A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma

The European Intergroup Trial of the European Myeloma Network EMN (EMN02/HO95 MM)

PROTOCOL

Principal Investigators :		P.Sonneveld (HOVON)
Co-investigators	:	M. Cavo (GIMEMA)
		H.Einsele (DSMM)
		U. Mellqvist (NMSG)
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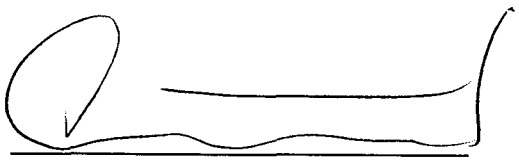
GIMEMA NMSG DSMM CEMSG

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:



17 SEP. 2012

Signature of Investigator

Date

P. SANNEVELD

Printed Name of Investigator

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

Local Investigator:

_____ _____

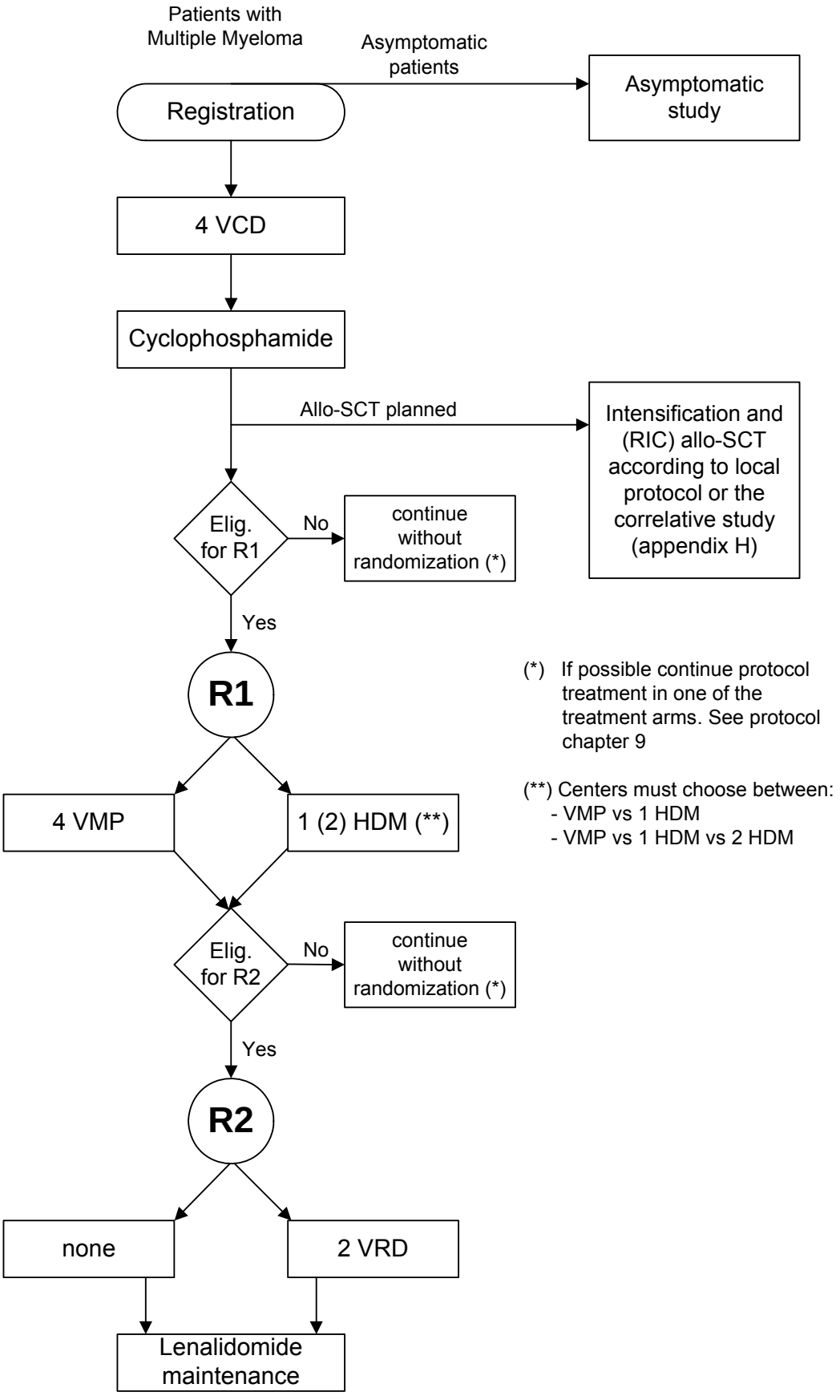
Signature of Investigator Date

_____

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices 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

Study phase	Phase III
Primary study objectives	– Comparison of Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed autologous stem cell transplantation (ASCT) – Comparison of Bortezomib, Lenalidomide, Dexamethasone (VRD) as consolidation versus no consolidation – Comparison of single versus tandem high dose Melphalan with ASCT
Patient population	Patients with symptomatic multiple myeloma, previously untreated, ISS stages 1-3, age 18-65 years inclusive
Study design	Prospective, multicenter, intergroup, randomized
Duration of treatment	Expected duration of induction, stem cell collection and intensification is 7 - 10 months. Consolidation with VRD will last 2 months Maintenance therapy with Lenalidomide will be given until relapse. All patients will be followed until 7 years after registration.
Number of patients	1500 patients registered
Expected duration of accrual	3 years
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported.
End of trial	The end of the study is defined as the last patient's last visit.

4 Investigators and study administrative structure

IMPORTANT NOTE

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

Responsibility	Name	Affiliation/Address
Sponsor	HOVON Foundation	VU University Medical Center, P.O.Box 7057 1007 MB Amsterdam The Netherlands tel: +31 20 4443797
Co-sponsor	Fonesa Onlus	c/o Divisione Universitaria di Ematologia Via Genova 3 10129 Turin, Italy
Representative of Sponsor (HOVON)	P.C. Huijgens, chairman P. Sonneveld, treasurer	VU University Medical Center Amsterdam, The Netherlands Erasmus MC Rotterdam, The Netherlands
Principal Investigator	P. Sonneveld (HOVON) Contact information for trial related medical decisions: +31-10-7033589	Erasmus MC Rotterdam, The Netherlands
Co-investigators	M. Cavo (GIMEMA) H. Einsele (DSMM) U. Mellqvist (NMSG)	University of Bologna, Italy University Hospital Wurtzburg, Germany Sahlgrenska Hospital, Göteborg, Sweden
Coordinating investigators	H. Ludwig (CEMSG) H.Lokhorst (HOVON) A. Palumbo (GIMEMA) A. Waage (NMSG) P. Gimsing (NMSG) K. Wu (HOVON)	Vienna, Austria Utrecht Medical Center, Utrecht, The Netherlands University of Torino, Italy St. Olav Hospital, Trondheim, Norway Rigshospitalet, Copenhagen, Denmark ZNA Stuivenberg, Antwerp, Belgium
HOVON MM working group chair	H. Lokhorst	Utrecht Medical Center, Utrecht, The Netherlands
Writing Committee	M. Boccadoro S. Bringhen	University of Torino, Italy University of Torino, Italy

	M. Cavo	University of Bologna, Italy
	M. Dimopoulos	University of Athens, Greece
	H. Einsele	University of Wurzburg, Germany
	P.Gimsing	Rigshospitalet, Copenhagen, Denmark
	M. Kropff	University of Munster, Germany
	H.M. Lokhorst	Utrecht Medical Center, Utrecht, The Netherlands
	H. Ludwig	Vienna, Austria
	U. Mellqvist	Sahlgrenska Hospital, Göteborg, Sweden
	A. Palumbo	University of Torino, Italy
	P. Sonneveld	Erasmus MC, Rotterdam, The Netherlands
	A. Waage	St. Olav Hospital, Trondheim, Norway
Statistician	G. Ciccone (GIMEMA)	C.P.O. Piemonte, Turin, Italy……
	B. van der Holt (HOVON)	HOVON Data Center, Rotterdam, The Netherlands
Registration	EMN Data Center	Headquarter: University of Turin Contact Information: MJ Fornaro Via Genova 3 10126 Turin Italy tel. +39 .011 6336107 fax. +39 011 6334301 fax +39 011 6963737
Monitoring	For HOVON sites HOVON Data Center	Erasmus MC-Daniel den Hoed P.O.Box 5201 3008 AE ROTTERDAM The Netherlands tel. +31.10.7041560 fax +31.10.7041028
Laboratory sites	- For HOVON sites	Erasmus MC Rotterdam, The Netherlands
	- For Nordic sites	Aalborg Hospital, Denmark
	- For German sites	University of Wurzburg, Germany
	- For Italian sites	University of Bologna, Italy
	- For Swiss, Greek, Austrian and Turkish sites	Erasmus MC Rotterdam, The Netherlands
	- For CMG sites	University Hospital Brno, Czech republic
Trial management	HOVON Data Center	Erasmus MC - Daniel den Hoed, Rotterdam, The Netherlands
Data management	EMN Data Center	Contact information for trial related data-managing decision +39 0116336107; +39 0116334301
Serious Adverse Events (SAEs) notification	EMN Data Center	fax +39 011 6963737

5 Introduction

Multiple myeloma is a malignancy of the plasma cells. It represents the second most common hematological malignancy. The annual incidence rates in northern Europe are 4-5/100.000. Approximately 6 cases of multiple myeloma per 100.000 inhabitants are diagnosed in Western Europe each year. Multiple myeloma is uniformly fatal. As the disease progresses, morbidity and eventual mortality are caused by reduced immunoresistance to infections, significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, and, less commonly, neurological complications and hyper viscosity. Despite the use of high-dose chemotherapy and autologous stem cell transplantation, this cancer remains incurable. The 5-year survival rate for patients with multiple myeloma among patients treated with conventional chemotherapy is 25%, while with intensified therapy this may increase to 50%. Novel agents are urgently needed to improve the treatment results of this disease.

