A randomized phase II study for the evaluation of T cell depleted non-myeloablative allogeneic stem cell transplantation followed by early consolidation with lenalidomide or lenalidomide combined with bortezomib and subsequent DLI for patients with multiple myeloma in progression or relapse following first line therapy

PROTOCOL

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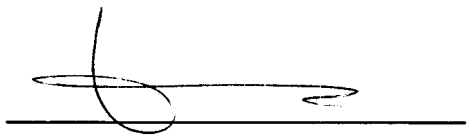
Sponsor : HOVON

EudraCT number : 2010-018494-37
Final protocol (version 01): 21 April 2010
Version 02 : 5 August 2010
Version 03 : 02 February 2011
Version 04 : 25 February 2011
Version 05 : 7 April 2011
Version 06 : 16 September 2011
Version 07 : 15 December 2011

PRINCIPAL INVESTIGATOR SIGNATURE PAGE



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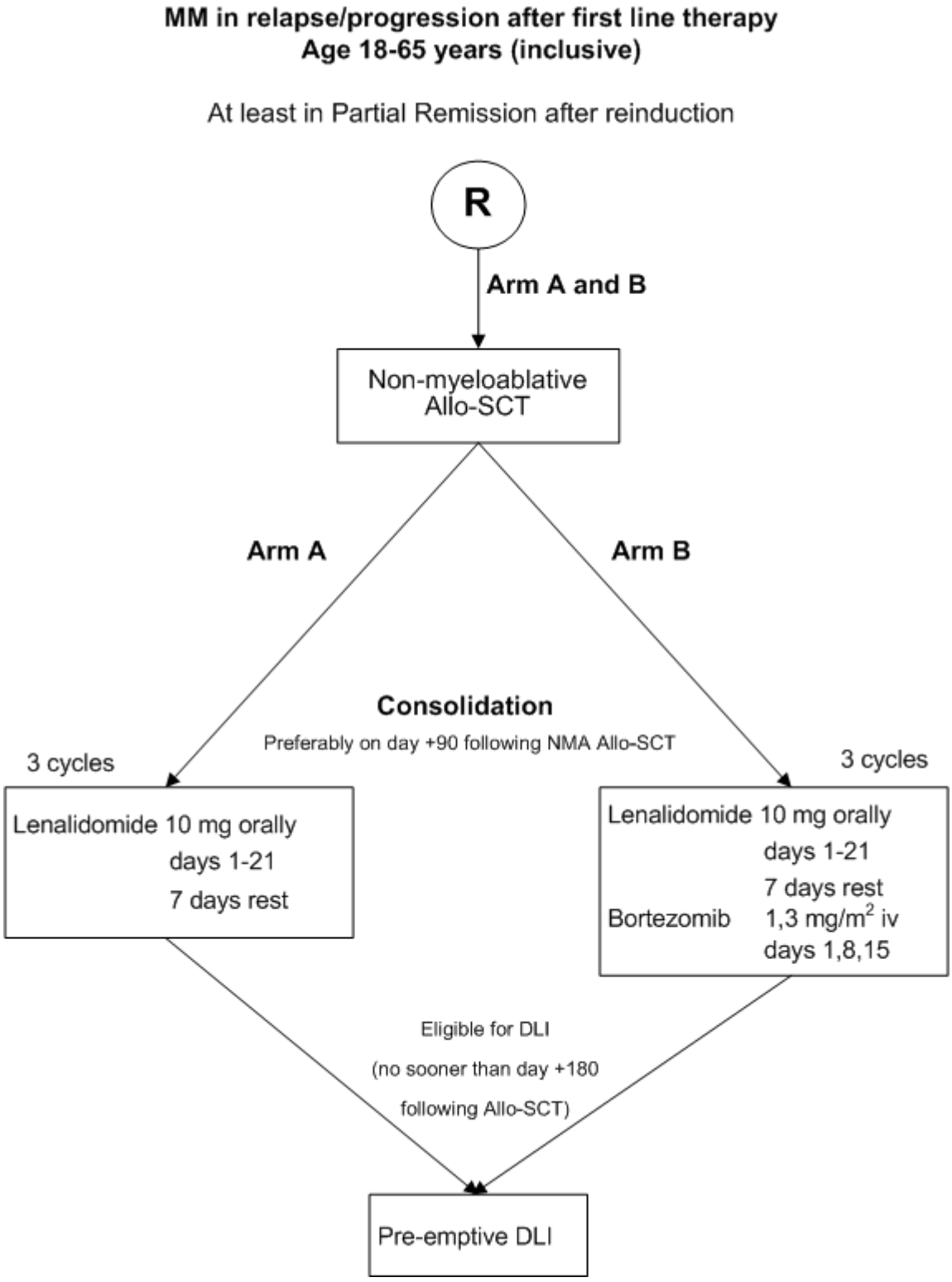
By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG),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

1 Scheme of study



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3 Synopsis

Rationale	Patients with multiple myeloma in first relapse or with progression after first line therapy may benefit from a non-myeloablative (NMA) allogeneic stem cell transplantation (Allo-SCT) followed by early consolidation with the novel anti-myeloma agents lenalidomide or lenalidomide combined with bortezomib and subsequent DLI (Donor Lymfocyte Infusion).
Study objectives	Primary objective: Assessment of feasibility and toxicity of T cell depleted NMA Allo-SCT followed by lenalidomide or lenalidomide combined with bortezomib, and subsequent DLI; as treatment of relapsed multiple myeloma. Secondary objectives: To investigate the efficacy of this regimen in terms of complete remission rate, overall and progression free survival. To evaluate quality of life with these regimens.
Study design	Randomized phase II trial
Patient population	Patients 18 - 65 years inclusive, with high risk multiple myeloma in relapse or progression following first line therapy and achieving at least PR after reinduction with an HLA-identical sibling or unrelated donor.
Intervention	T cell depleted NMA Allo-SCT followed by 3 cycles of lenalidomide 10 mg/daily or lenalidomide 10 mg/daily combined with weekly bortezomib 1.3 mg/m^2, and pre-emptive DLI. The conditioning of NMA Allo-SCT is performed with melphalan/fludarabine and in vitro and in vivo T cell depletion with Alemtuzumab in combination with ciclosporin.
Duration of treatment	9 months. Subsequently patients will be followed until 5 years after registration.
Target number of patients	110
Expected duration of accrual	4 years

Main study endpoints	Failure free duration, toxicity profile, progression free survival, overall survival and CR rate
Benefit and nature and extent of the burden and risks associated with participation	Patients with relapsed multiple myeloma have a limited life expectancy. Allo-SCT can induce prolonged remissions especially when this procedure is followed by early consolidation with novel anti-myeloma agents and subsequent pre-emptive DLI which may enhance the Graft versus Myeloma effect. The risks associated with this procedure are an estimated Treatment Related Mortality between 10-15 % associated with Allo-SCT, and reduced quality of life due to acute and chronic GvHD.
Planned interim analysis and DSMB	One interim analysis per treatment arm, when 9 failures (defined in par.13.1) in a treatment arm have been reported

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5 Introduction and rationale

5.1 Description of disease and current treatment

5.1.1 Allogeneic Stem Cell Transplantation

Allogeneic Stem Cell Transplantation (Allo-SCT) is probably the only treatment for multiple myeloma with a curative potential. This is likely due to the graft-versus-MM effect (GvM) which was proven by the achievement of sustained complete remissions by Donor Lymphocyte Infusions (DLI) without any other therapy in patients with a relapse after Allo-SCT (1-5). Clinical responses to DLI after myeloablative and non-myeloablative conditioning have been reported in up to 50% of patients, including 20% of patients with a Complete Remission (CR) (4-5). In several patients these CR's were durable for more than 10 years (9-10).
The role of Allo-SCT in multiple myeloma however is debated due to the high mortality and morbidity related with this procedure. Particularly myeloablative conditioning in MM has an unacceptable high Transplant Related Mortality (TRM) (6-12). Due to better selection of patients, improved surveillance and therapies for opportunistic infections and the use of Peripheral Blood Stem Cells (PBSC) instead of bone marrow stem cells, the European Bone marrow Transplantation (EBMT) reported a reduction in TRM from 46% to 30%. However survival at 3 years improved from 35% to 56% without a plateau in Progression Free Survival (PFS) and Overall survival (OS) curves (13).

5.1.2 Reduced Intensity Conditioning

Retrospective studies and phase 2 studies

The initial promising results of transplantations with Non Myeloablative Conditioning (NMA) has renewed the interest in Allo-SCT as a treatment option for multiple myeloma. Establishing donor lympho-hematopoises without the acute toxicity associated with ablative SCT could be a major advantage for a disease like multiple myeloma which affects older patients and may be sensitive to allo-reactivity as shown by DLI. The pioneering studies in multiple myeloma were performed by the Seattle group who showed that donor engraftment could be achieved with the combination of low dose TBI only (2Gy) and high dosed immune suppressive drugs ciclosporin and mycophenolic acid (MMF) (14). The Seattle group introduced the strategy of tandem autologous transplantation followed 2-4 months later by a RIC allograft. In 52 patients treated with this tandem modality a CR was achieved in 48 % of patients and progression free (PFS) and overall survival (OS) at 48 months were 48% and 69% respectively. However TRM was still 22% (14). A wide variety of conditioning regimens for MM have since then been pioneered and published, ranging from low-intensity schemes such as cyclophosphamide/fludarabine to fairly dose-intense regimens with moderately high dose melphalan.

In a recent review by the EBMT 26 different conditioning schemes with and without T cell depletion were identified for myeloma. No definite conclusions however could be drawn from these studies as most were retrospective evaluations of small number of patients which in many cases had been heavily pre-treated (15).

Prospective studies of NMA Allo-SCT as part of first line therapy

The definite value of NMA Allo-SCT for MM should be determined by prospective phase III studies with newly diagnosed patients that include a donor versus no donor comparison. Two such studies have been published. In the French IFM study patients with an HLA identical sibling donor and high risk MM defined by B2 microglobulin 3 mg/l and deletion of chromosome 13 were candidate for auto-SCT followed by Allo-SCT after NMA with busulfan, fludarabine and 5 days ATG. Patients without a sibling donor were treated with double autologous SCT. The intention to treat analysis showed no significant difference in EFS (25 months auto/allo versus 30 months double auto) and OS (35 auto/allo versus 41 months double auto). A major criticism on this study design was the use of high dose ATG included in the conditioning which results in profound in vivo T cell depletion. The beneficial effects of this in vivo T cell depletion are the low incidence of acute and chronic GvHD, the detrimental effect however is the elimination of the GvM effect (16).

