<th>Day 2-14 of Cycle</th>
<th>≥ Day 15 of Cycle</th>
</tr>
</thead>
</table>
| Sustained (≥ 7 days) Grade 3 neutropenia (neutrophils < 1.0 - 0.5 x 10^{9} /L) without other toxicities | • Treat with G-CSF  
• Dose of lenalidomide does not have to be interrupted | • Treat with G-CSF  
• Dose of lenalidomide does not have to be interrupted |
| Sustained (≥ 7 days) Grade 3 neutropenia (neutrophils < 1.0 - 0.5 x 10^{9} /L) with other toxicities or ≥ Grade 3 neutropenia (neutrophils < 1.0 x 10^{9} /L) associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia (neutrophils < 0.5 x 10^{9} /L) | • Hold (interrupt dose).  
• Follow CBC weekly.  
• If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21. | • Omit lenalidomide for remainder of cycle |
| Thrombocytopenia ≥ Grade 3 (platelet count < 50 x 10^{9} /L) | • Hold (interrupt dose).  
• Follow CBC weekly.  
• If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21. | • Omit lenalidomide for remainder of cycle |
| Non-blistering rash Grade 3 | • If Grade 3 hold (interrupt) dose.  
Follow weekly.  
• If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. | • Omit lenalidomide for remainder of cycle |
| Non-blistering rash Grade 4 | • Discontinue lenalidomide study drug. | • Discontinue lenalidomide study drug. |
| Desquamating (blistering) rash- any Grade | • Discontinue lenalidomide study drug. | • Discontinue lenalidomide study drug. |
| Erythema multiforme ≥ Grade 3 | • Discontinue lenalidomide study drug. | • Discontinue lenalidomide study drug. |
| Neuropathy Grade 3 | • If Grade 3 hold (interrupt) dose.  
Follow weekly.  
• If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. | • Omit lenalidomide for remainder of cycle |
| Neuropathy Grade 4 | • Discontinue lenalidomide study drug. | • Discontinue lenalidomide study drug. |
| Sinus bradycardia/ other cardiac arrhythmia Grade 2 | • Hold (interrupt) dose.  
Follow at least weekly.  
• If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. | • Omit lenalidomide for the remainder of the cycle |
<p>| ≥ Grade 3 | • Discontinue lenalidomide study drug. | • Discontinue lenalidomide study drug. |</p>
<table>
<thead>
<tr>
<th>CTC AE Grade</th>
<th>Day 2-14 of Cycle</th>
<th>≥ Day 15 of Cycle</th>
</tr>
</thead>
</table>
| Allergic reaction or hypersensitivity Grade 2-3                            | • Hold (interrupt) dose. Follow at least weekly.  
• If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.                                    | • Omit lenalidomide for the remainder of the cycle.                                                                                                               |
| Grade 4                                                                     | • Discontinue lenalidomide study drug.                                                                                                                                                                                  | • Discontinue lenalidomide study drug                                                                                                                                 |
| Constipation Grade 1-2                                                       | • Initiate bowel regimen and maintain dose level.                                                                                                                                                                     | • Initiate bowel regimen and maintain dose level.                                                                                                                 |
| ≥ Grade 3                                                                   | • Hold (interrupt) dose. If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.                                                                 | • Omit lenalidomide for the remainder of the cycle.                                                                                                               |
| Venous thrombosis/embolism Grade 3                                          | • Hold (interrupt) dose and start anticoagulation; restart at investigator’s discretion (maintain dose level).                                                                                                   | • Omit lenalidomide for remainder of cycle and start anticoagulation.                                                                                             |
| other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3 | • Hold (interrupt) dose. Follow at least weekly.  
• If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.                                    | • Omit lenalidomide for remainder of cycle.                                                                                                                                 |
| Hyperthyroidism or hypothyroidism                                           | • Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).                                                | • Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level). |
| GVHD Grade 2                                                                | • Hold (interrupt) dose. If toxicity resolves to ≤ grade 1 within 2 months, restart lenalidomide at next cycle (decrease dose by one dose level)                                                                               | • Hold (interrupt) dose. If toxicity resolves to ≤ grade 1 within 2 months, restart lenalidomide at next cycle (decrease dose by one dose level)                                                                               |
| Grade 3                                                                     | • Discontinue lenalidomide study drug permanently                                                                                                                                                                     | • Discontinue lenalidomide study drug permanently                                                                                                                                 |

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1.0 x 10^9/l;
- The platelet count ≥ 50 x10^9/l;
- Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other lenalidomide-related adverse event that may have occurred has resolved to ≤ grade 2 severity.
If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of lenalidomide will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. There is only one-level dose reduction, if the subject experiences side-effects that prevent dosing at 5 mg/day the study treatment has to be discontinued.