5.1 Treatment

Melphalan and Prednisone (MP) have long been used for front-line therapy of patients with newly diagnosed myeloma (MM). In younger patients autologous stem cell transplantation (ASCT) prolongs survival compared to conventional chemotherapy [1]. For many years, VAD (Vincristine, Adriamycin, Dexamethasone) or pulsed high-dose Dexamethasone was used in patients who were candidates for ASCT. Front-line regimens have now changed with new agents such as thalidomide, Bortezomib, and Lenalidomide. New induction regimens not only control the disease and its symptoms in preparation for ASCT, but also offer high overall response (OR) and very good partial response (VGPR) rates, approaching levels previously noted only with ASCT.

5.1.1 High dose therapy with ASCT

High dose therapy with ASCT for myeloma is offered primarily to patients less than 65 years of age. Many different induction regimens have been used to reduce tumor load prior to transplantation. VAD was used for many years as pre-transplant induction therapy for patients considered candidates for ASCT. However, the activity of VAD is primarily due to the high-dose Dexamethasone component. The importance of reducing tumor load prior to transplantation and to achieve a CR has been emphasized by many groups.[2-4] Attempts have been made to improve the outcome of myeloma by performing double transplants. The rationale of this approach was based on the observation that the achievement of CR after intensive therapy was a favorable prognostic factor for EFS and OS. The largest series of double transplants has been performed by the group led by Barlogie.[5] In previously untreated patients the CR rate increased from 26% after the first transplant to 41% after the second.

Median OS and EFS durations were 68 months and 43 months, respectively. In a randomized study by the “Intergroup Français de Myelom” (IFM), single versus double stem cell transplantation was compared in previously untreated patients. The results show that patients who did not achieve at least VGPR had a slightly better OS after double transplants. [6] Cavo et al found a significantly improved CR rate and EFS in patients following double transplant.[7] The majority of these results, however, have been obtained before the introduction of novel agents, leaving the role of a double transplantation still open.

5.1.2 Induction regimens with novel agents: Thalidomide

Cavo and colleagues in a matched case-control study of 200 patients demonstrated that response rates with VAD were significantly lower compared to Thal/Dex; 76% versus 52%, respectively [8]. In Total Therapy 2 addition of Thalidomide improved survival beyond 5 years in patients with cytogenetic abnormalities. [9] Randomized trials from Germany and the Netherlands comparing VAD with Thalidomide/Doxorubicin/Dexamethasone confirmed the superior response with Thalidomide induction.[3, 10]

5.1.3 Bortezomib based induction regimens

Bortezomib (VELCADE®, JNJ-26866138) is a small molecule proteasome inhibitor which is being developed through a joint collaboration between Millennium Pharmaceuticals, Inc. and Johnson & Johnson Pharmaceutical Research & Development. Bortezomib is a potent, reversible, and specific inhibitor of the proteasome and represents a first-in-class anti-neoplastic cytotoxic agent that is distinguished from conventional cytotoxic agents by a favorable side effect profile, including its lack of significant myelosuppression, hair loss and mucositis. Bortezomib is a modified dipeptidyl boronic acid derived from leucine and phenylalanine; its chemical name is N pyrazinecarbonyl L phenylalanine L leucine boronic acid and has a molecular weight of 384.25 daltons.
Inhibitors of the 26S proteasome act through multiple mechanisms to suppress tumor survival pathways, arrest tumor growth, tumor spread, and angiogenesis. Unlike conventional chemotherapeutics, Bortezomib represents a novel class of anti-cancer agents because it has the ability to affect a combination of cellular regulatory mechanisms. This multiple mechanistic approach potentially represents a more effective anti-cancer strategy compared to the anti-tumor activity afforded by conventional chemotherapy.

Bortezomib has been studied extensively first in relapsed myeloma [11, 12] and later in newly diagnosed myeloma, both in patients who are candidates for transplantation and in elderly patients [13, 14]. In newly diagnosed myeloma, Bortezomib produces response rates of approximately 40% as

a single-agent. Significantly higher response rates (approximately 70-90%) have been observed with Bortezomib plus Dexamethasone (Vel/Dex, VD) in phase II studies [13, 15]. The CR plus VGPR rate is approximately 30% with Vel/Dex. Harousseau and colleagues reported preliminary results of a randomized trial comparing VAD versus Vel/Dex as pre-transplant induction therapy [15]. With 482 patients enrolled, preliminary results show superior response rates and progression-free survival with Vel/Dex compared to VAD. The incidence of grade 3-4 adverse events was comparable between the two regimens. No adverse effect on stem cell mobilization has been noted with Vel/Dex.
Bortezomib, Adriamycin, Dexamethasone (PAD) has shown high activity in newly diagnosed myeloma in a phase II study with an overall response rate (ORR) of 95% and a CR rate of 24% [16]. HOVON and GMMG tested PAD versus VAD in a randomized, open-label, phase III trial (ASH 2008 # 653). Patients with newly diagnosed myeloma ages 18-65 were randomly assigned to 3 cycles of VAD or PAD. VAD was administered at a dose of Vincristine 0.4 mg, Adriamycin 9 mg/m^2 days 1-4, Dexamethasone 40 mg days 1-4, 9-12, and 17-20. PAD was administered at a dose of Bortezomib 1.3 mg/ m^2 days 1,4,8,11, Adriamycin 9 mg/ m^2 days 1-4, and Dexamethasone 40 mg days 1-4, 9-12, and 17-20. After induction therapy, all patients were to receive ASCT (one or two transplants) followed by maintenance with either thalidomide 50 mg daily in the VAD arm or Bortezomib, 1.3 mg/ m^2 once every 2 weeks in the PAD arm for 2 years. A total of 833 patients were randomized, and preliminary results on the first 300 patients were available. The overall response rate prior to ASCT was superior with PAD compared with VAD, 83% versus 59%, P<0.001. Corresponding CR rates were 5% versus 1%. Post transplant CR rates were 23% versus 9%, respectively, P<0.001. Eighty percent of patients achieved at least VGPR with this regimen of PAD followed by ASCT. Again, following PAD, stem cell harvest was adequate in all patients.
Cavo et al have compared Thal/Dex to Bortezomib, Thalidomide, Dexamethasone (VTD) as pre-transplant induction therapy in a randomized controlled trial (ASH 2008 # 158). A total of 399 patients (199 randomized to VTD and 200 to TD) could be evaluated for primary study and secondary end points. On an intent to treat basis, VTD had significantly higher response rates compared with Thal/Dex, 92% versus 78.5% respectively, P<0.001) following the 3 cycles of induction. CR rates were also better (21% versus 6% respectively, P<0.001). Serious adverse events occurred in 14% of patients randomized to VTD versus 13% with Thal/Dex. There were no problems with stem cell mobilization, with median yields of 9.3 and 10.6 (x10^6 $CD34^+$ cells/kg), respectively. On an intention-to-treat basis, post-transplant CR was higher with VTD compared with Thal/Dex, 41% vs. 20%, respectively, P<0.001. PFS was significantly superior with VTD as compared to Thal/Dex, P=0.04, but overall survival is similar so far. Also the Spanish Pethema group has found superior response rates of VD in a phase II trial [17] and is now comparing VTD with conventional chemotherapy (ASH 2008 # 654). Thus, combining VD with an immunomodulatory drug (IMiD) gives a highly active induction

regimen, and has the additional advantage of not requiring major dose modifications in renal failure.

Bortezomib-based regimens are of particular value in patients with renal failure and in patients with high-risk myeloma (see below). Bortezomib is not associated with an increased rate of thrombosis, and hence is a useful option for patients who are at high-risk of thrombosis or in whom anticoagulation or aspirin are contraindicated.
The role of other pre-transplant induction regimens need to be weighed in terms of the added side-effects that can affect quality of life, and should be considered investigational until future studies show that the addition of these agents improves long-term outcome compared to the regimens discussed above. One exception is patients presenting with very aggressive disease including plasma cell leukemia features or rapidly progressive disease with or without extramedullary features. In these patients, 2 cycles of the combination chemotherapy regimen VDT-PACE (Bortezomib (Velcade®), Dexamethasone, Thalidomide, Cisplatin (Platinum), Doxorubicin (Adriamycin), Cyclophosphamide, and Etoposide) [18] developed by Barlogie et al as part of total therapy III is highly effective in controlling the disease rapidly Bortezomib, Lenalidomide, Dexamethasone (VRD), Cyclophosphamide, Bortezomib, Dexamethasone (CyBorD), and Bortezomib, Cyclophosphamide, Lenalidomide, Dexamethasone (VCRD) have shown high activity in phase II studies (ASH 2008 # 92, 93, 3601). The final results and phase III studies with these regimens are awaited.
In MM patients subcutaneous (sc) and intravenous (iv) administration of bortezomib are equally effective, however the sc administration has less CTC AE grade 3 and 4 side effects, especially less induction of polyneuropathy.[15] Fifty-seven percent of patients experienced mild redness at the injection site.