A more positive result was published by Bruno et al. In this study 58 patients with an HLA identical sibling donor assigned to be treated with tandem auto/RIC (conditioning low dose TBI only) achieved higher CR (55 % versus 26%) and after a median follow-up of 45 months had significant prolonged EFS (35 versus 29 months) and OS (80 versus 54 months) as compared to the 59 patients assigned to be treated with double myeloablative auto-SCT. Criticisms on this study were the small number of patients and the relatively inferior outcome of the double autologous arm (17). Encouraging is that TRM of RIC in the upfront setting may be strongly reduced (IFM 10.9 %, Bruno et al: 11%). However it is clear that both studies cannot be compared due to differences in patient selection and conditioning regimens. A more definite conclusion about the role of RIC in MM may come from 2 other prospective donor versus no donor studies with larger groups of patients in both arms that were performed by Dutch Hovon (Hovon 50, 54 studies) and the EBMT. In the HOVON 50 study in which the effect of thalidomide as part of induction therapy before and as a maintenance following HDM 200 mg/m^2 was evaluated, patients with an HLA identical sibling donor could proceed to NMA Allo-SCT between 2 and 6 months after HDM. On the basis of an intention to treat analysis no differences in PFS and OS were found during an interim analysis that included 122 patients with a donor and 139 patients without a donor (18). *All data taken together indicate there is no definite proof that NMA Allo-SCT as part of first line therapy improves the outcome of multiple myeloma patients.*

NMA Allo-SCT as part of treatment for relapse, the UMCU experience

Thirty eight patients received an allogeneic stem transplantation from a sibling (n=20) or unrelated donor (n=18). A total of 27 patients (71%) were transplanted after their first relapse and 11 (29%)

after second or third relapse. 33 patients (87%) had received an Auto-SCT before. The patients received a median of two (range, two to four) treatment lines before Allo-SCT. *(Prognostic factors and outcome in relapsed multiple myeloma after nonmyeloablative Allo-SCT: a single center experience. MC Minnema et al. Bone Marrow Transplantation (2010), 1–6)*

At the time of Allo-SCT 3 patients were in CR, 11 in very good PR (VGPR), 23 in PR and 1 patient had progressive disease. After Allo-SCT, the remission status improved in 16 patients (42%) without the use of additional chemotherapy. In this group of 16 patients, 12 achieved a CR (7 from PR and 5 from VGPR) and 4 patients who were in PR before Allo-SCT achieved a VGPR. In eight patients (21%), including the patient who was progressive before Allo-SCT, but in none of the patients in CR, progression was detected within 6 months after Allo-SCT while using immunosuppressive therapy.

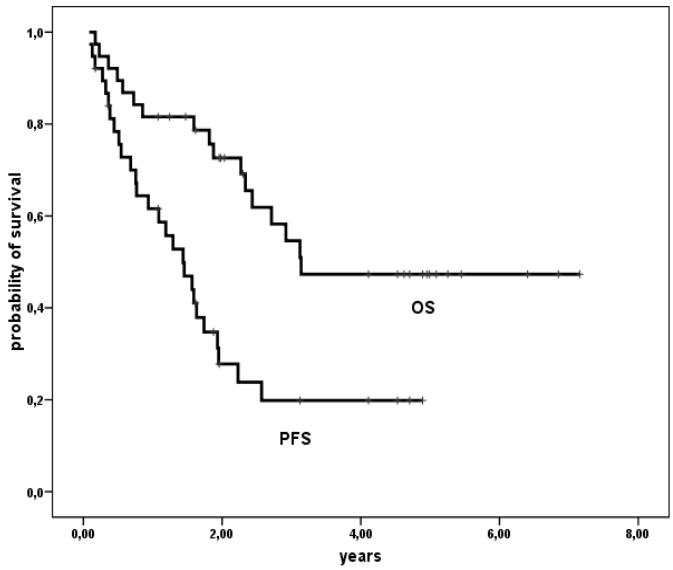

Figure 1: Overall (upper curve) and progression free survival (lower curve) of 38 patients with relapse myeloma treated with non-myeloablative Allo-SCT

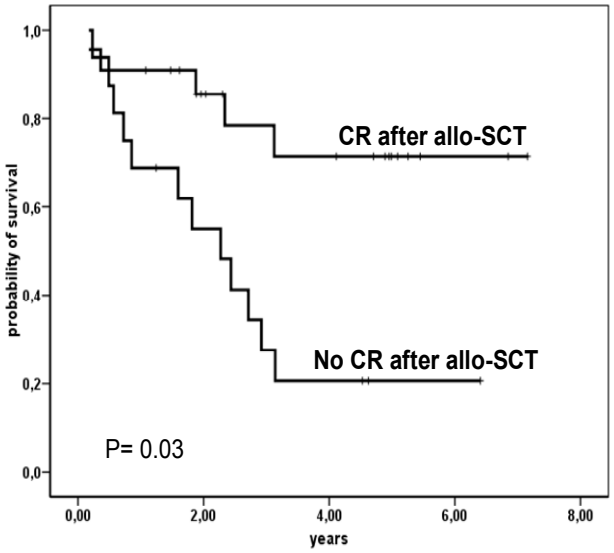

Figure 2: Survival of patients achieving CR (upper line) versus patients achieving PR after non-myeloablative Allo-SCT for relapsed myeloma

This study shows that prevention of early relapse in this setting is warranted and that patients who achieve a CR have an excellent prognosis. This may be achieved by early consolidation following the Allo-SCT and subsequent preventive donor lymphocyte infusions in patients not achieving a CR.

NMA Allo-SCT using alemtuzumab for T cell depletion, the Leiden University Medical Center experience

The use of T cell depletion in NMA Allo-SCT reduces TRM due to acute and chronic graft-versus-host-disease (GvHD). In vivo T cell depletion of the patient with horse anti-thymocyte globulin (ATG) in combination with in vitro T cell depletion of the graft using alemtuzumab (the so-called “Campath in the bag”) has been shown to be a very effective way of T cell depletion resulting in engraftment in almost all patients and hardly any GvHD after transplantation. Many patients become mixed chimeric after transplantation, requiring donor lymphocyte infusion (DLI) for conversion to full donor chimerism. Although after DLI acute and chronic GvHD is observed in 50–60% of patients, it is responsive to therapy in many patients, resulting in a low incidence of persisting chronic GvHD (Reference: von dem Borne PA, Starrenburg CW, Halkes SJ, Marijt WA, Fibbe WE, Falkenburg JH, Willemze R. Reduced-intensity conditioning allogeneic stem cell transplantation with donor T-cell depletion using alemtuzumab added to the graft ('Campath in the bag') Curr Opin Oncol. 2009; 21 Suppl 1:S27-9).
Due to the inavailablity of horse ATG from 2007, in vivo T cell depletion of the patient was switched from horse ATG to low dose alemtuzumab. Between 2007 and 2009, 29 patients were transplanted

with an unrelated donor, and 28 patients with a related donor using a fludarabine - busilvex regimen in combination with 30 mg alemtuzumab administered directly to the patient and 20 mg alemtuzumab administered in vitro to the graft. Patients were transplanted for various hematological diseases. No post-transplant immunosuppressive therapy was used. The median Gratwohl transplantation risk score was 3 in the related group (range 1-5), and 5 in the unrelated group (range 3-6).
All patients engrafted, two patients had secondary graft failure. In patients transplanted with a related donor, grade 1-2 and 3-4 acute GVHD was observed in 36% and 4% of evaluable patients, respectively, resolving in all patients. NRM was 0% at 3 months and 4% at 1 year. Overall survival was 100% at 3 months and 89% at 1 year. In patients transplanted with an unrelated donor more acute GVHD was observed (59% grade 1-2, 15% grade 3-4 of evaluable patients). 24% of evaluable patients developed chronic GVHD, which was limited in 75% and extensive in 25% of these patients. NRM was 7% at 3 months and 24% at 1 year. Overall survival was 93% at 3 months and 55% at 1 year.
This study shows that NMA SCT using low dose alemtuzumab in vivo combined with alemtuzumab-mediated in vitro T cell depletion of the graft is feasible. Results are excellent in patients transplanted with related donors with low NRM. Although results are good in patients transplanted with unrelated donors considering the high Gratwohl score in this group, too much grade 3-4 acute GvHD is observed in this group, warranting additional post-transplantation immunosuppressive therapy.

5.2 NMA Allo-SCT, DLI, Lenalidomide and Bortezomib

5.2.1 NMA Allo-SCT and DLI in myeloma

Allo-SCT is, as already described under 5.1.1, probably the only treatment for multiple myeloma with a curative potential due to the graft-versus-MM effect (GvM). One of the major drawbacks is the occurrence of GvHD which is responsible for excessive morbidity and mortality associated with this procedure. For this reason Allo-SCT as part of first line therapy is heavily debated since patients may live now for many years following first line therapy that includes the novel anti-myeloma agents. As the prognosis for patients with a relapse is poor, especially when they have been treated with novel agents, new strategies are necessary. One of these new strategies is Allo-SCT followed by immune therapy to boost the Graft versus Myeloma effect.
Profound T cell depletion as proposed in this study prevents GvHD and creates a platform for post Allo-SCT immune therapy with pre-emptive DLI (34-36). Clinical responses to DLI after myeloablative and non-myeloablative conditioning in the relapse setting have been reported in up to 50% of patients, including 20% of patients with a Complete Remission. (4-5, 9-10). The efficacy of DLI in a pre-emptive setting may even be higher as in this situation tumor load is lower than in the relapse setting. The risk of GvHD following DLI is reduced when a strategy is applied of starting with low dose

DLI followed by gradual dose escalating lymphocyte infusions as is proposed in this protocol. As profound T cell depletion is associated with increased risk of relapse, early consolidation after Allo-SCT is warranted as a bridge to pre-emptive DLI. For this consolidation novel anti-myeloma agents are used as described below.

Post transplant strategies to improve the graft versus multiple myeloma effect
A role for the novel anti-myeloma agents?

Lenalidomide is an immunomodulatory drug with potent stimulatory effects on host anti-tumor T and Natural Killer (NK) cell immunity and cytotoxicity. Lenalidomide is 50-2000 times more potent than its analog thalidomide. It increases the proliferation, secretion of IFN-γ by T-cells and enhances cytotoxic T cell and NK cell mediated killing of MM tumors (19-21). With these properties, lenalidomide is expected to have a significant impact on the GvM effect. On the other hand however, lenalidomide may also increase the risk for GvHD due to powerful immune stimulatory effects. Thus careful dose escalation studies and determining the proper schedule of administration after Allo-SCT are necessary to optimize the use of lenalidomide. In addition, lenalidomide may be combined with other agents that can downregulate GvHD without affecting the GvM effect. In fact, as explained below, one of these agents is bortezomib, and this is the main rationale why we aim at combining these two drugs.

Bortezomib is a proteasome inhibitor and blocks the activation of NF-κB, a highly important pathway for MM cell survival. Since proteasomes and NF-κB pathway are also important components of antigen processing and cell mediated cytokine responses, a number of studies explored the influence of bortezomib on the cellular immune system. Bortezomib inhibited in vitro alloreactive mixed lymphocyte responses but increased the T cell-dependent killing of the tumor cells (22). Consistently, in a murine BMT model, bortezomib downregulated cytokine production, induced T cell apoptosis and prevented GvHD, while the GvT effect was preserved (22). Nonetheless, delayed bortezomib administration appears to accelerate GvHD (23), underscoring the necessity for careful further studies toward the timing and schedule of administration. On the other hand, bortezomib can downregulate HLA class I on MM cells, while this is not the case for normal cells like B-cells, lymfocytes, monocytes, CD34 progenitor cells en dendritic cells (24). Thus, bortezomib sensitizes tumor cells toward NK-cell mediated lysis by down regulating MHC class I. Taken together, these results indicate that bortezomib may be highly beneficial in tempering the potential immune side effects of lenalidomide, in particular GvHD.