9.5 Special precautions

It should be considered that the proposed treatment of lenalidomide may evoke or aggravate symptoms including GvHD that are due to the prior non myeloablative Allo-SCT. Hospital admission for treatment of GVHD may be necessary. (GVHD is the major toxicity associated with allografting or infusion of donor PBSC. It has occurred in >50% of patients.) Also, the clinician should be aware of enhanced bone marrow suppression (neutropenia) especially due to the combination of MMF and lenalidomide.

When GvHD grade 2 occurs, lenalidomide should be interrupted. If toxicity resolves to ≤ grade 1 within 2 months, restart lenalidomide at next cycle (decrease dose by one dose level).

The onset of GvHD grade 3 must lead to discontinuing of lenalidomide study drug permanently.

10 End of protocol treatment

Treatment with study drug is permanently discontinued when any of the following occurs:

- Completion of protocol treatment
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm, which rule out continuation of study drug and or indicate a dose level below 5 mg/day.
- Progression of Multiple Myeloma
- Major violation of the study protocol.
- No compliance of the patient
- Death
- Suspected pregnancy
• ≥ grade III acute GvHD

11. Visit schedule and assessments

Aim of the clinical evaluation at entry is to check eligibility. Aim of the evaluation during treatment and follow up is to determine toxicities and efficacy. In addition follow-up blood samples will be taken to measure possible in vivo modulation by lenalidomide in relation to response and GvHD. Apart from toxicity evaluation, routine evaluations of disease status will be performed as well. Evaluation of response is described in appendix B.

11.1 Time of clinical evaluations

Screening assessments occur ≤ 14 days from Baseline (Baseline: first day of study drug administration, Cycle 1, Day 1). Screening pregnancy tests for women of child-bearing potential must occur ≤ 7 days from Baseline.

Schedule the Discontinuation from Study Drug Visit as soon as possible after a subject has been discontinued from the study treatment, regardless of the reason. Follow up contact with the subjects should occur every 3 months. An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF.

11.2 Required minimum clinical and laboratory evaluations

See next page for overview.
Overview of required minimum clinical and laboratory evaluations

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Cycles 1 and 2</th>
<th>Cycles 3-24</th>
<th>Discontinuation From Study Drug</th>
<th>Follow-Up Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤≤≤≤ ≤≤≤≤ 14 days from Baseline (First day study drug administration)</td>
<td>Day 1</td>
<td>Day 8, 15</td>
<td>Day 22</td>
<td>Cycles 3-12: start week 1/ cycles 13-24: every other cycle</td>
</tr>
<tr>
<td>Medical history</td>
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<td>X^2</td>
<td>X</td>
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<td>Physical examination</td>
<td>X</td>
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<td>Hematology</td>
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<td>Immunochemistry</td>
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<td>X^2</td>
<td>X^6</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Bone marrow aspirate and biopsy^7</td>
<td>X^1</td>
<td>X^2</td>
<td>X^6</td>
<td>X</td>
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<td>Special investigations</td>
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<td></td>
<td></td>
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<tr>
<td>ECG</td>
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<td>X^2</td>
<td>X</td>
<td>X^1</td>
<td>X</td>
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<td>X^2</td>
<td>X</td>
<td>X^1</td>
<td>X</td>
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<tr>
<td>Chimerism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grading of GvHD</td>
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<td>X^2</td>
<td>X</td>
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<td>X</td>
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<td>Immunological status</td>
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<td>X^6</td>
<td>X</td>
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</tr>
<tr>
<td>Record adverse events</td>
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<td>X^2</td>
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<tr>
<td>Record concomitant therapies/procedures</td>
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<td>X^2</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispense study drug for next cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perform drug accountability</td>
<td>X</td>
<td>X^2</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Obtain Follow-Up anti-cancer treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain Follow-Up survival information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^1: only if not performed between autologous and Allo-SCT. Bone marrow examination will be repeated to confirm CR in case of a negative immunofixation of M-protein and in case relapse is suspected which cannot be confirmed by the

Page 27 of 62
standard laboratory investigations. Response must be evaluated within 3 weeks before start of treatment in order to exclude patients who developed progressive myeloma.

2: not at cycle 1

3: chimerism of peripheral blood cells according to local protocol.

4: Immune status at cycle 1, day 1 (before start lenalidomide) and day 15. At cycle 2, day 1 (before start of lenalidomide). At cycle 9, day 1 (before start lenalidomide) and day 15. And at cycle 10, day 1 (before start lenalidomide).

5: Once the treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur once every 4 weeks of use.

6: special chemistry and immunochemistry in cycles 3-12 every 2 months

7: once a year and extra to confirm CR and in case relapse is suspected which cannot be confirmed by the standard laboratory investigations.

11.2.1 Medical History

A complete medical history to include descriptions of all prior and ongoing diseases and disorders. Documentation of all medications, treatments and therapies used in the prior 4 weeks as well as those currently being taken. Record all anti-cancer therapies given prior to enrollment on study. Also record the WHO performance status.