5.1.4 Lenalidomide based induction regimens

Lenalidomide (Revlimid®) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It is derived from Thalidomide and it offers potential benefit over this first generation IMiD in terms of safety and efficacy in human subjects [19]. The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be multi-factorial in that they depend on both the cell type and the triggering stimulus. To date, Lenalidomide has been associated with TNF-α inhibitory, T cell co-stimulatory and anti-angiogenic activities. Lenalidomide is a 50.000 times more potent inhibitor of TNF-α than Thalidomide, it augments IL-2 and IFN-gamma production and it inhibits IL-6 and VEGF production.
Lenalidomide has been used for induction in a SWOG trial, comparing Lenalidomide with standard dose Dexamethasone or low dose Dexamethasone. Although the results have not yet been published, preliminary analyses indicate a high response rate (42% VGPR+CR). [20]

5.1.5 Consolidation and maintenance

Post-transplant consolidation and maintenance has been studied for several years. Two trials showed a superior effect of Thalidomide when given in this setting, particularly in patients failing at least VGPR after ASCT(s).[21, 22]. The results of other trials have been presented as abstract only (ASH 2008 # 157,656).
Bortezomib has also been investigated in the maintenance and consolidation setting in two small studies. Data from the Nordic Myeloma Study Group show that consolidation with Bortezomib may induce a significantly higher CR rate (Mellquist et al, ASH 2009, abstract #530). In addition, consolidation treatment with Bortezomib plus Thalidomide and Dexamethasone (VTD) induces molecular remissions in newly diagnosed patients (Ladetto et al,ASH 2008 abstract 3683)Ongoing randomized studies by several European study groups are further investigating Bortezomib as consolidation and maintenance therapy (Sonneveld et al, ASH 2008, abstract # 653; Rosinol et al, ASH 2009, abstract # 120).
Lenalidomide was used as maintenance in an Italian trial (ASH 2008 # 159) as well as in a large prospective phase III trials by the French IFM group and by Celgene (MM015). Safety data indicate that Lenalidomide maintenance is well tolerated. Two recent presentations of large prospective randomized trials demonstrated a significant superior response and progression-free survival of Lenalidomide maintenance over placebo in elderly patients treated with MP-based regimens (Palumbo et al, ASH 2009, abstract # 613) and as maintenance therapy after HDM/ASCT for MM (Attal et al, IFM 2005-02 ASCO 2010) These trials have established Lenalidomide as the best candidate for maintenance treatment because of good tolerability and high efficacy.

The combination of Bortezomib plus Lenalidomide has been explored in the Dana Farber Cancer Institute in a phase 1/2 trial in relapsed and/or refractory patients with MM, in which the dose of Bortezomib and Lenalidomide were escalated. The maximum Tolerated Dose (MTD) was Bortezomib 1.0 mg/m^2 per gift, days 1,4,8,11 with Lenalidomide 15 mg/day for 21 days (P. Richardson ASH abstract # 365,2005). The dose limiting toxicity was neutropenia. In 17 heavily pretreated patients this combination was well tolerated and a CR + PR was achieved in 59 % even in patients who had been exposed to either agent alone. Subsequently, a phase 2 trial performed in newly diagnosed patients, using standard dose Bortezomib at 1.3 mg/m^2, Lenalidomide 25 mg and Dexamethasone 20 mg showed good tolerability and a high, good quality response rate (100%), which was independent from ISS stage and/or cytogenetics (P. Richardson, ASH 2008 # 92)

5.2 Prognostic factors

Current risk models classify patients into high-risk and standard-risk myeloma based on deletion 13 or hypodiploidy on metaphase cytogenetic studies, deletion 17p- or immunoglobulin heavy chain (IgH) translocations t(4;14) or t(14;16) on molecular genetic studies, or plasma cell labeling index > 3%. Patients with high-risk myeloma tend to do poorly with median overall survival of approximately two years even with tandem ASCT. The main option for these patients is novel therapeutic strategies. Bortezomib containing regimens should be considered early in the disease course as primary therapy. In at least 3 separate studies, Bortezomib appears to overcome the adverse effect of deletion 13.[23-25] Clearly clinical trials and new agents specifically designed for high-risk myeloma are needed.
In patients who are not transplant candidates, the combination of Bortezomib with MP (VMP) has been explored in the large phase 3 VISTA trial.[25] The ORR, determined using the stringent EBMT criteria, was 71% with VMP compared with 35% with MP, with an immunofixation-negative CR rate of 30% with VMP versus 4% with MP (P<0.000001). Although median OS was not reached in either arm after a median follow-up of 25.9 months, VMP demonstrated a significantly superior 3-year OS compared with MP: 72% with VMP vs 59% with MP (P=0.0032). These and other data indicate that also in the non-transplant setting, Bortezomib has become a vital (?) novel agent in the front-line treatment of multiple myeloma. Based on VISTA, VMP has been approved for the European market.

5.3 Rationale for the trial

This is a phase III study to test the efficacy and feasibility of Bortezomib combined with Melphalan and Prednisone (VMP) versus intensive treatment (HDM) followed by ASCT(s) and secondly to evaluate the role of short term consolidation treatment with VRD (Bortezomib, Lenalidomide, Dexamethasone) versus no consolidation. In a subgroup of patients, 2 cycles of HDM + ASCT will be compared to 1 cycle of HDM + ASCT. Finally, the overall efficacy of these treatments in relation to clinical and molecular prognostic factors in multiple myeloma will be evaluated.

The rationale for including Bortezomib in VCD induction chemotherapy is based on the different mechanisms of actions and the potential synergism of Bortezomib with Cyclophosphamide and/or Dexamethasone. Previous observations showed that Bortezomib (1.3 mg/ m^2) can be safely combined with Doxorubicin and/or Dexamethasone (BD, PAD) or Cyclophosphamide and/or Dexamethasone. [15, 16, 26] Among these, the CR rate ranges from 10 to 20 % after induction, prior to transplantation. The VCD regimen (Bortezomib, Cyclophosphamide, Dexamethasone) combines good tolerability with high efficacy, which is not affected by unfavourable cytogenetic abnormalities (Einsele et al, ASH 2009, abstract # 131).

Since, several regimens have combined Bortezomib with a variety of other conventional drugs and/or Thalidomide or Lenalidomide. More recently, the combination of Bortezomib, Lenalidomide and Dexamethasone has been tried in refractory/relapse patients resulting in high response rates (PG Richardson, ASH 2007). This regimen has subsequently been used for induction in previously untreated patients, resulting in a 100% response rate including CR and VGPR (ASH 2008 #92).
In another setting, Bortezomib has been combined with Melphalan/Prednisone for patients who were not eligible for transplantation resulting in a high CR (35 %) and significant prolongation of remission duration and survival.[23, 25]
These results have prompted the rationale for the use of Bortezomib during induction therapy of MM. In addition, the results of VISTA show response and CR rates which are equivalent to those observed with high-dose therapy and stem cell transplantation. Therefore, it seems feasible to compare the standard treatment of induction followed by high-dose therapy and stem cell transplantation with a Bortezomib based approach that includes the same induction followed by VMP.
Secondly, it is time to examine whether consolidation treatment using an effective combination of Bortezomib and Lenalidomide (VRD) may further improve the CR rate, progression-free survival and overall survival.
During the 4th Trialist Forum of the European Myeloma Forum (EMN), held in May 2011, response data after VCD (not from the EMN02/HOVON 95 MM) were presented by prof. Einsele. The response rate seemed somewhat lower than what had been reported previously after Velcade, Thalidomide, Dexamethason (VTD). Therefore it was decided to perform an additional analysis - although not specified in the protocol - in the first 80 registered patients, of response after VCD. This analysis, performed in April 2012, showed a VGPR+CR rate of only 28%. During the 5th Trialist Forum meeting, held in May 2012, it was therefore decided to give 4 cycles of VCD instead of 3 cycles of VCD.

6 Study objectives

- To assess the efficacy of VMP versus high-dose therapy (HDT) and stem cell transplantation in patients with previously untreated multiple myeloma, as measured by the progression free survival.
- To evaluate the effect of consolidation with VRD followed by Lenalidomide maintenance with no consolidation but Lenalidomide maintenance alone on progression free survival.
- To compare VMP versus single HDT+ ASCT; or VMP versus tandem HDT + ASCT; or single versus tandem HDT + ASCT.