Clinical efficacy of thalidomide, lenalidomide and bortezomib in patients treated with NMA Allo-SCT.
In line with the experimental data, lenalidomide, its analog thalidomide and bortezomib are remarkably effective in patients with relapsed multiple myeloma after Allo-SCT. Kröger et al showed that thalidomide increased the response to DLI without stimulation of GvHD (25). Others

demonstrated that bortezomib may have the same effect (26). However, when given too soon after Allo-SCT, bortezomib may have severe toxicity, mainly neurotoxicity and infectious complications (26). Bortezomib treatment is associated with increased Herpes Zoster reactivation, suggesting an *in vivo* influence on T-cell function. Furthermore, when given after Allo-SCT it decreases $CD3^+$ cells, while B-cells remain stable (28). Others have used bortezomib for the treatment of chronic GvHD (29). The results of 63 patients who received a DLI in 8 transplant centers were recently analyzed. Survival after DLI was remarkably long, probably due to the fact that 15 (83.3%) of 18 patients not responding to DLI were sensitive to additional treatment with bortezomib and thalidomide. All 7 patients treated with bortezomib responded, including 2 patients with a very good partial response (VGPR). Six of 9 patients achieved a PR after treatment with thalidomide (100-300 mg daily), and 2 of 2 patients receiving both drugs achieved CRs that are still ongoing at 8 and 19 months. Two patients received bortezomib after treatment failure to thalidomide; one of these patients achieved CR. One patient received thalidomide after treatment failure to bortezomib and achieved PR. In 2 patients treated with thalidomide, a transitory flare up of GvHD was observed (30).

Clinical efficacy of lenalidomide in patients with relapse after NMA Allo-SCT.
In a group of 16 MM patients who relapsed after an Allo-SCT 13 patients (81%) responded to lenalidomide (30). 15 patients had received several other treatments for multiple relapses after Allo-SCT including thalidomide (given to 14 patients; 10 became refractory) and bortezomib (given to 11 patients; 7 became refractory). Eight patients were refractory to their last treatment line and 8 patients switched to lenalidomide as relapse treatment due to peripheral polyneuropathy.
This high response rate is remarkable for relapsed or refractory MM patients and may be due to the direct anti-tumor effects of these drugs. However, the clinical responses observed with lenalidomide alone were probably also accountable to its immunostimulatory effects. Supporting this idea, 5 out of 13 patients starting with lenalidomide alone developed acute GvHD between 2 -13 days after start of treatment, and the occurrence of acute GvHD was a good predictive factor for clinical response: 4 out of 5 GvHD patients developed a good response (the 5^{th} GvHD patient lived too short to determine the anti-tumor response) while there were only 3 patients responding to lenalidomide alone without developing GvHD.

Lenalidomide maintenance following tandem Auto SCT/NMA Allo-SCT: the HOVON 76 study.
In the HOVON 76 study Lenalidomide 10 mg daily maintenance therapy was started between 1 and 6 months after tandem Auto-Allo-SCT that was part of first line therapy of myeloma patients ≤ 65 years. A safety analysis performed on the first 28 patients included in the study showed that in more than 40% of patients only 1 cycle of lenalidomide could be given mainly due to the induction of acute GvHD ≥ grade 2. These data illustrate the strong immune modulating effects of Lenalidomide but also indicate lenalidomide is not feasible in the setting of full graft Allo-SCT .

Taken together, the clinical experience with lenalidomide and bortezomib demonstrates a potent immunostimulatory effect of lenalidomide on T cells *in vivo.* These effects are associated with an increased clinical response but can also result in enhanced acute GvHD especially, when lenalidomide is given soon after non manipulated Allo-SCT. T cell depleted NMA Allo-SCT and/or a combination therapy with bortezomib may temper the excess immunostimulatory effects of lenalidomide and separate the GvM effect from GvHD.

5.3 Rationale of the study

This study will explore the feasibility of T-cell depleted NMA Allo-SCT, followed by early consolidation with lenalidomide with or without bortezomib and subsequent DLI in relapsed myeloma patients. Patients with relapsed disease after first line therapy have a poor prognosis. This is illustrated by the median survival of only 19 months after relapse from thalidomide maintenance of patients who were included in the HOVON 50 study (32). T cell depleted NMA Allo-SCT will avoid the occurrence of acute and chronic GvHD and will make it possible to create a platform for subsequent immune therapy like pre-emptive donor lymphocyte infusion. Timely consolidation after T cell depletion however is necessary to avoid early relapse. As consolidation strategy we will use either the thalidomide analog lenalidomide (CC-5013) or lenalidomide combined with bortezomib: lenalidomide because this drug has a low toxicity profile, is highly effective against myeloma and has strong immune modulating effects and bortezomib once weekly because this may increase the efficacy of lenalidomide while on the other hand it may temper undesirable excessive immune stimulatory effects of lenalidomide and helps to separate the GvM effect from GvHD.
A low dose of lenalidomide, 10 mg, is chosen based on the efficacy and feasibility as maintenance following conventional and intensive treatment of multiple myeloma, and the expectation that prolonged administration of “full therapeutic” lenalidomide 25 mg daily may be associated with increased (non) hematological toxicity. In the HOVON 76 study 10 mg lenalidomide was not feasible after NMA Allo-SCT due to the induction of GvHD in many patients. This side effect however is not expected to occur after T cell depletion as proposed in the current study. The combination of low dose lenalidomide with once weekly bortezomib has proven to be feasible as shown by the early results of the HOVON 86 study in which this combination was tested in first relapsed patients.

6 Study objectives

Primary objectives

- To assess the feasibility and toxicity of T cell depleted NMA Allo-SCT followed by early consolidation with lenalidomide or lenalidomide combined with bortezomib, and subsequent DLI in patients aged 18-65 years with relapsed or progressive multiple myeloma after first-line therapy who are at least in PR after reinduction therapy.

Secondary objectives

- To assess the efficacy of early consolidation as determined by response and number of patients that receive subsequent DLI.
- To assess the overall efficacy of the regimen as determined by response rate (especially CR), progression free survival and overall survival.
- To evaluate quality of life in patients treated with allogeneic SCT followed by lenalidomide without or with bortezomib.

7 Study design

The trial is designed as a randomized phase II trial. The Allo-SCT will be performed after conditioning with melphalan/fludarabine. In vitro T-cell depletion of the stem cell graft will be done with Alemtuzumab and ciclosporin is given as additional Graft versus Host prophylaxis.
All eligible patients will be randomized up front between early consolidation after T cell depleted Allo-SCT with 3 cycles of lenalidomide 10 mg daily for 21 days followed by 1 week rest or early consolidation after T cell depleted Allo-SCT with 3 cycles of lenalidomide 10 mg daily for 21 days combined with weekly bortezomib 1.3 mg/m^2 on day 1, 8, 15 of each lenalidomide cycle. Following completion of 3 courses of consolidation therapy (≥ 14 days after the last administration of lenalidomide / bortezomib) the patients will receive subsequent DLI (of the same donor that has given stem cells for Allo-SCT).
A total of 55 patients will be included in each arm.
One interim analysis per treatment arm will be performed when 9 failures (defined in par. 13.1) in a treatment arm have been reported.
This may lead to closure of one arm or both arms of the study.

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

8 Study population

8.1 Eligibility for registration/randomization

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

8.1.1 Inclusion criteria

- Patients with multiple myeloma with a first relapse or progression after first line therapy;
- Relapsed or progressive patients have received reinduction therapy before entering this trial;
- At least a PR after reinduction treatment;
- 18-65 years,inclusive;
- HLA-identical sibling or unrelated donor completely matched (10/10) (excluding identical twins);
- WHO-performance status 0-2;
- Written informed consent.

8.1.2 Exclusion criteria

- Previous Allo-SCT;
- Severe pulmonary dysfunction (CTCAE grade III-IV, see appendix D);
- Severe neurological or psychiatric disease;
- Patients with neuropathy, CTC grade 3 or higher;
- Significant hepatic dysfunction (serum bilirubin or transaminases ≥ 3 times upper limit of normal);
- Significant renal dysfunction (creatinine clearance < 30 ml/min after rehydration);
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.);
- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or or carcinoma “in situ” of the cervix or breast;
- Patient known to be HIV-positive;
- 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;

- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, lenalidomide or borium;
- Pregnant or breast-feeding female patients. Negative pregnancy test at study is mandatory for female patients of childbearing potential;
- Not able and not willing to use adequate contraception during therapy;
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E).

9 Treatment

9.1 Treatment schedule

9.1.1 NMA Allo-SCT

Stem cell collection:

Donors will be treated with rhu G-CSF, at a dose of 10 microgram/kg/day subcutaneously divided in 2 doses for 5 days. Leukapheresis will be undertaken at day 5. The aimed cell number is between 5-10 x 10^6 CD34+ cells/kg.

The allogeneic transplantation is performed after conditioning with Melphalan/Fludarabine.

Agent	**Dose/day**	**Route of administration**	**Days**
fludarabine	50 mg/m^2	orally	-9 to -4
melphalan	100 mg/m^2	Intravenously	-3
Alemtuzumab Prednison	15 mg 2 mg/kg	Intravenously Iv or orally	-3, -2 -3,-2,-1,0
alemtuzumab	20 mg	"In the bag"	day 0
Stem cell infusion			day 0
Ciclosporin	3.5 mg/kg 2dd *Blood levels 0.20-0.30* mg/l	orally	day -3 to +90, taper to zero starting at day + 90 or, in case of experienced GvHD, starting at day +150 In patienst with sibling donors who experienced no GvHD tapering may start at day +60

T cell depletion of the blood stem cell graft

T-cell depletion of the blood stem cell graft will be performed by an in-vitro incubation of the cells with 20 mg alemtuzumab for 30 minutes at 20º C. Following in vitro incubation, the stem cell graft will be infused into the patient without further manipulation.

Additional Graft versus Host prophylaxis

All patients will receive additional GvHD prophylaxis consisting of ciclosporin-A, 3.5 mg/kg twice daily orally from day -3 until day +90. Ciclosporin blood levels should be maintained between 0.20 and 0.30 mg/l. In the absence of GvHD Ciclosporin is rapidly tapered to zero in 4 weeks starting at day +90. In patients with sibling donors rapid tapering may start at day + 60 when no GvHD has occured in the post Allo period In patients that experienced GvHD ciclosporin is tapered to zero in 8 weeks (starting at day +150).

Chimerism status

Chimerism in peripheral blood cells (T-nonT) will be determined at day +28, +56, before start of consolidation, at the end of consolidation therapy (2-3 weeks before the planned donor lymphocyte infusion so that chimerism status is reported before the infusion) and 90 days after donor lymphocyte infusion. .

9.1.2 Lenalidomide or lenalidomide + bortezomib consolidation

Eligibility for lenalidomide or lenalidomide + bortezomib consolidation

Inclusion criteria for lenalidomide +/- bortezomib consolidation

- Laboratory test results within these ranges:
  - Absolute neutrophil count $\geq$ 1.0 x 10^9/L[1]
  - Platelet count $\geq$ 75 x 10^9/L
  - Serum creatinine cleareance ≥ 30 ml/min
  - Total bilirubin $\leq$ 30 µmol/l
  - AST (SGOT) and ALT (SGPT) $\leq$ 3 x Upper Limit of Normal (ULN);
- Negative pregnancy test if female of child bearing potential;
- Patient is willing and able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;

Prior use of and resistance to lenalidomide and or bortezomib is allowed.

[1.] Consider pre-treatment with G-CSF in case of absolute neutrophil count ≤ 1.0x10^9/L

Exclusion criteria for lenalidomide +/- bortezomib consolidation

- Acute Graft versus host Disease ≥ grade 2;

- Extensive chronic GvHD;
- 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;
- Patients with neuropathy, CTC grade 3 or higher;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E).