11.2.2 Physical Examination

Physical examination, to include vital signs, height (at screening only) and weight.

11.2.3 Clinical Laboratory Evaluations

The following clinical laboratory evaluations will be performed for study reasons, extra evaluations according to local hospital guidelines are allowed:

- Hematology: hemoglobin, hematocrit, MCV, WBC and differential, and platelet count.
- Serum Chemistry general: sodium, potassium, creatinine, glucose, alkaline phosphatase, total bilirubin, ALT, LDH.
- Serum Chemistry special: calcium, albumin, total protein. Only at baseline, after every 6 cycles and at discontinuation visit: Uric acid and TSH
- Immunochemistry: Serum and urine M-protein: Quantitative serum M-protein, including immunofixation to confirm CR and a quantitative urine M-protein in 24 hrs urine, including immunofixation to confirm CR.
11.2.4 Electrocardiogram (ECG).

A 12-lead ECG.

11.2.5 Chimerism

Chimerism of peripheral T and non-T cells will be determined before start of lenalidomide (≤ 14 days of baseline) according to local protocols.

11.2.5 Grading of GvHD

Acute and chronic Graft versus Host Disease will be scored according to the criteria defined in appendix F.

11.2.6 Pregnancy test

Before prescribing lenalidomide, females of childbearing potential should have 2 negative pregnancy tests (sensitivity of at least 50 mIU/mL). The first test should be performed within 10 – 14 days, and the second test within 24 hours prior to prescribing lenalidomide. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur once every 4 weeks in females with regular menstrual cycles. A similar schedule of one pregnancy test every 4 weeks should be implemented if menstrual cycles are irregular. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

11.2.7 Immunological status

Evaluation of immune-status and modulation after lenalidomide treatment by means of assessment of cytokines (TNFα, IL-8, IL-10, IL-12, IL-2, sIL-2R), cellular subsets (T cells, NK T cells Treg cells) and functional analyses, including the induction of host and or myeloma reactive T cell clones during follow-up of the patients. Changes in the immune-status will be correlated with response (Graft versus Myeloma) and toxicity (GvHD and infections). The collection of material for these evaluations should be obtained at cycle 1, day 1 (before start lenalidomide) and day 15. At cycle 2, day 1 (before start of lenalidomide) and day 15. At cycle 9, day 1 (before start lenalidomide) and
day 15. And at cycle 10, day 1 (before start lenalidomide) (see also flow chart). An indication for additional immune status evaluation is the occurrence of GvHD or DVT.

For this 40 ml Natrium-heparin blood samples (cells and plasma) should be gathered, prepared and frozen immediately after collection at a temperature of -70 °C (please record date of obtaining the sample). There are no contra indications for postponing the immune status evaluation. The sites will receive further information on the collection of these samples by UMCU. Questions on sampling for immunological status can be directed to E. Kneppers (tel. 088 755 9771), M. Minnema or H. Lokhorst (tel. 088 755 8380 or 088 755 9771).

11.2.8 Query for Concomitant Therapies

From the concomitant therapies given the immunomodulating therapies will be queried at interim and discontinuation of treatment visits Mycophenolate Mofetil (MMF), cyclosporine-A, prednisone and MTX.

11.3 Evaluation of response

Response will be evaluated according to EBMT, IBMTR and ABMT criteria (see appendix B).

Time points are day 1 of each new cycle (= every 4 weeks) during cycles 1 and 2, every 2 cycles in cycles 3-24 and in case of suspected relapse (before start lenalidomide, after cycles 1 and 2 and every other cycle thereafter). Evaluations will primarily consist of serial measurements of myeloma proteins in serum and urine. Bone marrow evaluation will be performed to confirm CR and in case relapse is suspected which cannot be confirmed by the standard laboratory investigations.

Response will be evaluated in relation to the status before start (V)AD.

12 Toxicities

Toxicities will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 3.0 (Appendix C).

Lenalidomide

Most frequently reported adverse events during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, urinary tract infection (UTI),
upper respiratory infection, cellulitis, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

Graft versus Host Disease
The major toxicity associated with allografting or infusion of donor PBSC is GVHD. GVHD has occurred in >50% of patients. The use of lenalidomide may influence the occurrence of GVHD. Hospital admission for treatment of GVHD may be necessary. GVHD will be scored according to the grading given in appendix F.

13 Safety evaluations and adverse events reporting

13.1 Definitions

Adverse event (AE)
An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE 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.

Adverse reaction (AR)
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.

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

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- significant / persistent disability
• a congenital anomaly / birth defect
• any other medically important condition (i.e. important adverse reactions 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 other outcomes listed above, especially DVT and ≥ grade III acute GvHD)

Note that ANY death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected SAE
Unexpected Serious Adverse Events are those SAE’s of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company’s Investigator’s Brochure will serve as a source document in that country.