- To compare overall response rate and CR + VGPR (complete and very good partial response) after induction therapy, after VMP or HDT, after consolidation and during maintenance.
- To evaluate overall survival.
- To assess safety and toxicity
- To assess the prognostic value of risk factors at diagnosis, including β2-microglobulin, FISH abnormalities del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p as analyzed in purified bone marrow plasma cells with respect to progression free survival.
- To analyze the prognostic value of myeloma gene expression profiles on the overall response on induction of all patients and of patients treated in the different randomization arms.
- To assess quality of life.

7 Study design

Details of all treatments (dose and schedule) are given in chapter 9.
Patients with multiple myeloma, meeting all eligibility criteria (see paragraph 8) will be registered on entry and treated with 4 induction cycles with VCD, followed by Cyclophosphamide for stem cell mobilization and collection.
After induction patients will be randomized to compare two intensification regimens VMP vs. HDM (R1), except if a patient will proceed to allogenic SCT (see 9.8). In hospitals with a policy of double intensification, all patients will be randomized at R1 between VMP, 1 HDM and 2 HDM, in order also to evaluate 1 HDM vs. 2 HDM (also see 15.1)
After intensification treatment there will be a 2nd randomization to compare VRD consolidation vs. no consolidation (R2), followed by Lenalidomide maintenance in both arms.

It is the intention that all patients should follow this study scheme. However it is possible that a patient is not eligible for randomization and treatment in one of the randomization arms is not possible. In that case, the patient should continue treatment without randomization in the other treatment arm if possible. This is described in detail in chapter 9.

8 Study population

8.1 Eligibility for registration

All symptomatic multiple myeloma patients who fullfill the eligibility criteria below have to be registered before start of treatment.
Asymptomatic patients will be registered according to the correlative study (see chapter 20)

8.1.1 Inclusion criteria

- Patients with a confirmed diagnosis of symptomatic multiple myeloma stage I to III according to the International Staging System ISS (see appendix A), i.e. at least one of the CRAB criteria should be present;
- Measurable disease as defined by the presence of M-protein in serum or urine (serum M-proteïn > 10 g/l or urine M-proteïn > 200 mg/24 hours or abnormal FLC ratio with involved free light chain (FLC) > 100 mg/l) or proven plasmacytoma by biopsy;
- Age 18-65 years inclusive;
- WHO performance status 0-3 (WHO=3 is allowed only when caused by MM and not by co-morbid conditions) (see appendix D);
- Negative pregnancy test at inclusion if applicable;
- Written informed consent.

8.1.2 Exclusion criteria

- Known intolerance of Boron;
- Systemic AL amyloidosis;
- Primary Plasmacell Leukemia;
- Non-secretory MM;
- Previous chemotherapy or radiotherapy except local radiotherapy in case of local myeloma progression or corticosteroids maximum 5 days for symptom control;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E);
- Significant hepatic dysfunction (serum bilirubin $\geq$ 30 mmol/l or transaminases $\geq$ 2.5 times normal level), unless related to myeloma;
- Patients with GFR <15 ml/min,
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- Patients with neuropathy, CTC grade 2 or higher;

- Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;
- Patients who are not willing or capable to use adequate contraception during the therapy (all men, all pre-menopausal women);
- Lactating women.

8.2 Eligibility for randomization 1

8.2.1 Inclusion criteria

- WHO performance 0-2;
- Bilirubin and transaminases < 2.5 times the upper limit of normal values;
- A suitable stem cell graft containing at least 4 x 10^6 CD34+ cells/kg (or according to national guidelines).

8.2.2 Exclusion criteria

- Severe pulmonary, neurologic, or psychiatric disease;
- CTCAE grade 3-4 polyneuropathy during Bortezomib treatment;
- Allogeneic Stem Cell Transplantation (Allo SCT) planned;
- Progressive disease.

8.3 Eligibility for randomization 2

Eligible patients will be randomized 8 weeks after HDM or the last dose of VMP

8.3.1 Inclusion criteria

- Bilirubin and transaminases < 2.5 times the upper limit of normal values;
- ANC $\geq$ 0.5 x 10^9/l and platelets > 20 x 10^9/l;
- Patient is able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan.

8.3.2 Exclusion criteria

- Progressive disease;
- Neuropathy, except CTCAE grade 1;
- CTCAE grade 3-4 polyneuropathy during Bortezomib treatment.

9 Treatment

All men and pre-menopausal women should use adequate contraception during the study. Sperm should be frozen from men with child wish before start of treatment.

9.1 VCD induction phase

9.1.1 Treatment schedule

All patients will receive 4 cycles of VCD by rapid infusion, according to the schedule below:

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Agent	Dose/day	Route	Days
Bortezomib	1.3 mg/m^2	s.c.	1,4,8,11
Cyclophosphamide	500 mg/m^2	i.v. rapid infusion	1,8
Dexamethasone	40 mg	p.o.	1, 2, 4, 5,8, 9,11, 12,

Cycle 2 will start at day 22, cycle 3 will start at day 43, cycle 4 will start at day 64.

For patients with GFR 15 - 30 ml/min: Dose reduction of Cyclophosphamide to 400 mg/m^2 will be applied for the first cycle. If tolerated without neutropenia (ANC<1.0 x 10^9/l), increase to full dose at next cycle.
Patients will be evaluated for response after cycle 4 as described in appendix B.
In case of progressive disease patients will go off protocol treatment.

All other patients who meet the inclusion criteria for Cyclophosphamide and stem cell collection will continue with Cyclophosphamide (4 g/m^2) + G-CSF, independent from the response after VCD.
Patients who do not meet the eligibility criteria for stem cell collection will not be randomized but may continue with VMP and may be randomized in the 2nd randomization.

9.1.2 Special management in conjunction with Bortezomib during VCD therapy

Patients may be treated on an outpatient basis. The appropriate amount of Bortezomib will be drawn from the injection vial and administered subcutaneously. 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 thrombocytopenia and neuropathy that may have occurred after the previous dose(s).

It is strongly recommended to give prophylactic treatment for pneumococcus infections, PCP prophylaxis and anti-fungal prophylaxis according to local protocols. Acyclovir prophylaxis, 200-400 mg daily, profylactic Valaciclovir 2 x 500 mg daily, is mandatory to reduce/abrogate the risk of Herpes Zoster infection during Bortezomib-based treatment.
See chapter 9.9 for dose modifications of Bortezomib in case of toxicities.

9.2 Stem cell mobilization and collection

All eligible patients will be given Cyclophosphamide followed by G-CSF for stem cell collection. Cyclophosphamide will start 4-6 weeks after start of the fourth VCD cycle.

9.2.1 Eligibility criteria for Cyclophosphamide and stem cell collection

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

9.2.2 Stem cell mobilization with Cyclophosphamide and G-CSF

In all eligible patients stem cell collection will be performed after priming with Cyclophosphamide and G-CSF, according to local protocols.

Agent	Dose/day	Route	Days
Cyclophosphamide	2000 mg/m^2	i.v.	1
G-CSF (filgrastim)	10 μg/kg (divided in 2 gifts daily, according to local rules)	s.c.	day 5 until last leucopheresis

Alternative mobilization procedures are acceptable for individual study groups. These procedures need to represent the established clinical practice in the respective country, and be specified in a respective country-specific addendum of the trial.

9.2.3 Special management orders in conjunction with Cyclophosphamide

Selective gut decontamination may be performed according to local protocols.

9.2.4 Stem cell collection

Stem cell collection will be performed as soon as $CD34^+$ cells are present in peripheral blood, which is usually between 9-14 days after first day of Cyclophosphamide. Stem cells will be harvested at a minimum of 4 x 10^6 $CD34^+$ cells/kg and cryopreserved. In case insufficient stem cells are collected the procedure may be repeated or alternatively bone marrow stem cell collection may be performed.

All patients who meet the eligibility criteria for randomization 1 will be randomized between VMP or HDM. In hospitals with a policy of double intensification, patients will be randomized between VMP, 1 HDM and 2 HDM.

All other patients will go off protocol treatment with the exception of:

- **Patients who have to stop Bortezomib treatment because of CTCAE grade 3- 4 toxicity during induction with VCD. These patients will not be randomized at the 1st or 2nd randomization. They stay on protocol and will continue to be treated according to the HDM1 or HDM 2 schedule and with Lenalidomide maintenance.**
- **Patients who do not fulfill the criteria for succesfull stem cell harvest. These patients will not be randomized for VMP vs HDM. They will be treated with VMP and may still be randomized for consolidation treatment.**

9.3 Intensification with High Dose Melphalan

All patients randomized to intensification with High Dose Melphalan will start intensification with HDM between 4 and 6 weeks after stem cell collection.

9.3.1 High Dose Melphalan followed by stem cell reinfusion

Patients will be treated with High Dose Melphalan followed by autologous stem cell reinfusion according to the schedule below.

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

* Patients with renal insuffency 100 mg/m² only at day –3.