9.1.2.1 Arm A: Lenalidomide

Lenalidomide treatment will start preferably at day +90 following Allo-SCT, unless hematological repopulation following NMA Allo-SCT is delayed or other inclusion criteria as defined in section 9.1.2, are not met. There is no maximal time interval after Allo-SCT.

Patients will continue lenalidomide treatment for a maximum of 3 courses unless relapse occurs. 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 9.2).

Agent	**Dose/day**	**Route**	**To start at day ≥ + 90 after Allo-SCT**
Lenalidomide	10 mg	Orally	Day 1-21 followed by 7 days rest for a total of 3 cycles

9.1.2.2 Arm B Lenalidomide combined with bortezomib

Lenalidomide treatment will start preferably at day +90 following Allo-SCT unless hematological repopulation following NMA Allo-SCT is delayed or other inclusion criteria as defined in chapter 9.1.2 are not met. There is no maximal time interval.

Treatment will be performed as described for the patients randomized to Arm A. In addition Bortezomib 1.3 mg/m^2 i.v. will be administered once weekly, on day 1, 8 and 15 of each lenalidomide cycle. Subjects experiencing adverse events may need study treatment modifications (see section 9.2).

Agent	Dose/day	Route	To start at day ≥ + 90 after Allo-SCT
Lenalidomide	10 mg	orally	Day 1-21 followed by 7 days rest for a total of 3 cycles
Bortezomib	1.3 mg/m^2	i.v.	Day 1,8,15 of each lenalidomide cycle for a total of three cycles.

9.1.3 Donor Lymfocyte Infusions (DLI)

Inclusion criteria for DLI:

- presence of residual myeloma (any disease state less than stringent CR) and/or persistent patient chimerism defined as less than 95% donor peripheral blood cells or according lo local protocols.

Exclusion criteria for DLI:

- acute GvHD or chronic GvHD requiring the use of systemic immunosupressive drugs;
- unavailability of the donor for donation of peripheral blood for DLI in case no donor cryopreserved PBMC are available;
- rapidly progressive disease requiring systemic anti-myeloma therapy other than the consolidation therapy with lenalidomide or bortezomib-lenalidomide.

9.1.3.1 Pre-emptive DLI

Pre-emptive DLI will be given following completion of 3 courses of consolidation therapy (≥ 14 days after last gift of lenalidomide / bortezomib). If the consolidation therapy was interrupted and discontinued permanently before 3 full courses were given, DLI should not be given before day +180 following Allo-SCT. For DLI using fresh PBMC, infusion will take place in the afternoon of the day of the PBMC collection.
Pre-emptive DLI will consist of $3x10^6$ T cells/kg from sibling and $1.5x10^6$ T cells/kg from unrelated donors. Infusions of cryopreserved PBMC will be performed as per standard practice for infusions of cryopreserved PBSC, taking into account a loss of T cells of 50% by the freezing and thawing of the product or alternatively based on the percentage of viable T cells after thawing.
After one pre-emptive DLI patients go off protocol treatment.

9.1.3.2 Patients with progressive disease

Patients with asymptomatic signs of progression i.e a slow increase in M-protein before DLI are not considered as failures and the response to consolidation and DLI can be awaited. Only patients with symptomatic myeloma based on CRAB criteria and/or very rapid increase in M-protein are considered as failures (secundary endpoint) because they may benefit from salvage therapy other than the consolidation therapy.

9.2 Dose adjustments

9.2.1 Dose adjustments in NMA Allo-SCT

Ciclosporin toxicity should be monitored by frequent checking of liver and renal function tests and optimal ciclosporin dosing should be maintained by testing ciclosporin blood levels regularly.

9.2.2 Dose adjustments of lenalidomide with or without bortezomib

When GvHD grade 2 occurs, lenalidomide and bortezomib should be interrupted. If toxicity resolves to ≤ grade 1 within 2 months, restart lenalidomide and bortezomib at next cycle (decrease dose of lenalidomide by one dose level)(for treatment of GvHD refer to section G).
The onset of GvHD grade 3 must lead to discontinuation of lenalidomide and bortezomib permanently and withdrawal from the protocol. (for treatment of GvHD refer to section 9.3.4).

Also the onset of extensive chronic GvHD with the exception of GvHD limited to the oral cavity, leads to discontinuation of lenalidomide and bortezomib permanently and withdrawal from protocol.

Lenalidomide and bortezomib treatment may cause bone marrow suppression. Lenalidomide increases the risk of venous trombosis and patients should be closely watched for bortezomib induced polyneuropathy and adequate dose reductions for both drugs should be performed as described below and in appendix F below.
For grade 3 neutropenia it is advised to support the next treatment cycle with neulasta 6 mg at day 1 while maintaining the same dose level.

Dose levels for lenalidomide

Dose Levels	**Lenalidomide**
Starting Dose	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5 mg once daily on days 1-21 every 28 days
Dose Level -2	no lenalidomide

Dose modification Instructions for lenalidomide for hematologic toxicity*

Toxicity	Lenalidomide Dose Modification
Grade 4 Neutropenia (Neutrophil < 0.5 x 10^9 /L) Febrile neutropenia (fever ≥ 38.5 °C and ANC < 1 x 10^9 /L)	Stop the dose for remainder of cycle. Decrease by 1 dose level when lenalidomide is restarted at next cycle. (at start of a new couse the criteria given below must have been met)
Grade 4 Thrombocytopenia (Platelets < 25 x 10^9 /L)	Stop the dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle. (at start of a new cycle the criteria given below must have been met)

* Exclude other causes, especially progressive disease.

Dose modification instructions for lenalidomide for non-hematologic toxicity

Toxicity	Dose modification lenalidomide
Rash = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when lenalidomide is restarted at next cycle (rash must resolve to ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue lenalidomide and withdraw subject from study
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when lenalidomide is restarted at next cycle (Constipation must resolve to ≤ Grade 2).
Thrombosis/embolism ≥ Grade 3	Hold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when lenalidomide is restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when lenalidomide is restarted at next cycle at discretion of treating physician.
Any other grade 3 toxicity that is related to lenalidomide	Discontinue lenalidomide and consult the PI for subsequent measurements and dose reductions.

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 is ≥ 75 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 consolidation treatment has to be discontinued.
If neutropenia is the only dose limiting toxicity, G-CSF (neulasta 6 mg day 1), is added and lenalidomide dose level and time schedule may be maintained.

Special dose reduction of lenalidomide + bortezomib therapy
Lenalidomide dose reductions and dose reductions and prescription of hematopoietic growth factors are recommended as described under 9.2.2.
Before each Bortezomib dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). All previously established or new toxicities observed any time, *with the exception of neuropathic pain and peripheral sensory neuropathy for which separate guidelines are defined in Appendix F*, are to be managed as follows:

Bortezomib doses should be withheld if the following events occur and are thought to be related to Bortezomib:

- febrile neutropenia;
- grade 4 hematological toxicity, with the exception of anemia;
- grade ≥ 3 non-hematological toxicity

Febrile neutropenia
Bortezomib should be withheld until resolution of this condition, according to the judgement of the threating physician.

Hematological toxicities
For grade 4 hematological toxicities, with the exception of anemia, the Bortezomib and lenalidomide should be stopped for the remainder of the cycle and should be withheld for at least 2 weeks, to start with the next cycle, when the following values are reached: ANC ≧ 1 x 10^9/l, **and** platelet count ≥ 75 x 10^9/l.
Dose interruption or treatment discontinuation is not required for lymphopenia or anemia of any grade.

Non-hematological toxicities
For any grade ≥ 3 non-hematological toxicities, Bortezomib is to be withheld for up to 2 weeks until the toxicity returns to at least grade 2.
If the toxicity does not resolve after dosing has been withheld for two weeks, then the patient must be discontinued from consolidation treatment.

Dose adjustments of Bortezomib in case of toxicities (grade 4 hematological and grade 3 non-hematological)

If withholding the Bortezomib dosing results in resolution of the toxicity, the dose may be reduced by 25%, as follows:

- Dose level -1: If the patient was receiving 1.3 mg/m^2, reduce the dose to 1.0 mg/m^2.
- Dose level -2: If the patient was receiving 1.0 mg/m^2, reduce the dose to 0.7 mg/m^2.
- Dose level -3: If the patient was receiving 0.7 mg/m^2, then the Bortezomib must be discontinued.

Neuropathic pain and/or peripheral sensory neuropathy

Patients who experience Bortezomib related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in the table in Appendix F.

According to that scheme, for example, if a patient had peripheral sensory neuropathy with objective sensory loss or paresthesia that interfered with function but not ADLs (grade 2) and mild neuropathic pain not interfering with function (grade 1), then the Bortezomib dose is to be reduced as described above.

Once patients have been changed from full schedule to an attenuated schedule of bortezomib, this should be used during the further consolidation treatment.

9.2.3 Additional measurements following DLI.

No GvHD prophylaxis is given following DLI and no specific anti-myeloma therapy in the absence of GvHD and progression of myeloma.

9.3 Special precautions and use of co-intervention

9.3.1 Special precautions for NMA Allo-SCT

Conditioning with fludarabine and Melphalan, combined with alemtuzumab may induce severe bone marrow suppression and humoral and cellular immunodeficiency. This may lead to mucositis in the early post transplant period (< 3 weeks) and increased susceptibility for bacterial, opportunistic infections and reactivations of viral infections. Patients should be closely watched including frequent monitoring of CMV and EBV status by PCR.

9.3.2 Infection prophylaxis

Patients will receive prophylaxis for PCP, HSV and candida according to local protocols.

Standard CMV prophylaxis and monitoring should commence at the time of transplant and should continue until at least 90 days post-DLI (last dose given). CMV practice should be as for regular allografts. Patients who do not engraft can discontinue this infection prophylaxis at 3 months post-transplant.
Standard toxoplasmosis prophylaxis should be started at the time of hematological reconstitution after transplantation and should be continued until day +60.

9.3.3 Therapy of post transplant lymfoproliferative disease (PTLD)

Rituximab 375mg/m^2 will be given for EBV copy numbers in peripheral blood of >1000 geqs/ml. Repeat if EBV copies are higher than 50% of starting level after 72 hrs.
For treatment of rituximab refractory PTLD DLI with $1x10^5$ T cells/kg will be infused in the absence of the exclusion criteria as defined above.

9.3.4 Staging and handling of Graft versus Host Disease

Acute and chronic GvHD will be staged according to the criteria described in appendix G.

When GvHD grade 2 occurs during consolidation treatment, lenalidomide and bortezomib should be interrupted (for further information on dose adjustments in case of GvHD refer to section 9.2).

The onset of GvHD grade 3 must lead to discontinuation of lenalidomide and bortezomib permanently and the patient is withdrawn from protocol.

Also in case of extensive chronic GvHD (with the exception of GvHD limited to the oral cavity) the patient is withdrawn from protocol treatment.

Treatment of Acute GvHD grade ≥2

- Prednisone 2 mg/kg p.o. should be given for 2 weeks and then tapered over 6 weeks.
- In case of insufficient response Ciclosporin A 4.5 mg/kg p.o. twice daily may be added if patient is not already on ciclosporin. If there is concern of GI absorption use IV route (1.5 mg/kg twice daily),. Optimise CSP levels if patient is already on CSP.
- Prednisone (2 mg/kg) to be added if severe and progressive GvHD and no GvHD response to CSP by 72 hours, or at 1 week with less severe GvHD and no GvHD response to CSP. Prednisone should be given at 2 mg/kg for 2 weeks and then tapered over 6 weeks.
- Steroid refractory GvHD is treated according to local guidelines.