Suspected unexpected serious adverse reaction (SUSAR)
All suspected ARs which occur in the trial and that are both unexpected and serious.

Protocol treatment period
The protocol treatment period is defined as the period from the first study-related procedure until 30 days following the last dose of protocol treatment or until the start of another systemic anti-cancer treatment off protocol, if earlier.

13.2 Reporting of (serious) adverse events

Adverse event
All adverse events, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient’s outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must evaluate all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, it should be considered to be an adverse event and the investigator must provide details as specified above. If a laboratory abnormality is one component of a diagnosis or a syndrome, then only the diagnosis or syndrome should be recorded as AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.
All AEs of CTCAE grade 2 or higher, with the exception of progression of the disease under study, Alopecia, Nausea, Vomiting and Hematological side effects with grade \( \leq 2 \), have to be reported on the Adverse Events CRF.

Adverse events occurring after the protocol treatment period should also be reported if considered related to protocol treatment. Follow up of ongoing adverse events ends at day 30 following the last dose of protocol treatment.

**SAE and Unexpected serious adverse event**

All SAEs occurring during the protocol treatment period must be reported to the HOVON Data Center by fax *within 24 hours of the initial observation of the event*, except hospitalizations for:

- a standard procedure for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). 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.
- a procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the protocol treatment remains a reportable serious adverse event.

All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 2 working days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the protocol treatment period, Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, *within 24 hours after the SAE was known to the investigator*. 
The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following:

<table>
<thead>
<tr>
<th>RELATIONSHIP</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNRELATED</td>
<td>There is no evidence of any causal relationship to the protocol treatment (also include pre-existing conditions)</td>
</tr>
<tr>
<td>UNLIKELY</td>
<td>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).</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>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).</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>DEFINITELY</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
<tr>
<td>NOT ASSESSABLE</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td>
</tr>
</tbody>
</table>

13.3 Processing of serious adverse event reports

The HOVON Data Center will forward all reports within 24 hours of receipt to the principal investigator, the study central datamanager and to Celgene Europe Drug Safety. The report of an SAE will be the signal for the central datamanager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF’s for the involved patient with details of treatment and outcome.

Any suspected unexpected serious adverse reactions (SUSARs), from any source, will be reported by Celgene to the investigators, the Ethics Committee which approved the study, and to all applicable Health Authorities within required timelines.

13.4 Pregnancies

Pregnancies occurring while subjects are on study drug or within 4 weeks after a subject’s last dose of study drug are considered events to be reported immediately to Celgene. If the subject is...
on study drug the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy must be reported to Celgene within 24 hours of the Investigator’s knowledge of the pregnancy by phone and facsimile using the SAE Form. The pregnancy must also be reported to the sponsor. The Investigator will follow the subject until completion of the pregnancy, and must notify the sponsor and Celgene of the outcome 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 immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs. 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 study drug should also be reported. In the case of a live “normal” birth, Celgene should be informed as soon as the information is available.

Any suspected foetal exposure to lenalidomide must be reported to Celgene within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Contact details for Celgene Europe Drug Safety:

Celgene International
Fax: +41 32 729 8409
Celgene International Sarl
Faubourg du Lac 11
2000 Neuchatel
Switzerland
Tel : +41 32 729 8476
Email : drugsafetyeurope@celgene.com

13.5 Adverse event updates/IND safety reports

Celgene shall notify the investigators and the sponsor via an investigational new drug (IND) safety report of the following information:

- any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
• any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. The sponsor shall notify the EC and the relevant regulatory authorities of any new significant risks to subjects as required

14 Endpoints

Primary endpoint is:
♦ PFS (defined as time from start lenalidomide maintenance until progression, relapse or death from any cause, whichever comes first)

Secondary endpoints are:
♦ OS (defined as time from start lenalidomide maintenance until death form any cause)
♦ CR rate of patients not in CR at start lenalidomide
♦ Ongoing response defined as the achievement of new VGPR and CR following start of lenalidomide treatment
♦ Adverse events
♦ Acute and chronic GvHD
♦ In vivo immune modulation of lenalidomide

15 Data collection

15.1 CRFs

Data will be collected on Case Report Forms (CRF) 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;
♦ 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.
Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient namecode (as documented at registration) to be filled out before completing the form.

The CRF will be completed on site by the local investigator or an authorised staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents. The CRF and written instructions for completing the CRF will be provided by the HOVON Data Center.

Copies of the CRF will be kept on site. The original CRF pages must be sent to the HOVON Data Center at the requested time points. How and when to send in forms is described in detail in the CRF header and the CRF instructions.

All data from the CRF will be entered into the study database by the HOVON Data Center.

Investigator responsibilities are described in appendix G and the monitoring plan for this study is described in a separate document.