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

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

9.3.3 Supportive care during Melphalan 200 mg/m² induced aplasia

- Placement of an indwelling central venous catheter;
- Anovulatory drugs for menstruating females;
- Antibacterial and antifungal prophylactic antibiotics ;
- Antistreptococcus prophylaxis is recommended from day +4 until day +14.
- G-CSF 3 μg/kg/d from day +5 until hematological recovery is optional

9.3.4 Second course of Melphalan 200 mg/m^2 total followed by stem cell reinfusion

If a patient is randomized to receive 2 HDM + ASCT a second course of High Dose Melphalan may be administered between 2 and 3 months after the first course when the patient achieved at least PR.
Patients have to meet the eligibility criteria for randomization 1 before starting the second course.
Patients will be evaluated for response after each course of High Dose Melphalan. Patients with progressive disease will go off protocol treatment

All patients who meet the eligibility criteria for randomization 2 will be randomized between consolidation with VRD or no consolidation.
Patients who do not meet the eligibility criteria may continue with Lenalidomide maintenance.

9.4 Intensification therapy with VMP

All patients randomized to VMP treatment, will be treated with Bortezomib, Melphalan, Prednisone (VMP, 4 cycles) and will start intensification with VMP between 4 and 6 weeks after stem cell collection.

Agent	Dose/day	Route	Days
Bortezomib	1.3 mg/m^2	s.c.	days 1,4,8,11,22, 25, 29, 32
Melphalan	9 mg/m²	p.o.	days 1–4
Prednisone	60 mg/m²	p.o.	days 1-4

Cycle 2 will start at day 43, cycle 3 will start at day 85, cycle 4 will start at day 127.
Patients will be evaluated for response after the 2nd and 4th course of VMP. Patients with progressive disease will go off protocol treatment.

All patients who meet the eligibility criteria for randomization 2 will be randomized between consolidation with VRD or no consolidation.
Patients who do not meet the eligibility criteria may continue with Lenalidomide maintenance.

9.5 Consolidation therapy with VRD

In patients randomized to consolidation treatment, 2 cycles of Bortezomib, Lenalidomide, Dexamethasone (VRD) will start at 8 weeks after the end of the last course of VMP or HDM.

Agent	Dose/day	Route	Days
Bortezomib	1.3 mg/m^2	s.c.	days 1,4,8,11
Lenalidomide	25 mg	p.o.	days 1–21
Dexamethasone	20 mg	p.o.	days 1,2,4,5,8,9,11,12

Cycle 2 will start at day 29.
Patients will be evaluated for response after the 2nd course of VRD. Patients with progressive disease will go off protocol treatment.

Patients will continue to Lenalidomide maintenance. Patients who do not tolerate Lenalidomide will go off protocol treatment.

9.6 Maintenance therapy with Lenalidomide

In patients who did not receive consolidation treatment with VRD Lenalidomide maintenance will start 8 weeks after the end of the last course of VMP or HDM
In patients who received consolidation treatment with VRD, Lenalidomide maintenance will start immediately after the end of the last course of consolidation.

Lenalidomide maintenance can only start if ANC $\geq$ 0.5 x 10^9/l and platelets > 20 x 10^9/l

Agent	Dose/day	Route	Days
Lenalidomide	10 mg	p.o.	days 1–28

Cycles will be repeated at day 29 until relapse/progression.
See chapter 9.8 for dose modifications of Lenalidomide in case of toxicities.

9.7 Dose adjustments during VCD, VMP and VRD

9.7.1 Induction with VCD

Cyclophosphamide dose modifications

For grade 4 hematological and grade 3-4 non-hematological toxicities specifically related to cyclophosphamide, the drug should be held for up to 4 weeks until the toxicity resolves to grade 2 and dose decreased as follows:

Cyclophosphamide dose reduction steps

Starting dose Cyclophosphamide 500 mg/m^2 days 1, 8, 15
Dose Level 0 Cyclophosphamide 400 mg/m^2 days 1, 8, 15
Dose Level-1 Cyclophosphamide 300 mg/m^2 days 1, 8, 15
Dose Level-2 Cyclophosphamide 200 mg/m^2 days 1, 8, 15

Initiation of a new VCD cycle

In order to initiate a new cycle of VCD, the following parameters must be met:

- ANC > 1.0 x 10^9/L
- Platelet count > 75 x 10^9/L
- All non-hematologic side effects must be resolved to at least < grade 2

If those parameters are not satisfied, then delay the start treatment for a week (with a maximum of 4 weeks) and follow instructions for dose modification.

Dexamethasone dose modifications

For grade 3-4 non-hematological toxicities specifically related to dexamethasone the dose should be decreased as follows:

Dexamethasone dose reduction steps

Starting dose Dexamethasone 40 mg days 1, 2, 4, 5, 8, 9, 11, 12

Dose Level 0 Dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12

Dose Level-1 Dexamethasone 10 mg days 1, 2, 4, 5, 8, 9, 11, 12

9.7.2 Intensification with VMP

Melphalan and Prednisone dose modifications for non-hematologic toxicity

If a subject experiences any grade 3 or 4 non-hematological toxicity considered by the investigator to be drug-related, then Melphalan and Prednisone are to be held until the toxicity returns to at least grade 2 or less. After recovery of the toxicity to a level allowing continuation of therapy, a dose reduction should be instituted for Melphalan.

Prednisone dose reduction should only occur in case of and after recovery from grade 3 or 4 corticosteroid toxicities.

Melphalan and Prednisone dose modifications

For Melphalan, 2 dose reductions are permitted (25% and 50%)

For Prednisone, 2 dose reductions are permitted (25% and 50%).

Melphalan dose modification for hematologic toxicity

All following hematological parameters must be met on the first day of a new course:

- Platelet count > 75 x 10^9/L
- ANC > 1.0 x 10^9/L

If the above parameters are not met, the start of the next course will be held for a week (with a maximum of 4 weeks) until recovery above these levels is noted.

Neutropenia

If grade 4 neutropenia, with a duration of 5 days or more, was observed the Melphalan dose will be reduced by 25% (9 mg/m^2 to 6.75 mg/m^2) in the next cycle. The start of the next cycle will be held until recovery of toxicity to a level allowing continuation of therapy.

Alternatively, the current dose of Melphalan can be continued if colony stimulating factors (such as G-CSF or GM-CSF) support is provided.

If grade 4 neutropenia, with a duration of 5 days or more, recurs then an (additional) 25% reduction in the Melphalan dose is indicated. Alternatively, if prophylactic treatment with colony stimulating factors had not been started, this may be instituted instead of a further dose reduction.

Thrombocytopenia

If thrombocytopenia (with a platelet count < 25 x 10^9/L) was observed in the previous cycle, the Melphalan dose will be reduced by 25% (9 mg/m^2 to 6.75 mg/m^2) in the next cycle. The start of the next cycle will be held until recovery of toxicity to a level allowing continuation of therapy. If thrombocytopenia recurs, an additional 25% reduction in the Melphalan dose is required (6.75 mg/m^2 to 4.50 mg/m^2).

Dose interruption or study discontinuation is not required for lymphopenia of any grade.

Dose (re-)escalations of Melphalan are not allowed.

9.7.3 Consolidation with VRD

For grade 3-4 non-hematological toxicities specifically related to dexamethasone the dose should be deceased as follows:

Dexamethasone dose reduction steps

Starting dose Dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12

Dose Level 0 Dexamethasone 10 mg days 1, 2, 4, 5, 8, 9, 11, 12

9.8 Dose adjustments of Lenalidomide

9.8.1 Consolidation therapy with VRD

The start dose of lenalidomide will be reduced depending on renal function. Patients with impaired renal function (calculated or measured creatinine clearance < 50 mL/minute) will have lenalidomide dose reduction as outlined in the appendix at the end of this paragraph, otherwise they will receive full dose Lenalidomide (25 mg).

Table 1 outlines the dose modification instructions to be followed for hematological toxicity during a cycle in the Consolidation Phase.

Table 1: Dose modification for hematological toxicity during consolidation cycle

NCI CTC TOXICITY GRADE	Lenalidomide dose modification
Grade 3	No action
Grade 4 neutropenia (ANC 0.5 x 10^9/L) > 4 days	Hold therapy. If the subject was not receiving G-CSF therapy, initiate G-CSF therapy. If neutropenia has been overcome by G-CSF, on day 1 of next cycle, continue G-CSF as needed and maintain dose of lenalidomide if neutropenia was the only toxicity. Otherwise, decrease by one dose level at start of next cycle.
Grade 4 thrombocytopenia (PLT < 25 x 10^9/L)	Hold therapy. Decrease by one dose level when dosing restarted at next cycle.
Grade 4 anemia (Hb < 6.5 g/dl in the absence of bleeding and despite therapy with an erythropoietin agent)	Hold therapy. Decrease by one dose level when dosing restarted at next cycle if anaemia study-drug related.

Table 2 outlines the dose modification instructions to be followed for non-hematological toxicity during a cycle in the Consolidation Phase.