Treatment of extensive chronic GvHD

Ciclosporin A daily and prednisone (1mg/day) is given under prophylaxis against pneumocystis, pneumococci infection and toxoplasmosis (e.g. cotrimoxazol for toxoplasmosis).

9.3.5 Special precautions for consolidation treatment with lenalidomide without or with bortezomib

It should be considered that the proposed treatment of lenalidomide with or without bortezomib 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 occurs in >50% of patients.)

Special precautions during treatment with lenalidomide

Lenalidomide might be teratogenic. In order to prevent pregnancies during the use of lenalidomide, both patient information, patient registration and patient counseling will occur as defined in the Lenalidomide Pregnancy Prevention Risk Management Plan.

Special management in conjunction with Bortezomib therapy

Patients may be treated on an outpatient basis. The appropriate amount of Bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration. The patient should be considered clinically stable by their physician before discharge.

Before each Bortezomib dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). All previously established or new toxicities observed, *with the exception of neuropathic pain and peripheral sensory neuropathy for which separate guidelines are defined in Appendix F*, are to be managed as described in section 9.2.2.

9.3.6 Special precautions for donor lymphocyte infusion

As with NMA Allo-SCT Donor lymphocyte infusion 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 an important toxicity associated with infusion of donor PBSC. It occurs in 30-50% of patients. When late onset acute GvHD > grade 1 or chronic GvHD occurs standard treatment should be started.

No GvHD prophylaxis is given following DLI and no specific anti-myeloma therapy in the absence of GvHD and progression of myeloma.

9.3.7 Prohibited concomitant therapy

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

9.4 Investigational Medicinal Products

9.4.1 Summary of known and potential risks

Bortezomib

Most common side effects of Bortezomib (ie, incidence ≥ 30%) observed in patients are weakness, fatigue, and general discomfort; gastrointestinal (GI) effects such as constipation, diarrhea, nausea, vomiting and anorexia, which may result in dehydration and/or weight loss; fever; peripheral neuropathy (including painful sensations or numbness and tingling in hands and feet that may not get better after discontinuation of bortezomib); thrombocytopenia that may increase the risk of bleeding, and anemia.

Very common side effects of Bortezomib (ie, incidence 10–29%) observed in patients are neutropenia that may increase the risk of infection; abdominal pain; dyspepsia; nasopharyngitis; arthralgias; myalgias; skin rash that can be erythematous, pruritic and display leukocytoclastic vasculitis at biopsy; rigors; hypotension; dizziness; fluid retention; pain in limbs and bones; paresthesia; dysesthesia; dyspnea; cough; epistaxis; headache; blurred vision; changed sense of taste; insomnia; anxiety; herpes zoster, and lower respiratory/lung infections including pneumonia.

Common side effects of Bortezomib (ie, incidence 1–9%) observed in patients are lymphopenia; pancytopenia; palpitations; tachycardia; atrial fibrillation; angina pectoris; acute onset of congestive heart failure including pulmonary edema (patients with risk factors for, or existing, heart disease should be closely monitored); pleural effusion; tinnitus; conjunctivitis; abdominal distension; oral and esophageal mucositis; oral candidiasis; upper and lower GI bleeding; bronchitis; sinusitis; urinary tract infection; gastroenteritis; sepsis; hyponatremia; hyperglycemia; hypoglycemia (Patients on oral antidiabetic agents may require close monitoring of their blood sugar levels.); dehydration; orthostatic hypotension; syncope; convulsions; renal failure; hematuria; depression; confusion; increases in serum AST, ALT, GGT and alkaline phosphatase.

Further details on the potential risks of Bortezomib may be found in the Summary of Product Characteristics (SPC).

9.4.2 Preparation and labeling

Bortezomib will be used with commercial labeling and packaging.

9.4.3 Storage and handling

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

9.4.4 Study drug supply

The investigator should use commercially available bortezomib. Bortezomib is to be supplied via the hospital pharmacy.

9.4.5 Drug accountability

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

10 Study procedures

10.1 Time of clinical evaluations

- At entry: within three weeks before Allo-SCT
- Within 2 weeks before first day of first consolidation cycle with lenalidomide and/or bortezomib
- During each cycle of lenalidomide and/or bortezomib
- Within two weeks before DLI and monthly after DLI
- During follow up every two months. All patients will be followed until 5 years after registration.

10.2 Required investigations

Overview of required minimum clinical and laboratory evaluations at entry, during treatment and during follow up

Procedure	**At entry**	**≤ 14 days from first day cycle 1**	**Cycles 1, 2 and 3**			**Before and after DLI**	**Discontinua-tion From Study Drug**	**Follow-Up until 5 years after registration**
			Day 1	Day 8, 15	Day 22			**Every 2 months**
Medical history	X	X	X[2]			X	X	X
Physical examination	X	X	X[2]	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X		X	X	
Immune status	X[4]		X[4]			X[4]		
Immunochemistry[6]	X	X	X[2,6]			X[6]	X	X[6]
Bone marrow aspirate and biopsy[7]	X[1]						X[7]	X[7]
Chimerism[3]		X[3]	X[3]			X	X	
Specific investigations								
ECG	X[1]						X	
Chest X-ray	X[1]						X	
Skeletal Survey	X[1]						X	X[7]
Grading of GvHD		X	X			X	X	X
Pregnancy test	X	X	X[5]			X[5]	X[5]	
Record adverse events/baseline concomitant diseases	X	X	X			X	X	X
Record concomitant therapies/procedures			X			X	X	X
Obtain Follow-Up anti-cancer treatments								X
Obtain Follow-Up survival information								X
Quality of life	X			X[8]	X[8]		X[8]	X[8]

[1] only if not yet performed after autologous and before 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 standard laboratory investigations.

[2] not at cycle 1

[3] chimerism of peripheral blood cells will be determined at day 28 +, 56+, < 14 days before consolidation and on additional time points when indicated according to local protocol.

[4] the collection of material for evaluation of immune status should be done pre-allo-SCT (before the start of the conditioning!), at the start of each Lenalidomide/Bortezomib cycle and at the start of DLI. See 10.4 side study

[5] before start of and during Lenalidomide treatment according to the Pregnancy Prevention Risk Management Plan

[6] immunochemistry every month from cycle one until month 12 and every 2 months until the end of follow-up of 5 years

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

[8] Quality of life at admission prior to the initiation of the conditioning regimen, at 3, 6 and 9 months after Allo-SCT and at off protocol.

Medical history

Standard medical history, with special attention for:

- WHO performance status
- Bone pain
- Infections
- Bleeding tendency
- Obstipation
- Polyneuropathy

Only at entry:

- Occupational history
- Prior and present other diseases
- Antecedent hematological or oncological diseases, including non-melanoma skin cancer
- Previous chemotherapy or radiotherapy
- Ethnicity

Physical examination

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

- Macroglossia
- Kyphoscoliosis
- Orthostatic hypotension
- Carpal tunnel syndrome
- Polyneuropathy or other neurologic symptoms
- Edema

- Infections
- Bleeding tendency

Hematology

- Hemoglobin
- Leukocyte count, differential count
- Platelets

Blood chemistry

- Creatinin
- Liver enzymes
- Total bilirubin
- Alkaline phosphatase
- Total proteins
- Albumin
- LDH
- CRP
- Calcium
- Phosphate
- Uric acid

Immune status

Sampling for the side study of immunological status and immune effects of lenalidomide+/-bortezomib translational research is described in appendix H (only applicable if patient gave informed consent).

Immunochemistry

- Quantitative serum immune-electropheresis and immunofixation for identification and quantification of M-protein
- Quantitative serum light chain (FLC, Free Lite)
- Quantitative urine light chain in 24 hrs urine, including immunofixation to confirm CR
- Serum β_2-microglobulin

Bone marrow

- Bone marrow biopsy
- Bone marrow aspirate at entry for:
  - Morphology, immunophenotyping
- Bone marrow aspirate during treatment and follow up for:
  - Morphology
  - Immunophenotyping

Chimerism

Chimerism of peripheral T and non-T cells will be determined at day 28 +, 56+, < 14 days before consolidation and on additional time points when indicated according to local protocols.

Specific investigations

- Creatinin clearance if increased serum creatinin
- ECG
- X-Thorax
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones
- Alternatively whole body CT scan may be performed
- MRI if patient experiences pain without specific abnormalities on X-Ray
- Cardiac ejection by scintigraphy or cardiac echo; it is advised to perform a Left Ventricular Ejection Fraction (LVEF) in all patients at entry. In addition it is recommended to repeat the LVEF after stem cell collection, as part of the pre-transplantation screening prior to HDM.
- Grading of GvHD
  Acute and chronic Graft versus Host Disease will be scored according to the criteria defined in appendix G.
- Pregnancy test
  With regards to pregnancy testing and lenalidomide treatment, the risk management program of lenalidomide is to be followed.
- Query for Concomitant Therapies
  From the concomitant therapies given the immunomodulating therapies that may be required to treat GvHD will be queried.

Additional investigations

Only on clinical indication

10.3 Response evaluation

Response will be evaluated according to the IMWG criteria (32) (see appendix B). Response will be evaluated in relation to the status before start Allo-SCT.
Complete staging will be done before start of Allo-SCT, before start cycle 1, after cycle 3 of lenalidomide +/- bortezomib, 3 months after the DLI cycle, when the patient goes off protocol and in case of suspected relapse. Bone marrow evaluation will be performed to confirm CR (immunofixation is required) and in case relapse is suspected which cannot be confirmed by the standard laboratory investigations.

10.3.1 Evaluation of patients eligible for lenalidomide +/- bortezomib cycles

Time points of response evaluation are day 1 of each new lenalidomide cycle +/- bortezomib cycle (= every 4 weeks) during cycles 1, 2 and 3, 6 weeks after start of the last cycle, when patients go off protocol and in case of suspected relapse.

10.3.2 Evaluation of patients not eligible for lenalidomide +/- bortezomib consolidation.

All patients will be followed until 5 years after registration.

10.3.3 Cytogenetic review

Central review will be performed only for those patients not registered before in a HOVON study with cytogenetic review for MM. A filled out (Cyto)Genetic Analysis Form together with 2 representative karyotypes and a copy of the original cytogenetic report should be sent to the HOVON Data Center for central review.
If additional FISH analysis was performed, these are to be filled out on the (Cyto)Genetic Analysis Form also and, together with a copy of the original FISH report, it is requested to be sent with the cytogenetic data for central review. FISH analysis will be performed for chromosome 13q deletions, the presence of 14q32 abnormalities (t(4;14)(p16;q32) and t(14;16)(q32;q23)) and deletion of p53 (17p13). Conditions for FISH will be standardized by the HOVON Cytogenetic Working Party. In case FISH analysis has not been performed at entry, it will be performed either on cryopreserved buffy coat bone marrow or bone marrow slides.

10.4 Side study

Immunological status and imuune effects of lenalidomide+/- bortezomib
Apart from routine laboratory investigations, the immune-status of the patients and modulation after lenalidomide or lenalidomide combined with bortezomib will be evaluated by phenotypic and

functional analysis of peripheral blood that will be obtained from recipients **pre-allo-SCT (before the start of the conditioning!), at the start of each Lenalidomide / Bortezomib cycle and at the start of DLI**. For this 40 ml Natrium-heparin blood samples (cells and plasma) should be gathered at each timepoint, prepared and frozen immediately after collection at a temperature of -70˚C (please record date of obtaining the sample).
From the obtained blood samples, plasma and PBMC will be isolated and cryopreseved to execute the immunological monitoring as described under appendix H.
Questions on sampling for immunological status can be directed to M. Minnema or H. Lokhorst (tel. 088 755 8380 or 088 755 9771).