16 Registration

The patient should be registered after confirmation of eligibility and before start of maintenance treatment. Patients need to be registered at the HOVON Data Center of the Erasmus MC - Daniel den Hoed by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00 or via the Internet via TOP (Trial Online Process; https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient's initials or code
5. Patient's hospital record number
6. Sex
7. Date of birth
8. Patient study number in HOVON 65 MM (if applicable)
9. Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or email.
17 Statistical considerations

17.1 Sample size and accrual

The aim of this study is to assess in patients who received a NMA Allo-SCT after one HDM and Auto-SCT in or according to the HOVON 65 MM trial the efficacy of lenalidomide maintenance. The primary end point in this trial will be progression-free survival (PFS), see section 14.

Preliminary data as of January 5, 2007, on 79 patients who had received a NMA Allo-SCT in the HOVON 54 MM trial, but without additional maintenance therapy, did not show a plateau in PFS during the first 2 years after NMA Allo-SCT. Actuarial estimates of PFS at 12 and 24 months after D90 (including 90% confidence intervals) are 67% (56-75%) and 52% (38-65%). D90 was considered as date start, because in the HOVON 76 MM trial most patients will probably start with lenalidomide within 90 days after NMA Allo-SCT. Currently 26 patients witnessed an event after D90, 20 of them had progression or relapse after NMA Allo-SCT. Of the 76 patients with a follow up of at least 3 months after NMA Allo-SCT, 12 were already in CR before transplantation, while another 19 have already achieved a CR after median 6 months (range, 3-21 months) after transplantation without any further treatment.

PFS at 1 year (PFS_{1y}) will be considered as primary end point for the sample size calculation.

- Let P_0 be the largest PFS_{1y} probability which, if true, implies that the therapeutic activity is too low and therefore the present HOVON-76 schedule does not warrant further investigation. In the present trial, P_0 has been taken as 59%.
- Let P_1 be the lowest PFS_{1y} probability which, if true, implies that the therapeutic activity is sufficiently high and therefore the proposed HOVON-76 schedule warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 75%.
- Let \(\alpha\) be the accepted probability of recommending for further investigation a regimen with a true “success” rate equal to or lower than P_0. In the present trial, \(\alpha\) has been taken as 0.05.
- Let \(\beta\) be the accepted probability of rejecting for further investigation a regimen with a true “success” rate at least equal to P_1. In the present trial, \(\beta\) has been taken as 0.10.

The required number of eligible patients is 80.

- One interim analysis will be performed as soon as 12 events for PFS have been reported. The total time at risk for all patients who entered the trial will be calculated. Assuming an exponential distribution for the PFS during the first 12 months, we calculate the hazard rate, estimate PFS_{1y} and its 90% CI, and the trial will be considered for early termination when the upper limit of the 90% CI is less than 75%.
- If the trial was not discontinued early, the final analysis will be performed when complete information is available for all eligible patients who started with lenalidomide maintenance. If the upper limit of the 90% CI of PFS$_{1y}$ is less than 75%, the trial will conclude that the proposed HOVON-76 schedule is not active enough. Otherwise, the trial will conclude that the treatment is active and warrants further investigation in this patient population.

10,000 Monte Carlo simulations were performed to obtain the following operations characteristics of the monitoring schedule:

<table>
<thead>
<tr>
<th>True PFS$_{1y}$</th>
<th>Probability to recommend HOVON-76</th>
<th>Probability of early termination</th>
<th>Expected number of patients entered</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td>0.084</td>
<td>0.623</td>
<td>54.5</td>
</tr>
<tr>
<td>75%</td>
<td>0.940</td>
<td>0.047</td>
<td>78.2</td>
</tr>
</tbody>
</table>

In order to have up-to-date data for the interim analysis, a short questionnaire will be sent out every 3 months starting 3 months after entry of the 12th patient until 12 events (i.e. progression/relapse or death) have been observed.

It is assumed that about 400 HOVON patients will be entered in the combined HOVON 65 MM/GMMG-HD4 trial as well as 100 patients from Heidelberg. It is expected that about 15% of those patients will be given a NMA Allo-SCT. Moreover, some patients will have been treated according to but not been entered in the HOVON-65 protocol. Therefore it should be possible to enter 80 patients in this trial, which would be achieved in 2-2.5 years.

17.2 Analyses

All eligible patients who start with lenalidomide maintenance will be included in the analysis.

The estimated PFS at 1 year along with a 90% CI interval will be presented. A 90% CI is chosen because for the primary endpoint, $\alpha = 0.10$.

Analyses of safety will be done by tabulation of the incidence of adverse effects with CTC grade 2 or more (appendix C).

The estimated CR rate along with a 95% CI will be presented for all patients, as well as for only those patients who were not yet in CR when lenalidomide was initiated.
The actuarial curves for PFS and OS will be computed using the Kaplan-Meier method and 95\% CIs will be constructed.