Table 2: Dose modification for non-hematological toxicity during consolidation cycle

NCI TCT TOXICITY GRADE	Lenalidomide dose modification
Rash Grade 2 Grade 3 Grade 4	 Add antihistaminic therapy Hold therapy, add antihistaminic therapy and decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1). Discontinue study drug and discontinue subject from study.
Constipation ≥ Grade 3	Hold therapy. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ Grade 2).
Thrombosis/embolism ≥ Grade 3	Hold therapy. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold therapy. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Peripheral Neuropathy Grade 3 Grade 4	Hold therapy. Decrease by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ Grade 1). Discontinue study drug and discontinue subject from study.
Other ≥ Grade 3 lenalidomide-related adverse events	Hold therapy. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ Grade 2).

Table 3: Lenalidomide dose reduction steps

Starting dose	Lenalidomide 25 mg daily for 21 days every 28 days
Dose Level-1	Lenalidomide 15 mg daily for 21 days every 28 days
Dose Level-2	Lenalidomide 10 mg daily for 21 days every 28 days
Dose Level-3	Lenalidomide 7.5 mg daily for 21 days every 28 days
Dose Level-4	Lenalidomide 5 mg daily for 21 days every 28 days
Dose Level-5	Lenalidomide 2.5 mg daily for 21 days every 28 days

Initiation of a new VRD cycle

In order to initiate a new cycle of VRD, the following parameters must be met:

- ANC > 1.0 x 10^9/L
- Platelet count > 75 x 10^9/L
- All non-hematologic side effects must be resolved to at least < grade 2

If those parameters are not satisfied, then hold treatment for a week (with a maximum of 4 weeks) and follow instructions for dose modification.

Appendix

Lenalidomide design for patients with impaired renal function

Renal Function (CLCr)	**LENALIDOMIDE DOSE**
Mild (CLCr ≥50 mL/min)	25 mg once a day (full dose)
Moderate (CLCr ≥30 to <50 mL/min)	10 mg once a day Dose may be escalated to 15 mg once a day after 2 cycles if patient is not responding to treatment
Severe (CLCr <30 mL/min, *not* requiring dialysis)	15 mg once per 48 hr
ESRD (CLCr <30 mL/min, requiring dialysis)	15 mg 3 times a week following each dialysis

9.8.2 Maintenance therapy

Special management with Lenalidomide maintenance requires anti-thrombotic prophylaxis according to international guidelines [27]. In case of hematological and non-hematological toxicity the following algorithm for dose reduction should be followed:

Dose Levels for Lenalidomide during Maintenance Therapy

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

Dose Modification Instructions for Lenalidomide for Haematologic Toxicity* during Maintenance

Toxicity	Lenalidomide Dose Modification
Neutropenia (Neutrophil < 0.5 x 10^9 /L) Grade 4 neutropenia (ANC < 0.5 x 10^9 /L) or Febrile neutropenia (fever ≥ 38.5 °C and ANC < 1 x 10^9 /L)	Stop the dose for remainder of cycle. If ANC is recovered / febrile neutropenia is resolved start next cycle. Decrease by 1 dose level when dosing restarts at next cycle.
Grade 4 Thrombocytopenia (Platelets < 25 x 10^9 /L)	Stop the dose for remainder of cycle. If platelets are recovered start next cycle. Decrease by one dose level when dosing restarts at next cycle.

* Exclude other causes, especially progressive disease.

Dose Modification Instructions for Lenalidomide for Non-Haematologic Toxicity during Maintenance

Toxicity	Dose modification Lenalidomide
Rash = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue Lenalidomide and discontinue subject from study
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing 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 dosing 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 dosing restarted at next cycle at discretion of treating physician

9.9 Dose adjustment of Bortezomib

Before each Bortezomib dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s).
In this protocol separate guidelines will be followed for Bortezomib-induced peripheral neuropathy (BiPN) and all other toxicities.

Neuropathic pain and/or peripheral sensory neuropathy

Patients who experience Bortezomib related neuropathic pain and/or peripheral sensory neuropathy are to be managed strictly as soon as BiPN grade 1 or higher occurs.
In case of any Bortezomib-induced Peripheral Neuropathy (BiPN), i.e. grade ≥1 neuropathic pain and/or grade ≥ 2 peripheral sensory neuropathy, the schedule of Bortezomib should be changed from 1.3 mg/m^2 twice weekly to 1.3 mg/m^2 once weekly. If BiPN does persist or further deteriorates, the dose of Bortezomib should be adapted as described in Appendix F. Once patients have been changed from full schedule to an attenuated schedule of Bortezomib, this should be used during the entire treatment with VCD, VMP and VRD, if applicable.

Non BiPN toxicities

All other toxicities observed at any time 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

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

Hematological toxicities

For grade 4 hematological toxicities, Bortezomib is to be withheld for up to 4 weeks until the following values are reached: hemoglobin ≥ 4.4 mmol/l (7.0 g/dl), ANC ≥ 0.5 x 10^9/l, and platelet count ≥ 50 x 10^9/l.
Dose interruption or treatment discontinuation is not required for lymphopenia of any grade.

Non-hematological toxicities

For any grade ≥ 3 non-hematological toxicities, Bortezomib is to be withheld for up to 4 weeks until the toxicity returns to grade 2 or less.
If the toxicity does not resolve after dosing has been withheld for 4 weeks, then the patient must be discontinued from Bortezomib and continue as described in section 9.

Dose adjustments of Bortezomib in case of non- BiPN toxicities

If withholding the Bortezomib dosing results in resolution of the toxicity to grade 2 or less within 14 days, Bortezomib may be restarted at a once weekly dose, i.e. dosing days 1,8,15 (VCD, VRD) or days 1,8,15,22,29,36 (VMP) without dose adaptions.

If Bortezomib has to be withheld for 15-28 days, Bortezomib may be restarted at a once weekly dose however the dose should be reduced by 25%, as follows:

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

9.10 Non-Myeloablative allogeneic stem cell transplantation

Patients with an HLA-identical sibling or unrelated donor may proceed to non-myeloablative allogeneic stem cell transplantation after intensification according to the center's discretion. These patients should not be included in the two randomizations. Once they are allocated to non-myeloablative AlloSCT, they will be treated with 4 courses of VCD, followed by Cyclophosphamide and stem cell apheresis. Next these patients will receive intensification with High Dose Melphalan 200 mg/m^2 followed by peripheral blood stem cell reinfusion according to protocol before proceeding to non-myeloablative AlloSCT between 2 and 6 months after the last intensification cycle. Due to the excellent survival of patients with standard risk features treated with novel anti-myeloma agents it is strongly recommended to restrict Allo-SCT to patients with high risk features including 17P-, (t) 4/14, (t) 14/16, and 1p/q abnormalities as determined by FISH in combination with ISS II/III.

In participating countries and centers patients will be included in the correlative study described in appendix H. In non-participating countries local and/or national protocols will be used.

9.11 Bisphosphonates

It is strongly recommended to start treatment with i.v. bisphosphonates at diagnosis and to continue this treatment every 4-6 weeks for maximum of 2 years. After 2 years, i.v. bisphosphonates may be stopped in patients with CR or at the discretion of the treating physician. A commonly used regimen consists of zoledronate 4 mg i.v. or pamidronate (APD) 30 mg i.v. once every 4 weeks.

9.12 Concomitant medication

9.12.1 Guidelines for platelet transfusions

Thrombocytopenia can occur as a consequence of bone marrow infiltration by myeloma cells or may be related to study drug administration. The clinical significance of thrombocytopenia experienced by a patient should be assessed in light of its etiology (Bortezomib or disease or both), the state of the underlying myeloma (stable versus worsening disease), and whether the patient is bleeding or being prepared for a surgical procedure.

The use of any platelet product should be considered in the following circumstances:

- As preparation for an invasive surgical procedure, transfuse in order to maintain a platelet count > 50 x 10^9/l to prevent bleeding.
- If the patient has an active infection, high fever, rapid decrease in platelet count to ≤ 20 x 10^9/l and/or coagulopathy, transfuse to maintain a platelet count to > 20 x 10^9/l as prophylaxis for spontaneous bleeding.
- If the patient is actively bleeding or has a platelet count below 10 x 10^9/l, transfuse in order to maintain a platelet count > 10 x 10^9/l.

9.12.2 Guidelines for red cell transfusions

The use of any red cell product should be considered in the following circumstances:

- If the patient has a hemoglobin < 4.3 mmol/l, transfuse to maintain a hemoglobin > 5.0 mmol/l in order to reduce the risk of inadequate oxygenation.
- If the patient is asymptomatic and has a hemoglobin between ≥ 4.3 and ≤ 5.0 mmol/l, the investigator may consider transfusion on a per-patient basis in order to maintain a hemoglobin > 5.0 mmol/l.
- If the patient is actively bleeding or has symptomatic cardiac or pulmonary disease or other extenuating circumstances where oxygenation is impaired, the investigator may elect to transfuse on a per-patient basis. In these instances, the trigger hemoglobin value may be > 5.0 mmol/l.
- The use of erythropoeitin (e.g. Eprex®/Erypo®) is allowed.

9.12.3 Forbidden concomitant medication during the study

- The use of steroids, other than < 10 mg Prednisone or equivalent, is not allowed.
- The use of antineoplastic therapy, other than protocol-specified study medication, is not allowed until progressive disease is established.