10.5 Quality of life assessment:

Quality of life (QoL) will be assessed by means of the following questionnaires:

- EORTC QLQ-C30 questionnaire: The QLQ-C30 is a multidimensional, cancer-specific quality-of-life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) Study Group on Quality of Life for use in international clinical trial settings. The questionnaire is designed for use with a wide range of cancer patient populations, irrespective of specific diagnosis. The QLQ-C30 includes 5 functional scales (physical, role, emotional, social and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale and a number of single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation and diarrhea) and perceived financial impact. For the majority of the QLQ-C30 items a 4-point Likert-type response scale is used. Exceptions are the items for the global quality of life scale (where a 7-point scale is used). All subscale and individual item responses are linearly converted to 0 to 100 scales. For the functional and global quality of life scales, a higher score represents a better level of functioning. For the symptom scales and items, a higher score reflects a greater degree of symptomatology.
- EORTC QLQ-MY20: This questionnaire measures specific aspects of multiple myeloma, i.e. specific pain complaints.

Collection of the QoL questionnaires will be performed in the following manner:
A QoL coordinator will be assigned in each participating center. This QoL coordinator will be responsible for collection of the QoL questionnaire. He/she will be informed about the trial and will receive questionnaires to hand out to each patient at baseline.
During informed consent the patient will be asked to participate in the quality of life part of this study. As soon as a patient is randomized at the HOVON Data Center (HDC), the QoL coordinator is notified

by e-mail. Patient subject number, date of birth, date of randomization are mentioned in this e-mail. The baseline questionnaire will be handed over to the patient by the QoL coordinator/local investigator. Patients are asked to fill out the questionnaire immediately and return it directly to the QoL coordinator, who will send it to HOVON Data Center.
The coordinator will be reminded in time by e-mail to hand over a questionnaire at the correct date. If a QoL questionnaire has not been received by HOVON Data Center within 14 days of the expected date, a reminder/request will be sent to the local QoL coordinator to collect and send in the questionnaire.
If the baseline questionnaire is not received at HOVON Data Center the patient wil not be eligible to continue in the quality of life part of the trial.

Quality of life will be measured:
- at admission prior to the initiation of the conditioning regimen
- at 3, 6 and 9 months after Allo-SCT
- at off protocol treatment

11 Withdrawal of patients or premature termination of the study

11.1 Specific criteria for withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons. Specific criteria for withdrawal are:

- Death
- Excessive toxicity
- Acute GvHD ≥ grade III
- Extensive chronic GvHD with the exception of extensive chronic GvHD limited to the oral cavity
- Progression/relapse during treatment requiring systemic therapy for uncontrolled myeloma other than the assigned study treatment of lenalidomide or lenalidomide/bortezomib and DLI
- No compliance of the patient (especially refusal to continue treatment)
- Not eligible for pre-emptive DLI between 6 and 9 months post Allo-SCT
- Suspected pregnancy

11.2 Follow up of patients withdrawn from treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in 10.2 for follow up.
For patients who are withdrawn from treatment because in hindsight they did not fulfil the eligibility criteria (see 8.1.) at time of enrolment, data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in 12.3
No further information will be collected for patients who have withdrawn their consent. If a patient withdraws consent please consult HOVON Data Center.
Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

11.3 Premature termination of the study

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

- One of the stopping rules has been reached (paragraph 14);
- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.

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

12 Safety

12.1 Definitions

Adverse event (AE)

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

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)

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.

Suspected unexpected serious adverse reaction (SUSAR)

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

12.2 Adverse event

12.2.1 Reporting of adverse events

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

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

Adverse Events have to be reported on the Adverse Events CRF. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4. (see appendix D).

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

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

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AE's of CTCAE grade 1
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Progression of the disease under study; complaints and complications as a result of disease progression remain reportable Adverse Events
- Alopecia, nausea, vomiting, and hematological side effects

12.2.2 Follow up of adverse events

All adverse events will be followed clinically until they have been resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information for grade 3 or 4 adverse events considered at least possibly related to the investigational medicinal product by the investigator should be reported on the AE CRF until recovery or until 6 months after the last dose of IMP, whichever comes first.
Follow up information for all other adverse events should be reported on the AE CRF until recovery or until 30 days after the last dose of any drug from the protocol treatment schedule, whichever comes first.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

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

SAEs must be reported to the HOVON Data Center by fax **within 24 hours** after the event was known to the investigator, using the SAE report form provided. This initial report should contain a minimum amount of information regarding the event, associated treatment and patient identification, as described in the detail in the instructions for the SAE report form. Complete detailed information should be provided in a follow-up report within a further 2 business days, if necessary.

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

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

12.3.2 Causality assessment of Serious Adverse Events

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

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

12.3.3 Follow up of Serious Adverse Events

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

12.3.4 Processing of serious adverse event reports

The HOVON Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator.
The principal investigator will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The SPC will be used as a reference document for expectedness assessment.
The HOVON Data Center will provide to the Ethics Committee(s) a six-monthly line listing of all disease and/or therapy related SAE's if this is required by national laws or regulations or by the procedures of the Ethics Committee.
Individual SAE's that are not a SUSAR but do require expedited reporting (unexpected SAE's, i.e. not disease and/or therapy related) will be reported in compliance with the procedures of the Ethics Committees involved if this is required by national laws or regulations or by the procedures of the Ethics Committee.

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

The HDC safety desk, on behalf of the sponsor, will ensure the reporting of any SUSARs to the Ethics Committees (EC), the Competent Authorities (CA), and the investigators in compliance with applicable laws and regulations, and in accordance with any trial specific agreements.
Expedited reporting of SUSARs will occur no later than 15 days after the HOVON Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

12.5 Pregnancies

Pregnancies of a female subject or the female partner of a male subject, occurring while the subject is on protocol treatment or within 30 days following the last dose of any drug from the protocol treatment schedule, should be reported to the sponsor and, if the patient is treated with lenalidomide, to Celgene. Pregnancies must be reported to the HOVON Data Center by fax and to Celgene within 24 hours after the event was known to the investigator, using the pregnancy report form provided.

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

The investigator will forward any information regarding (suspected) pregnancies of patients treated with lenalidomide immediately to HOVON Data Center by fax AND to Celgene by phone at + 31 (0)30 28 44 525 then by email at DrugSafety-netherlands@Celgene.com or by fax +31 (0)30 28 44 511.

Contact details for Drug Safety Celgene B.V.:
Fax: +31 (0)30 28 44 511
Celgene B.V. (The Netherlands)
P.O. Box 2507
3500 GM Utrecht
The Netherlands
Tel: +31 (0)30 28 44 525
Email: DrugSafety-netherlands@Celgene.com

In order to prevent pregnancies during the use of Lenalidomide, patient information, patient registration and patient counseling will occur as defined in the Lenalidomide Pregnancy Prevention Risk Management Plan running in each separate country.

12.6 Reporting of safety issues

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of findings that could affect adversely the safety of patients, impact the conduct of the trial, increase the risk of participation or otherwise alter the EC's approval to continue the trial. In the occurrence of such an event the sponsor and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The accredited Ethics Committee will suspend the study pending further review, except insofar as suspension would jeopardize the patient's health. The local investigator will inform the patients.

12.7 Annual safety report

The sponsor will submit, once a year throughout the clinical trial, a safety report to the Ethics Committees and Competent Authorities of the concerned Member States. The content of the annual safety report will be according to the EU guidance document '*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'.*

12.8 Data Safety and Monitoring Board

The DSMB consists of at least 3 members, among whom (at least) one statistician and minimally two physicians. The members of the DSMB are invited on personal title on the basis of their expert knowledge of the disease involved or the research methodology. Members of the DSMB will have ample experience with clinical trials with allogeneic stem cell transplantation.
The members of the DSMB will not be involved in the study, work at the HOVON Data Center, be a member of the HOVON board, or work in a hospital department participating in the study. The members will not have a conflict of interest due to ties with a company involved in the study.

The DSMB reports their written recommendations to the trial statistician. The report may consist of a confidential and a public part, where the confidential part contains references to unblinded data. The trial statistician forwards the public part of the DSMB recommendation to the Principal Investigator, the Co-investigator(s) and the chair of the HOVON working group involved. The DSMB recommendations are not binding.

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

- Interim analysis report (as described in 14.3).

13 Endpoints

13.1 Definition of failure

Patients count as a failure (= event) at the earliest time point at which any of the following events occurs within 9 months after Allo-SCT :

- Onset of acute GvHD grade 3-4 without prior DLI;
- Onset of extensive chronic GvHD without prior DLI;
- Non-hematological toxicity CTCAE grade 4;
- Systemic therapy for uncontrolled myeloma other than the assigned study treatment of lenalidomide or lenalidomide/bortezomib and DLI;
- Death not due to (progression of) MM, which is in fact TRM.

13.2 Primary endpoint

Failure free duration (FFD) at 9 months post-transplant.
Patients without a failure (as defined in 13.1) within 9 months post Allo-SCT will be censored at 9 months, at the date of progression, or when they go off protocol treatment, whichever comes first.

13.3 Secondary endpoints

- Toxicity profile and compliance related to each treatment step and intervals between treatment steps (Allo-SCT, consolidation chemotherapy as well as pre-emptive DLI);
- Percentage of patients with a pre-emptive DLI within 6-9 months from the date of Allo-SCT;
- Response, improvement of response, and conversion to full donor chimerism during the separate treatment phases (i.e. from Allo-SCT until consolidation; from consolidation to DLI; and after DLI);
- CR rate;
- Progression-free survival (PFS; i.e. time from registration until progression, relapse or death, whichever comes first);
- PFS from Allo-SCT;
- Overall survival (OS) measured from time of registration;
- OS from Allo-SCT;
- The poportion of patients that complete 1, 2 resp. 3 consolidation cycles;

- Quality of life as defined by the EORTC QLQ-C30 and QLQ-MY20.

14 Statistical considerations

The primary aim of this study is to assess in adult patients with relapsed MM, the feasibility and toxicity of T-cell depleted Allo-SCT followed by consolidation therapy and, if applicable, subsequent pre-emptive DLI. The DLI should be given between 6-9 months after Allo-SCT. In order to monitor the failures, we define failure free duration (FFD) from date of Allo-SCT. Events for FFD are failures as defined in 13.1.

14.1 Patient numbers and power considerations

FFD at 9 months post Allo-SCT ($FFD_{9\ mo}$) will be considered as primary end point for the sample size calculation of each treatment arm.

- Let P_0 be the largest $FFD_{9\ mo}$ probability which, if true, implies that the feasibility of a treatment arm is too low and therefore the present HOVON 108 schedule does not warrant further investigation. In the present trial, P_0 has been taken as 50%.
- Let P_1 be the lowest $FFD_{9\ mo}$ probability which, if true, implies that the feasibility of a treatment arm is sufficiently high and therefore the proposed HOVON108 schedule warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 70%.
- Let α be the accepted probability of recommending for further investigation a regimen with a true $FFD_{9\ mo}$ probability equal to or lower than P_0. In the present trial, α has been taken as 0.10.
- Let β be the accepted probability of rejecting from further trials a regimen with a true $FFD_{9\ mo}$ probability at least equal to P_1. In the present trial, β has been taken as 0.10.