Actuarial probabilities of acute and chronic GvHD will be calculated along with 95\% CIs.

For illustrative purposes, the results of the HOVON 76 MM-trial will be compared to those of the patients who received a NMA Allo-SCT in the HOVON 54 MM-trial and who were still alive without progression at D90.

Immune monitoring data will be analyzed to see whether lenalidomide maintenance has an immune modulating effect following non myeloablative Allo-SCT in myeloma. Immune monitoring data will be analyzed to see whether lenalidomide maintenance has an immune modulating effect following non myeloablative Allo-SCT in myeloma. Levels of cytokines and cellular subsets are measured and will be compared with data from the cohort of the immunological monitoring of non-myeloablative monitoring (IMMENS) study that included 80 patients, including 12 patients treated according to the HOVON 54 MM-study.

17.3 Interim analysis

One formal interim analysis is planned as described above. In addition, safety (i.e. adverse events reported on the CRF’s) will be closely monitored in the first 20 patients.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000) and the ICH-GCP Guidelines of 17 January 1997.

18.3 Patient information and consent

Written Informed consent of patients is required before registration. The patient and investigator have to sign 2 informed consent forms, 1 original has to be kept in the master file or source
document, the other one is to return to the patient. The procedure and the risks and the opinions for post-induction therapy in multiple myeloma will be explained to the patient.

More ethical and regulatory considerations (subject confidentiality) are described in Appendix H.

19 Trial insurance

The HOVON insurance program covers all patients from participating centers in the Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site [www.hovon.nl](http://www.hovon.nl).

Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary HOVON will extend the insurance to cover these patients.

Intergroup studies.

The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomized through their offices.

20 Publication policy

The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center, all co-authors and Celgene for review. After revision by the Data Center, the other co-authors and Celgene, the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the HOVON datamanager in charge of the trial, and others who have made significant scientific contributions.

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

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient randomized in the
trial, 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 end-points unless the final results of the trial have already been published.
21 Glossary of abbreviations

(in alphabetical order)

ABCM Adriamycin, BCNU, Cyclofosfamide, Melphalan
AD Doxorubicin (Adriamycin), Dexamethasone
AE Adverse Event
aGVHD acute Graft versus Host Disease
ANC Absolute Neutrophil Count
AR Adverse reaction
ALT Alanine Amino Transferase
AST Aspartate aminotransferase
Auto autologous
Allo allogeneic
BID Twice daily
BM Bone Marrow
CAD Cyclophosphamid, Doxorubicin (Adriamycin), Dexamethasone
cGVHD chronic Graft versus Host Disease
CI Confidence Interval
CKTO ‘Commissie voor Klinisch Toegepast Onderzoek’ (previously "CKVO")
CR Complete Remission
CRF Case Report Form
CSP Cyclosporin A
CTC Common Toxicity Criteria
DLI Donor Lymphocyte Infusion
DVT Deep venous thrombosis
EGC Electrocardiogram
ECOG Eastern Cooperative Oncology Group
EBMT European Group for Blood and Marrow Transplantation
EFS Event Free Survival
EORTC European Organization for Research and Treatment of Cancer
bFGF beta fibroblast growth factor
GCP Good Clinical Practice
G-CSF Granulocyte Colony-Stimulating Factor
GI Gastro-intestinal
GMMG German-speaking myeloma multicenter group
GVHD Graft versus Host Disease
GVM Graft versus Myeloma
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
IDM Intermediate Dose Melphalan
IFM: Intergroup Français de Myelom
IFN: Interferon
IgG / IgM / IgA: Immunoglobulin G / M / A
IND: Investigational New Drug
IU: International Units
LDH: Lactate Dehydrogenase
MCV: Mean corpuscular volume
MM: Multiple Myeloma
MMF: Mycophenolate Mofetil
MR: Minor response
MTD: Maximum tolerated dose
MTX: Methotrexate
NC: No Change
NCI: National Cancer Institute
NMA: Non Myeloablative
NYHA: New York Heart Association
OS: Overall Survival
PD: Progressive Disease
PBMC: Peripheral Bone Marrow Cells
PFS: Progression Free Survival
PR: Partial Response
SAE: Serious Adverse Event
SCT: Stem Cell Transplantation
SGOT: Transaminase glutamaat oxaloacetaat
SGPT: Transaminase glutamaat pyruvaat
SUSAR: Suspected unexpected serious adverse reaction
TBI: Total Body Irradiation
TNF: Tumour Necrosis Factor
TRM: Treatment Related Mortality
TSH: Thyroid stimulating hormone
TTP: Time to progression
ULN: Upper Limit of Normal
VAD: Vincristine, Doxorubicin (Adriamycin), Dexamethasone
VBAP/VMCP: Vincristin, BCNU, Adriamycin, Prednisone/Vincristin, Melphalan, Cyclofosfamide, Prednisone
VEGF: Vascular Endothelial Growth Factor
WBC: White blood count
WHO: World Health Organization
WMO: ‘Wet Medisch-Wetenschappelijk Onderzoek met mensen’
22 References