9.13 Study drug information

9.13.1 Physical description of study drugs

Bortezomib (Velcade®) for injection is an antineoplastic agent available for i.v. or s.c.use. Each single dose vial contains 3.5 mg Bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol.
Lenalidomide (Revlimid®) is an antineoplastic agent for oral use. Capsules of 5 mg, 10 mg, 15 mg and 25 mg are available. Patients must comply with the Lenalidomide (Revlimid®) Pregnancy Prevention Risk Management Program.

9.13.2 Packaging

All study medication will be dispensed in child-resistant packaging.
Bortezomib will be supplied as single-use vials containing 3.5 mg Bortezomib and 35 mg mannitol.
Lenalidomide will be supplied as capsules of 5 mg, 10 mg, 15 mg or 25 mg in blisters/wallets.

9.13.3 Drug supply

Bortezomib will be provided by Janssen Pharmaceuticals and shipped by B&C in Belgium.
Lenalidomide will be provided by Celgene International and shipped by Almac UK.

9.13.4 Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

9.13.5 Preparation and handling

Bortezomib for Injection drug product was found to be stable for at least 18 months under storage conditions from 2°C to 25°C with excursions permitted up to 30°C. The reconstituted product is preservative free and is chemically and physically stable for up to 8 hours when it is stored at 25 °C. The drug product is supplied in vials containing 3.5 mg of Bortezomib. The pharmacist must prepare the study drug under aseptic conditions. Each vial of Bortezomib for Injection should be reconstituted within 8 hours before dosing with 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains Bortezomib at a concentration of 2.5 mg/mL. The reconstituted solution is clear and colorless, essentially free from particles or foreign matter, and the pH of the reconstituted solution is approximately 5 to 6. Dissolution is completed in approximately 10 seconds.

Reconstituted Bortezomib for Injection should be administered promptly and in no case administered more than eight hours after reconstitution. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to eight hours in a syringe, however total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

Bortezomib for Injection drug product is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Bortezomib for Injection. Refer to published guidelines regarding the proper handling and disposal of anticancer agents. The pharmacist should prepare Bortezomib for Injection using a vertical laminar flow biological cabinet (hood) and proper aseptic techniques. It is recommended that gloves and protective garments be worn during preparation.

In case of skin contact, wash the affected area immediately and thoroughly with soap and water and diluted hydrogen peroxide for 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

See appendix J for the Bortezomib injection sites.

9.13.6 Drug accountability

The local investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented.

Study drug must be handled strictly in accordance with the protocol and the container label and will be stored under appropriate environmental conditions. Contents of the study drug containers must not be combined.

The return of used study drug will be documented. Unused study drug and returned used study drug will be destroyed at the investigational site. Vials and tablets should be discarded in a safe manner. Destruction must be documented.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

10 End of protocol treatment

Reasons for going off protocol treatment are:

- Normal completion (after alloSCT)
- Excessive toxicity (including toxic death)
- Progression / relapse at evaluation moments.
- Intercurrent death
- No compliance of the patient (especially refusal to continue treatment)
- Pregnancy (of female patient)

11 Required clinical evaluations

Aim of the clinical evaluation at entry is to know in which ISS stage of disease the patients are classified and to determine the presence of adverse prognostic factors and establish a baseline for response evaluations. Aim of the clinical evaluation during treatment and follow up is to determine response, toxicities and eligibility for further treatment. Before start of each treatment cycle, routine investigations like blood cell count and renal function will be performed according to local policy.

11.1 Time of clinical evaluations

- At entry: before start of treatment (results from diagnostic tests may be used, provided that they are no older than 4 weeks prior to registration)
- After VCD IV: 4 weeks after start of the 4th VCD cycle
- After VMP: after the 2nd VMP and 4 weeks after end of the 4th VMP cycle
- After HDM: 8 weeks after each course of HDM
- After VRD: 4 weeks after end of the 2nd VRD cycle
- During maintenance/follow up: every 2 months (after relapse/progression every 6 months)

11.2 Required investigations

	At entry	After each VCD	After 4th VCD	After each VMP	After 2nd and 4th VMP	After each course HDM	After 2nd VRD	During maintenance/ follow up until progression every 2 months[7)]	At relapse/ progres-sion
Medical history	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X
Immunochemistry[1)]	X		X		X	X	X	X	X
Urine M-protein (Bence Jones)	X		X		X	X	X	X	X
Blood chemistry	X		X		X	X	X	X	X
Creatinin clearance	X		X		X	X	X		X
Bone marrow aspirate[2)]	X		X		X	X	X	X	X
Bone marrow biopsy	X								
Skeletal survey	X[8)]								
MRI	o.i.		o.i.		o.i.	o.i.	o.i.	o.i.	o.i.
Neurologic evaluation	X		X		X		X		X
Cardiac ejection fraction	o.i.								
ECG	X		X			X	X		X
X-thorax	X		X						
Sperm cryopreservation[3)]	X								
PB cryopreservation[4)]	X								X
BM cryopreservation[5)]	X								X
Pregnancy test [6)]	X								
Additional studies	X								

o.i. on indication

1) Includes immuno-electropheresis, immuno-fixation, quantitative serum free light-chain analysis.

2) At diagnosis and at every response evaluation moment when there is immunofixation negativity in serum and urine. Must be analysed on morphology for CR and for immunophenotyping to confirm stringent CR (sCR). Flowcytometric MRD evaluations should take place after 4th VCD, after 4th VMP, after each course of HDM, after 2nd VRD and every 6 months during maintenance treatment when there is immunofixation negativity in serum and urine.

3) For male patients with active child wish.

4) For SNP analysis and paired-end whole exome sequencing.

5) For Gene Expression Profiling, miRNA profiling and paired-end whole exome sequencing.

6) At entry, and before and during Lenalidomide treatment according to the Pregnancy Prevention Risk Management Plan.

7) During maintenance: haematology and immuno-chemistry tested every two weeks in the first month, then every four weeks.

8) Skeletal survey every 12 months.

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
- Previous chemotherapy or radiotherapy
- HLA typing of patient and family
- 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

At entry: PB cryopreservation for SNP analysis (see paragraph 11.6)

Blood chemistry

Complete blood chemistry should be performed at entry and in case of abnormal values. Otherwise serum creatinin, albumin, calcium and total proteins are routine evaluations.

- BUN
- Creatinin
- Liver enzymes
- Total bilirubin
- Alkaline phosphatase
- Total proteins
- Albumin
- Serum β2-microglobulin
- LDH
- CRP
- Calcium
- Phosphate
- Sodium
- Potassium
- Uric acid

Immunochemistry

- Quantitative serum immune-electropheresis for identification and quantification of M-protein
- Immunofixation to confirm CR
- Quantitative serum light chain (for screening only)
- The 24hr proteinuria should be determined, and in case of a positive result (>150 mg/24hrs) a urine electrophoresis should be performed (in order to distinguish between excretion of albumin (and other proteins) and paraproteins. This will allow quantification of 24hr paraproteinuria also
- Quantitative urine M-protein (Bence Jones) in 24 hrs urine, including immunofixation to confirm CR

Only at entry:

- Qualitative serum M-protein
- Qualitative urine M-protein (Bence Jones)

Bone marrow

- Bone marrow biopsy
- Bone marrow aspirate at entry for:
  - Morphology, immunophenotyping
  - Labeling Index (by BRDU) or KI-67 (facultory)
  - FISH analysis (see 11.3)
  - Molecular analysis (Plasma cell purification and cryopreservation for RNA microarray analysis, see for collecting and handling of samples for RNA microarray analysis see 11.6)
- Bone marrow aspirate during treatment and follow up (when needed to confirm CR) for:
  - Morphology
  - Immunophenotyping

Specific investigations

- Creatinin clearance if increased serum creatinin
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones
- X-Thorax
- ECG
- 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.

Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis
- Bleeding time
- Cryoglobulins, cold agglutins
- Serum viscosity, funduscopy
- Spirometry

11.3 Cytogenetic analysis

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

11.4 Immunophenotyping

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

11.5 MRD analysis

In this trial the importance of flowcytometric Minimal Residual Disease (MRD) negativity will be investigated in a correlative study. Patients who are immunofixation negative in serum and urine need to undergo a bone marrow puncture in order to confirm flowcytometric MRD negativity. A bone marrow puncture needs to be performed at every response evaluation moment at which there is immunofixation negativity. Flowcytometric MRD analyses are typically performed regionally with an 8 colour FACS machine using the EMN-02 MRD protocol. At the 2-monthly examinations mandatory serum immunofixation and serum free light levels will be repeatedly performed, in order to mark the point when a patient turns from MRD-negative (=immunofixation-negative) to MRD-positive (=immunofixation-positive), i.e. before a clinical relapse has occurred. These immunofixations and serum-free light assessments can be performed locally. (See section 20.1)

11.6 Gene expression profiling, miRNA profiling, paired-end whole exome sequencing & single nucleotide polymorphism (SNP) analysis

Gene expression profiling, miRNA profiling, paired-end whole exome sequencing and SNP analysis will be performed to further characterize MM subgroups at the molecular level, to find new biomarkers with prognostic value, to elucidate mechanisms of drug resistance & disease progression and identify SNPs related to treatment outcome and side-effects. Bone marrow samples, peripheral blood and saliva will be drawn in the designated central treatment centres at the time of asymptomatic MM, at the time of symptomatic MM before start of treatment and at relapse/progression. Samples are handled according to the procedure described in the lab manual.