Per treatment arm, 50 eligible patients who start with Allo-SCT are required.
One interim analysis will be performed per treatment arm as soon as 9 failures have been reported in a treatment arm. The total time at risk for all patients who entered the trial will be calculated. Assuming an exponential distribution for FFD during the first 9 months after Allo-SCT, we calculate the hazard rate, estimate $FFD_{9\ mo}$ and its 90% confidence interval (CI), and the trial will be considered for early termination when the upper limit of the 90% CI is less than 70%.
If the trial was not discontinued early, the final analysis will be performed when complete information is available for all eligible patients in a treatment arm. If the upper limit of the 90% CI of $FFD_{9\ mo}$ is less than 70%, the trial will conclude that the proposed HOVON 108 schedule is not feasible. Otherwise, the trial will conclude that the treatment arm is feasible and may warrant further investigation in this patient population.

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

True $FFD_{9\ mo}$	Probability to recommend HOVON 108	Probability of early termination	Expected number of patients entered
50%	0.082	0.563	36.1
70%	0.917	0.051	48.8

In order to have up-to-date data for the interim analyses, a short questionnaire will be sent out every 2 months to the local investigators starting 2 months after entry of the first patient, until 9 failures have been observed per treatment arm.

In order to overcome dropouts due to ineligibility, 110 patients will be randomized. With an expected accrual rate of 30 patients per year, entry will be completed in about 4 years, depending on the speed of initiation in each center.

14.2 Statistical analysis

All randomized patients, eligible and who received an Allo-SCT, will be included in the analysis, according to the intention to treat.

14.2.1 Feasibility analysis

Per treatment arm, FFD will be calculated using the Kaplan-Meier method. Especially $FFD_{9\ mo}$ along with the 90% CI will be presented for each treatment arm.

14.2.2 Efficacy analysis

Per treatment arm, the response rate (especially CR) will be calculated along with the 95% CI.

Per treatment arm, the actuarial curves for PFS and OS will be computed using the Kaplan-Meier method and 95% CIs will be constructed.

Per treatment arm, actuarial probabilities of progression and death without progression with corresponding standard errors will be calculated using the competing risk method.

14.2.3 Toxicity analysis

Per treatment arm, the analysis of toxicity will be done by tabulation of the incidence of side effects and infections with CTCAE grade 2 or more (appendix D).

14.2.4 Statistical analysis of the quality of life assessment

All patients with at least one follow-up QoL questionnaire will be included in the analysis. To evaluate the change in QoL over time with respect to the multi-item scales of the QLQ-C30 and QLQ-MY20, the repeated measures will be analyzed using mixed ANOVA models. The single items will be analyzed using (ordinal) logistic regression with random effects. The items concerning the diagnosis-specific symptoms will be summarized using the unweighted sumscore.

14.2.5 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be made for the final analysis. It will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary analysis on which the sample size is based.

14.3 Interim analysis

One formal interim analysis per treatment arm is planned as described in paragraph 14.1.

14.4 Stopping rules

In paragraph 14.1 the stopping rules at the interim analyses are described.

14.5 Additional analysis

In this trial, all patients will receive an allogeneic transplantation. As an exploratory analysis (matched case-control) the results of this trial including efficacy and toxicity may be compared to those of the patients with a first relapse MM entered into HOVON-86 trial, in which patients are treated with lenalidomide, bortezomib and dexamethasone as reinduction therapy, followed by lenalidomide maintenenance, but without an allogeneic transplantation. The combination of lenalidomide/bortezomib and dexamethasone is considered as probably the current most effective anti-myeloma treatment.
As another exploratory analysis, we will also compare the quality of life data of the current trial to those of patients with newly diagnosed MM entered into the HOVON-95 trial.

15 Registration and Randomization

15.1 Regulatory Documentation

Required regulatory and administrative documents must be provided to the HOVON Data Center before enrolment of the first patient. This will always include an Ethics Committee approval for the investigational site. The HOVON Data Center will provide each investigator with an overview of the required documents. Each investigational site will be notified when all requirements are met and enrolment can start.

15.2 Registration and Randomization

Eligible patients should be registered before start of treatment. Patients need to be registered at the HOVON Data Center by one of the following options:

- Trial Online Process (TOP, https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.
- By faxing the completed registration/randomization CRF +31.10.7041028 Monday through Friday, from 09:00 to 17:00 CET
- By phone +31.10.7041560 Monday through Friday, from 09:00 to 17:00 CET

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Local patient code (optional)
- Sex
- Date of birth
- Date written informed consent
- Specific items patient gives consent for (see ICF)
- Eligibility criteria
- Stratification factors

All eligibility criteria will be checked with a checklist.
Patients will be randomized, stratified by center with a minimization procedure, ensuring balance within each stratum and overall balance.

Each patient will be given a unique patient study number (a sequence number by order of enrolment in the trial). Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.
Local Patient Code is a code assigned to the patient by the investigational site for local administrative purposes. The code may be up to 8 characters long (letters and numbers allowed). The code should be in compliance with privacy regulations. It should not contain identifying data, such as patient initials or the complete hospital record number. The local code will be visible in the confirmation messages sent by TOP to local participants after registration of the patient. The key to this local patient code should only be accessible by the local investigator and the local trial staff. Using or entering a local patient code is not obligatory.

16 Data collection and quality assurance

16.1 Case Report Forms

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;
- Baseline concomitant diseases and adverse events;
- Parameters for response evaluation;
- Any other parameters necessary to evaluate the study endpoints;
- Survival status of patient;
- Reason for end of protocol treatment.

Each CRF page will be identified by a trial number, and a combination of patient study number (assigned at registration) and hospital identification.
The CRF will be completed on site by the local investigator or an authorized staff member. All CRF entries must be based on source documents. The CRF and instructions for completing the CRF will be provided by the HOVON Data Center.
The CRF pages must be made available to the HOVON Data Center at the requested time points as specified in the CRF instructions.
All data collected in the study database by the HOVON Data Center.

16.1.1 Rapid reporting of failure and success data

Before the interim analysis, a few key data regarding treatment and events indicating treatment failure (see paragraph 13.1) will be actively requested for on a 2-monthly basis. For this purpose a short questionnaire will be generated – a Rapid Request Form -, which will be sent by email every 2 months to the local investigators.

16.2 Data quality assurance

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

16.3 Monitoring

Site evaluation visits
This trial is part of the HOVON Site Evaluation Visit program. Site evaluation visits are performed for HOVON studies to review the quality of overall trial conduct on a participating site and not the quality of one specific trial. The purpose is to collect quality data and facilitate improvement of the participating site. Data cleaning is not the goal of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan.
A fundamental ingredient of the site evaluation visit is the interview with an investigator regarding the site's organization and trial procedures. The site documents from a randomly selected HOVON trial will serve as a guide to review the results of these procedures: the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).
Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that during site evaluation visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

16.4 Audits and inspections

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

17 Ethics

17.1 Accredited ethics committee or Institutional Review Board

An accredited Ethics Committee or Institutional Review Board will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

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

17.3 Patient information and consent

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

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

17.4 Benefits and risks assessment.

Allogeneic stem cell transplantation is associated with potential considerable morbidity and mortality. This is mainly due to the occurrence of Graft versus Host reactions and increased susceptibility for bacterial, fungal and viral infections. Based on previous experience with Allo-SCT and profound T cell depletion acute GvHD may be expected in 20-30 of patients of which about 10% may be severe (grade 3-4) and chronic GvHD in 20-30% of patients of which 10 % may be extensive. Due to these side effects quality of life may be negatively affected and the transplant related mortality in the first 12 months is estimated between 10-15 %. As is usuall following Allo-SCT patients are frequently controlled on the policlinic (in the first month once to twice weekly, later on every week, every other week) with routine blood checks. In the first period after Allo-SCT no extra controls or investigations will be performed.
During lenalidomide and lenalidomide combined with bortezom treatment patients are routinely checked every week/every other week including standard blood checks. In the first and in the third cycle 2 extra (day 1 and day 15 of each cycle) blood samples will be taken. Each blood sample is 40 ml. Bone marrow samples will only be taken for routine indications, for staging of the disease in case serum evaluations are not sufficient. The other reason for taken a routine bone marrow sample is to confirm a CR. The frequent controls during this period are necessary to administer weekly bortezomib and to evaluate potential side effects like bone marrow suppression, polyneuropathy and GvHD.
DLI is given on the policlinic by rapid iv infusion. Standard controls following DLI are every 2/3 weeks with routine blood checks. The most important side effect is the occurrence of GvHD: acute GvHD may be expected in 20-30 of patients of which about 10% may be severe (grade 3-4) and chronic GvHD in 20-30% of patients of which 10 % may be extensive. TRM associated with DLI is expected to be around 5 %.
Patients with relapsed myeloma after autologous SCT have a poor prognosis especially when they have also been treated with a novel agent. This is illustrated by the fact that the overall survival was only 18 months for the patients with a relapse after intensive treatment combinened with thalidomide.

Novel anti-myeloma agents are now routinely given as part of first line therapy in myeloma. The unfavourable prognosis for patients with first relapse myeloma justifies a therapy that is associated with considerable morbidity and mortality but in the end may induce long lasting remissions of good quality. In order to reduce potential excessive toxicity in many patients the feasibility of non-myeloablitve Allo-SCT followed by early consolidation with novel ant-myeloam agents is tested in 2 small fase 2 studies. If feasible the new modalities will be tested in a larger patient population.

17.5 Trial insurance

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

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. In some cases date of birth is also listed.
The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting site staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies)

The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents should be retained for 15 years after the end of the trial. They should be destroyed after this time.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.1.4 Storage of samples

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

18.2 Amendments

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

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

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

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

18.3 Annual progress report

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

18.4 End of study report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority.

18.5 Publication policy

Final publication of trial results

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.
The final publication of the trial results will be written by the Principal Investigator, the Co-investigators and the trial statistician on the basis of the statistical analysis performed by the trial statistician. A draft manuscript will be submitted for review to:

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

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

Authorship

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

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

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

Interim and partial publications

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

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

Abstracts and presentations

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

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

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

Prior to it's public use, the abstract or presentation is submitted to the HOVON secretary for review of compliance with this policy.
the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.
The final publication of the trial results will be written by the Principal Investigator, the Co-investigator(s) and the trial statistician on the basis of the statistical analysis performed by the trial statistician. A draft manuscript will be submitted for review to:

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

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

Authors of the main manuscript will include the Principal Investigator, the Co-investigator(s), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion rate), the trial statistician and the trial manager. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement.
Authors of correlative manuscripts (e.g. results of side studies) will include the Principal Investigator, the Co-investigator(s), and those persons who have made a significant contribution to the published results.