12. Carella AM, Cavaliere M, Lerma E et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell


center, randomized, phase 2 study to evaluate the efficacy and safety of two CDC-5013 dose 
regimens when used alone or in combination with dexamethasone (Dex) for the treatment of 
relapsed or refractory multiple myeloma (MM). Blood 2003, Abstract #825.

frequency dexamethasone (d) and Revlimid (R) (DVd-R) a phase I/II trial in advanced 

37. Data on file. Celgene Corporation

38. Rajkumar SV, Hayman SR, Lacy MQ et al. Combination therapy with lenalidomide plus 
A. Diagnostic Criteria Multiple Myeloma

DIAGNOSIS OF MULTIPLE MYELOMA

Major criteria:
1. plasmacytoma (tissue biopsy)
2. > 30% plasma cells in bone marrow
3. monoclonal serum M-protein IgG > 35 g/l; IgA >20 g/l, or urine M-protein >1 g/24 hrs in the absence of amyloidosis

Minor criteria:
a. plasma cells in bone marrow > 10% but ≤ 30%
b. monoclonal serum M-protein IgG ≤ 35 g/l, IgA ≤ 20 g/l, urine M-protein ≤ 1 g/24 hrs
c. lytic bone lesions
d. normal IgG <6 g/l or IgM <0.5 g/l or IgA <0.2 g/l

Multiple Myeloma is diagnosed in case one of the following combinations of criteria is present:

1 + b or 1 + c or 1 + d
2 + b or 2 + c or 2 + d
3 + a or 3 + c or 3 + d
a + b + c or a + b + d
STAGING OF MULTIPLE MYELOMA

Staging according to Salmon & Durie criteria

Stage I  Low Tumor Mass – all of the following:

- Hemoglobin > 6.2 mmol/l
- Ca\(^{2+}\) < 2.65 mmol/l *
- IgG < 50 g/l
- IgA < 30 g/l
- Urine M-protein < 4 g/24 hrs
- Normal skeletal assessment or solitary plasmacytoma

Stage II Intermediate Tumor Mass:

Patients who qualify for neither Stage I nor III

Stage III High Tumor Mass – Any one of the following:

- Hemoglobin < 5.3 mmol/l
- Ca\(^{2+}\) > 2.65 mmol/l *
- IgG > 70 g/l
- IgA > 50 g/l
- Urine M-protein > 12 g/24 hrs
- ≥ 3 lytic bone lesions on skeletal survey (bone scans are not acceptable)

A Normal renal function (creatinin < 177 µmol/l)

B Renal insufficiency (creatinin ≥ 177 µmol/l)

* Correct the serum Ca\(^{2+}\) by adding 0.02 mmol/l for every g/l albumin below 40 g/l
Staging according to ISS criteria

**Stage I:** Serum $\beta_2$-microglobulin < 3.5 mg/l AND Serum albumin $\geq$ 3.5 g/dl (≥ 35 g/l)

**Stage II:** Patients who qualify for neither Stage I nor III

**Stage III:** Serum $\beta_2$-microglobulin $\geq$ 5.5 mg/l
B. Response Criteria for Multiple Myeloma

Based on EBMT, IBMTR and ABMT criteria (British J. Haemat. 102: 1115-1123, 1998)

**Complete response** (CR) requires all of the following:

1. Absence of the original monoclonal paraprotein (M-Protein) in serum and (10 x concentrated) urine by immunofixation, maintained for at least 6 weeks.
2. < 5% plasma cells in a representative bone marrow aspirate or otherwise in a bone marrow biopsy. Only in patients with non-secretory myeloma, bone marrow investigation must be repeated after an interval of 6 weeks to confirm CR.
3. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude CR)

Patients in whom some, but not all, criteria for CR are fulfilled are classified as PR or VGPR, providing the remaining criteria satisfy the requirements for PR/VGPR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

**Very good partial response** (VGPR) requires all of the following:

1. Meeting the criteria for partial response but show a 90% reduction of serum M-protein concentration for at least 6 weeks.

**Partial response** (PR) requires all of the following:

1. ≥ 50% reduction of serum M-protein concentration maintained for at least 6 weeks.
2. Reduction in 24 hrs urine M-protein either by ≥ 90% or to < 200 mg, maintained for at least 6 weeks.
3. In patients with non-secretory myeloma, ≥ 50% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks.
4. ≥ 50% reduction in size of soft tissue plasmacytoma.
5. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude PR).