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

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

Glossary of abbreviations

(in alphabetical order)

ADL	Activities daily life
Allo(-SCT)	Allogeneic (Stem Cell Transplantation)
AE	Adverse Event
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
Ca	Calcium
CA	Competent Authority
CKTO	Commissie voor Klinisch Toegepast Onderzoek'
CR	Complete Remission
CRi	Complete Remission with incomplete blood count recovery
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DLI	Donor Lymfocyt Infusion
DFS	Disease Free Survival
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
FFS	Failure Free Survival
FISH	Fluorescence In Situ Hybridisation
FLC	Free Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastro-intestinal
GvHD	Graft versus Host disease
GvM	Graft-versus-MM
GvT	Graft versus tumor
Hb	Hemoglobin
HDM	High Dose Melphalan
HIV	Human Immunodeficiency Virus

HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HRC	Hematocytology Review Committee
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFM	Intergroup Français de Myelome
IMP	Investigational Medicinal Product
ISS	International Staging System
ITT	Intention To Treat
IU	International Units
KCl	Potassium chloride
LDH	Lactate Dehydrogenase
METC	Medical Ethical Review Committee
MM	Multiple Myeloma
MUD	Matched Unrelated Donor
NaCl	Sodium Chloride
NCI	National Cancer Institute
NMA	Non Myeloablative
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PBMC	Peripheral blood mononuclear cell
PBSC	Peripheral Blood stem cells
PD	Progressive Disease
PET	Positron Emission Tomografy
PFS	Progression Free Survival
PO	Per Os
PR	Partial Response
PTLD	Post Transplant Lymfoproliferative Disease
QoL	Quality of Life
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SPEP	Serum protein electro-phoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Total body irridiation

TRM	Transplant related mortality
TMA	Tissue Micro Array
ULN	Upper Limit of Normal
UPEP	Urine protein electro-phoresis
VAD	Vincristine, Doxorubicin (Adriamycin), Dexamethasone
VGPR	Very good partial remission
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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A. Diagnostic Criteria Multiple Myeloma

CRITERIA FOR STAGING OF MULTIPLE MYELOMA

According to Salmon & Durie

Stage I	Low Tumor Mass – all of the following:
	Hemoglobin > 6.2 mmol/l
	Ca2+ < 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
	Ca2+ > 2.65 mmol/l *
	IgG > 70 g/l
	IgA > 50 g/l
	Urine M-protein > 12 g/24 hrs
	³ 3 lytic bone lesions on skeletal survey (bone scans are not acceptable)
A	Normal renal function (creatinin < 177 mmol/l)
B	Renal insufficiency (creatinin ≥ 177 mmol/l)

* Correct the serum Ca2+ by adding 0.02 mmol/l for every g/l albumin below 40 g/l

Staging according to ISS criteria

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

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

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

B. Response criteria

International Myeloma Working Group uniform response criteria for multiple myeloma[1]

Response subcategory	*Response criteria*
Stringent complete response (sCR)	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete responsea (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
Very good partial response (VGPR)[a]	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% or greater reduction in serum M-component plus urine M-component <100mg per 24 hr
Partial response (PR)	≥50% reduction of serum M protein and reduction in 24-h urinary M protein by ≥90% or to <200mg per 24 h If the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria. If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)[a]	Increase of 25% from lowest response value in any one or more of the following: Serum M-component (absolute increase must be ≥0.5 g/100 ml)[c] and/or Urine M-component (absolute increase must be ≥200mg per 24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l) Bone marrow plasma cell percentage (absolute % must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

[a]Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Adapted with permission from Durie et al. [1]

[c] for progressive disease, serum M-component increases of ≥1 g/100 ml are sufficient to define relapse if starting M-component is ≥5 g/100ml.

1. Durie BGM, Harousseau J-L, Miguel JS, Blade J, Barlogie B, Anderson K et al. International uniform response criteria formultiple myeloma. Leukemia 2006; 20: 1467–1473.

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

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

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

4 Unable to get out of bed

D. Common Toxicity Criteria

The grading of toxicity and adverse events will be done using the most recent version of the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4. A complete document may be downloaded from the following sites:

http://ctep.cancer.gov/reporting/ctc.html
http://www.hovon.nl (under Trials > General information about studies

E. NYHA scoring list

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

Grade 1 No breathlessness

Grade 2 Breathlessness on severe exertion

Grade 3 Breathlessness on mild exertion

Grade 4 Breathlessness at rest

F. Management of patients with bortezomib (Velcade®)-related neuropathic pain and/or peripheral sensory neuropathy

			Peripheral Sensory Neuropathy (NCI CTC Grade)				
			0	1	2	3	4
			Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling
Neuropathic Pain(NCI CTC Grade)	0	None	No action	No action	25% dose reduction	Hold; 50% dose reduction; Schedule Δ required	Discontinue bortezomib
	1	Mild pain not interfering with function	No action	No action	25% dose reduction	Hold; 50% dose reduction; Schedule Δ required	Discontinue bortezomib
	2	Moderate pain: pain or analgesics interfering with function, but not daily activities	25% dose reduction	50% dose reduction	Hold; 50% dose reduction	Hold; 50% dose reduction; schedule Δ required	Discontinue bortezomib
	3	Severe pain: pain or analgesics severely interfering with daily activities	Hold; 50% dose reduction; Schedule Δ required	Hold; 50% dose reduction; schedule Δ required	Hold; 50% dose reduction; schedule Δ required	Discontinue bortezomib	Discontinue bortezomib
	4	Disabling	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib

Key:

Hold: Interrupt bortezomib for up to 2 weeks until the toxicity returns to Grade 1 or less.

25% Dose reduction: Bortezomib dose reduction from 1.3 to 1.0 mg/m²/dose.
50% Dose reduction: Bortezomib dose reduction from 1.3 to 0.7 mg/m²/dose.
Schedule Δ Required: Schedule change from Bortezomib once per week (Days 1, 8, 15) to every other week (e.g. Day 1, Day 15).is required.

G. Diagnosis, staging and grading of GvHD

Diagnosis

Acute and chronic GvHD is defined according to the proposal of the recent National Institutes of Health (NIH) Consensus Conference, which recognizes 2 categories of GvHD [84]:

(1) **acute GvHD** (absence of features consistent with chronic GvHD), comprising:

(a) classic acute GvHD (before day 100), and,

(b) persistent, recurrent, or late acute GvHD (after day 100, often upon withdrawal of immunosuppression);

(2) **chronic GvHD**, comprising:

(a) classic chronic GvHD (no signs of acute GvHD), and,

(b) an overlap syndrome, in which features of both acute and chronic GvHD are present.

G.1 Staging and grading of acute GvHD

For staging and grading the Glucksberg classification updated according to Przepiorka et al [85;86] is used:

Stage	Skin Rash	Liver Total bilirubin (μmol/L)	Intestinal tract Diarrhea (ml/day)
1	<25%	34-50	500 –1000 or persistent nausea without diarrhea*
2	25-50%	50-102	1000-1500
3	> 50%	102-255	>1500
4	generalized erythroderma with bullous formation	>255	severe pain/ileus
Grade			
I	Skin: stage 1-2 and Liver: stage 0 and Gut: stage 0		
II	Skin: stage 3 or Liver: stage 1 or Gut: stage 1		
III	Skin: stage 3 or Liver: stage 2-3 or Gut: stage 2-4		
IV	Skin or Liver: stage 4		

*persistent nausea with histologic evidence of GvHD in the stomach or duodenum

G.2 Signs and symptoms of chronic GvHD according to the National Institutes of Health (NIH) Consensus Conference

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GvHD)	Distinctive (Seen in Chronic GvHD, but Insufficient Alone to Establish a Diagnosis of Chronic GvHD)	Other Features*	Common (Seen with Both Acute and Chronic GvHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes Ulcers		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions Fissures Ulcers		

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GvHD)	Distinctive (Seen in Chronic GvHD, but Insufficient Alone to Establish a Diagnosis of Chronic GvHD)	Other Features	Common (Seen with Both Acute and Chronic GvHD)
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal ALT or AST >2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

* Can be acknowledged as part of the chronic GvHD symptomatology if the diagnosis is confirmed
# Diagnosis of chronic GvHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

Seattle classification for limited and extensive chronic GvHD

Limited

Either or both:

1. Localized skin involvement
2. Hepatic dysfunction due to chronic GvHD

Extensive

Either

1. Generalized skin involvement, or
2. Localized skin involvement and/or hepatic dysfunction due to chronic GvHD, plus:

(a) Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or

(b) Involvement of eye (Schirmer's test with <5 mm wetting), or

(c) Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or

(d) Involvement of any other target organ

H. Side study - immunological status and immune effects of lenalidomide +/- bortezomib

Apart from routine laboratory investigations, the immune-status of the patients and modulation after lenalidomide or lenalidomide combined with bortezomib will be evaluated by phenotypic and functional analysis of peripheral blood that will be obtained from recipients **pre-Allo-SCT (before the start of the conditioning), at the start of each Lenalidomide / Bortezomib cycle and at the start of DLI**. From the obtained blood samples, plasma and PBMC will be isolated and cryopreseved to execute the immunological monitoring, outlined as follows:

A. Phenotypic analyses

The effect of lenalidomide or lenalidomide combined with bortezomib on the number of circulating T cell subsets will be studied by FACS based standard immunophenotyping methods after labeling the PBMC with antibodies specific for CD3 (T cells), CD16 and CD56 (NK cells), CD14 (monocytes), CD19 (B cells). The phenotypical analyses will also include the T cell subset markers CD4 and CD8. T Regulatory cell-frequencies will be determined by intracellular staining for Foxp3. Previous T cell activation will be determined by detection of HLA-DR on T cells, Activated NK T cells will be determined by $CD56^{dim}$ vs $CD56^{hi}$ expression on $CD3^-$ cells. Naïve, Central Memory and Effector Memory T cells will be discriminated by triple staining for CD45RO, CD62L and CCR7 on CD4 and $CD8^+$ T cells.

B. Functional analyses

1. Cytokine producing T cell subsets

An important goal of the functional analyses is to determine the effect of lenalidomide or lenalidomide combined with bortezomib on the number of functional T cell subsets related to GvHD and GvT responses, namely IFN-g producing Th1-like cells and IL-17-producing Th17 cells. For these measurements the PBMC will be stimulated with beads coated with CD3/CD28 for 16 hours. The (host) antigen specific activity of these cell subsets will be analyzed as outlined in the next section.

2. Analysis of host antigen and/or myeloma specific T cell responses

One of the objectives of the clinical study is to evaluate whether lenalidomide or lenalidomide combined with bortezomib modulates the host specific immune responses after allo SCT. Hence the collected PBMC samples will be also used to determine the host-specific T cell responses. To this end, collected PBMCs will be stimulated with donor and recipient derived antigen presenting cells (APCs; EBV transformed B cell lines and/or monocytes) for 48 hours. Whenever possible, malignant MM cells from patients will be also used as APCs. After T cell stimulation, the T cell activation will be determined by detection of the T cell activation marker CD137 on the surface of the $CD4^+$ and $CD8^+$ cells by FACS.

3. Analysis of minor H antigen (mHag) specific T cell responses

It may be possible that patient and donor are mismatched for already identified minor H antigens, which are the most important antigens involved in GvHD and GvT after allo-SCT. In such cases the immunomonitoring will also aim to evaluate whether lenalidomide or lenalidomide combined with bortezomib modulates the mHag specific T cell responses. For this, the frequencies and absolute numbers of mHag specific T cells in the collected PBMC samples will be determined by using tetrameric mHag peptide/MHC complexes.

For this 40 ml Natrium-heparin blood samples (cells and plasma) should be gathered at each timepoint, prepared and frozen immediately after collection at a temperature of -70 ^{o}C (please record date of obtaining the sample). There are no contra indications for postponing the immune status evaluation. Further information on collection, storage and shipment of samples will be given in a laboratory manual. Questions on sampling for immunological status can be directed to M. Minnema or H. Lokhorst (tel. 088 755 8380 or 088 755 9771).