Patients in whom some, but not all, criteria for PR are fulfilled are classified as MR, providing the remaining criteria satisfy the requirements for PR.
**Minimal response** (MR) requires all of the following:

1. $\geq 25\%$ reduction of serum M-protein concentration maintained for at least 6 weeks.
2. $\geq 50\%$ reduction in 24 hrs urine M-protein, maintained for at least 6 weeks.
3. In patients with non-secretory myeloma, $\geq 25\%$ reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks.
4. $\geq 25\%$ reduction in size of soft tissue plasmacytoma.
5. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude MR).

**No change** (NC)

1. Not meeting the criteria of either minimal response or progressive disease.

**Progressive disease** (for patients without prior response) requires one or more of the following:

1. $> 25\%$ increase in serum M-protein level, which must also be an absolute increase of at least 5 g/l and confirmed at least once.
2. $> 25\%$ increase in 24 hrs urine M-protein, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed at least once.
3. $> 25\%$ increase in plasma cells in a representative bone marrow aspirate or bone marrow biopsy
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of compression fractures does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium $> 2.80$ mmol/l) not attributable to any other cause.

**Plateau**

1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

**Relapse from CR** requires at least one of the following:

1. Reappearance of serum or urine M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
2. $\geq 5\%$ plasma cells in a representative bone marrow aspirate or bone marrow biopsy
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of compression fractures does not exclude continued response and may not indicate relapse).
4. Development of hypercalcaemia (corrected serum calcium > 2.80 mmol/l) not attributable to any other cause.

*Progression after PR / MR* requires one or more of the following:

1. > 25% increase in serum M-protein level compared to nadir, which must also be an absolute increase of at least 5 g/l and confirmed at least once.
2. > 25% increase in 24 hrs urine M-protein compared to nadir, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed at least once.
3. > 25% increase in plasma cells in a representative bone marrow aspirate or bone marrow biopsy compared to nadir.
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new bone lesions or soft tissue plasmacytomas (development of compression fractures does not exclude continued response and may not indicate progression).
6. Development of hypercalcaemia (corrected serum calcium > 2.80 mmol/l) not attributable to any other cause.
C. Common Terminology Criteria for Adverse Events

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse events, CTCAE version 3.0, revised Dec 12, 2003. A complete document may be downloaded from the following sites:

http://ctep.cancer.gov/reporting/ctc.html
http://www.hovon.nl

A hardcopy may be obtained from the HOVON Data Center on request.
D. 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
E. **NYHA* scoring list**

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

The *New York Heart Association functional and therapeutic classification applied to dyspnoea
F. Grading of GVHD

Acute GVHD

Severity of organ involvement

**Skin**
+1 maculopapular eruption involving less than 25% of the body surface
+2 maculopapular eruption involving 25-50% of the body surface
+3 generalized erythroderma
+4 generalized erythroderma with bullous formation and often with desquamation

**Liver**
+1 moderate increase in ASAT\(^1\) (150-170 IU) and bilirubin (20-40 \(\mu\)mol/l)
+2 bilirubin rise 40-75 \(\mu\)mol/l with or without an increase in ASAT
+3 bilirubin rise 75-200 \(\mu\)mol/l with or without an increase in ASAT
+4 bilirubin rise to > 200 \(\mu\)mol/l with or without an increase in ASAT

**GI**
Diarrhea, nausea and vomiting graded +1 to +4 in severity
The severity of GI involvement is assigned to the most severe involvement noted

**Diarrhea**
+1 > 500 ml of stool/day
+2 > 1000 ml of stool/day
+3 > 1500 ml of stool/day
+4 > 2000 ml of stool/day

\(^1\)Increases in ASAT temporally related to either the onset or worsening of the skin rash
Severity of acute GVHD

Grade I  
+1 to +2 skin rash  
no GI involvement  
no more than +1 liver involvement  
no decrease in performance

Grade II  
+1 to +3 skin rash  
+1 to +2 GI involvement and/or  
+1 to +2 liver involvement  
mild decrease in performance

Grade III  
+2 to +4 skin rash and  
+2 to +4 GI involvement with or without +2 to +4 liver involvement  
marked decrease in performance with or without fever

Grade IV  
pattern and severity of GVHD similar to grade III with extreme constitutional symptoms

Chronic GVHD

Limited  
Localized skin involvement and/or liver function abnormalities

Extensive  
Generalized skin involvement, or localized skin involvement and/or liver function abnormalities + other organ involvements
G. Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP). Investigators must enter study data onto CRFs or other data collection system. The Investigator, or a designated member of the Investigator’s staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject’s records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification.
H. Ethical and regulatory considerations

Subject confidentiality
HOVON affirms the subject’s right to protection against invasion of privacy. HOVON requires the Investigator to permit HOVON’s representatives and, when necessary, representatives of the regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject’s statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Study records requirements
The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject’s diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

Premature discontinuation of study

Single center
The responsible local clinical Investigator as well as HOVON have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.
Study as a whole

HOVON reserves the right to terminate this clinical study at any time for reasonable medical or ethical reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).