Since there are inter-ethnic differences in frequency of SNPs, it is necessary to document the ethnicity of patients included in the trial. This will allow us to perform multivariate analysis to find whether a certain SNP is an independent prognostic factor.

11.7 Response evaluation

Response will be evaluated according to the IMWG criteria [28] (see appendix B).
Time points are after the 4th VCD cycle, after the 2nd and 4th cycle of VMP, after each cycle of HDM, after the 2nd cycle of VRD and every 6 months during maintenance.

11.8 Quality of Life assessment

The EORTC QLQ-C30 version 3.0 questionnaire will be used supplemented by the myeloma module MY-24. The QLQ-C30 is a multidimensional, cancer-specific quality-of-life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC) Study Group on Quality of Life for use in international clinical trial settings.The QLQ-C30 includes 5 functional scales (physical, role, emotional, social and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life scale and a number of single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation and diarrhea) and perceived financial impact. For the majority of the QLQ-C30 items a 4-point Likert-type response scale is used. Exceptions are the items for the global quality of life scale (where a 7-point scale is used). All subscale and individual item responses are linearly converted to 0 to 100 scales. For the functional and global quality of life scales, a higher score represents a better level of functioning. For the symptom scales and items, a higher score reflects a greater degree of symptomatology

The QLQ-MY20 questionnaire contains 20 items, and is a reliable and valid instrument recommended for use in myeloma patients. The questionnaire contains the following scales: pain, side effects of treatment, social support, body image, and future prospectives
The frequency of the QoL assessments of the main protocol and of the Iron Deficiency Substudy coincides.
The first assessment will be done at registration before start of the initial VCD induction cycle to receive a baseline assessment. Thereafter a new questionnaire will be provided to the patient according to the following schedule:
- day 1 VCD cycle 4
- day 1 mobilization
- start HDM or VMP
- after HDM cycle 1 or VMP cycle 1
- after VRD cycle 2
- every 6 months during maintenance

The quality of life measurements will be stopped when patient goes off protocol treatment.

At entry the patient should be given an explanation of the objective of the questionnaire and instructions for filling out the questionnaires. The following issues should be explained to the patient:

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

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

12 Toxicity assessment

All the chemotherapeutic agents used in the protocol cause pancytopenia and can induce septic or hemorrhagic complications.

Bortezomib

Most common side effects of VELCADE (ie, incidence ≥30%) observed in subjects are thrombocytopenia and anemia; gastrointestinal effects such as constipation, diarrhea, nausea, and vomiting; fatigue, pyrexia, and peripheral neuropathy

Very common side effects of VELCADE (ie, incidence 10% to 29%) observed in subjects are neutropenia, abdominal pain (excluding abdominal pain arising from oral and throat gastrointestinal disorders), chills, peripheral edema, asthenia, upper respiratory tract infection, nasopharyngitis, pneumonia, Herpes zoster, decreased appetite, anorexia, dehydration, bone pain, myalgia, arthralgia, back pain, paresthesia, dizziness excluding vertigo, headache, anxiety, insomnia, cough, dyspnea, and rash.

Common side effects of VELCADE (ie, incidence 1% to 9%) observed in subjects are lymphopenia, pancytopenia, leucopenia, febrile neutropenia, tachycardia, atrial fibrillation, palpitations, cardiac failure congestive, blurred vision, conjunctivitis, conjunctival hemorrhage, dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage ± rectal hemorrhage, neuralgia, lethargy, malaise, chest pain, mucosal inflammation, lower respiratory tract infection, sinusitis, pharyngitis, oral candidiasis, urinary tract infection, sepsis, bacteremia, cellulitis, Herpes simplex, bronchitis, gastroenteritis, infection, fall, decreased weight, increased ALT, increased AST, increased blood alkaline phosphatase, abnormal liver function test, increased blood creatinine, hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia, muscular weakness, polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia, confusional state, renal impairment, renal failure, hematuria, epistaxis, exertional dyspnea, pleural effusion, rhinorrhea, hypoxia, pulmonary edema, pruritic rash, erythematous rash, urticaria, petechiae, hypotension, and orthostatic hypotension.

Uncommon side effects of VELCADE (ie, incidence <1%) observed in subjects are cardiogenic shock, atrial flutter, cardiac tamponade, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest, cardiac failure, pericardial effusion, pericarditis, pericardial disease, cardiopulmonary failure, deafness, hearing impaired, eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage, haematemesis, oral mucosal petechiae, ileus paralytic, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis,

intestinal obstruction, injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration, catheter-related complication, hyperbilirubinaemia, hepatitis, drug hypersensitivity, angioedema, septic shock, catheter-related infection, skin infection, disseminated Herpes zoster, lung infection, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis, aspergillosis, tinea infection, ophthalmic Herpes zoster, ophthalmic Herpes simplex, meningoencephalitis herpetic, varicella, empyema, fungal esophagitis, subdural haematoma, increased gamma-glutamyltransferase, decreased oxygen saturation, decreased blood albumin, decreased ejection fraction, limb discomfort, tumor lysis syndrome, convulsion, loss of consciousness, ageusia, encephalopathy, paralysis, autonomic neuropathy, reversible posterior leukencephalopathy syndrome, posterior reversible encephalopathy syndrome, delirium, micturition disorder, hemoptysis, acute respiratory distress syndrome, respiratory failure, pneumonitis, lung infiltration, pulmonary alveolar hemorrhage, interstitial lung disease, pulmonary hypertension, pleurisy, pleuritic pain, cutaneous vasculitis, leukocytoclastic vasculitis, and cerebral hemorrhage.
Complications arising from these Bortezomib toxicities may result in death.
The effect of Bortezomib on reproduction and its safety in pregnancy are unknown. Laboratory tests show that Bortezomib may damage DNA therefore it is possible that Bortezomib may cause infertility in men and women.
Further details on the potential risks of Bortezomib may be found in the Investigator Brochure.

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

Toxicities will be scored according to the NCI Common Toxicity Criteria, version 4.0 (Appendix C).

13 Safety

13.1 Definitions

Adverse event (AE)

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

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
- Second Primary Malignancy (SPM)
- 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), including suspected transmission of infectious agents by a medicinal product.

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).

13.2 Adverse event

13.2.1 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 electronic Adverse Events CRF for the relevant treatment phase. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 (see appendix C).
Comorbidities will be entered at baseline on the electronic CRF.

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
- Alopecia
- Nausea/vomiting
- Progression of the disease under study; complaints and complications as a result of disease progression remain reportable Adverse Events

13.2.2 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.

13.3 Serious Adverse Events

13.3.1 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.
SPM's should be reported from the first study-related procedure until the end of the follow up period.

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

- 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.

13.3.2 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.

13.3.3 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.

13.3.4 Processing of serious adverse event reports

The EMN Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator, Janssen-Cilag and Celgene International Sarl. The EMN Data Center will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The EMN Data Center will provide six-monthly line listings of all reported SAE's for EC submission as required by national regulation.

13.4 Reporting Suspected Unexpected Serious Adverse Reactions

The EMN Data Center, on behalf of the sponsor, will ensure the reporting of any SUSAR to the Competent Authorities (CA), J&JPRD and Celgene and the investigators in compliance with applicable laws and regulations, and in accordance with any trial specific agreements between the

sponsor and a co-sponsor or J&JPRD and Celgene. Each participating country will ensure the reporting of any SUSAR to the Ethics Committees (EC).
Expedited reporting of SUSARs will occur no later than 15 days after the EMN Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

13.5 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject, occurring while the subject is on protocol treatment or within 30 days following the last dose of any drug from the protocol treatment schedule, should be reported to the sponsor. Pregnancies, suspected pregnancies, or positive pregnancy tests must be reported to the EMN Data Center by fax immediately after the event was known to the investigator, using the pregnancy report form provided.

The investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor of the outcome of the pregnancy within 5 days or as specified below. The investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for 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 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 sponsor will forward any information regarding (suspected) pregnancies to Celgene immediately by phone at +41 32 729 8476 then by email DrugSafetyEurope@Celgene.com or by fax +41 32 729 8709 and to Janssen-Cilag (country specific local safety officer).

Contact details for Drug Safety Celgene International:
Celgene International Sarl
Route de Perreux 1

2017 Boudry
Switzerland
Tel: +41 32 729 8476
Fax: +41 32 729 8709
Email: DrugSafetyEurope@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 Risk Management Program.

13.6 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.

13.7 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, and J&JPRD and Celgene. The content of the annual safety report will be according to the EU guidance document

13.8 Data Safety and Monitoring Board

The Data and Safety Monitoring Board will advise the chair of the HOVON working group, the Principal Investigator and the Co-investigator(s) about the continuation of the study. The DSMB will evaluate the general progress and the feasibility of the study, the quality and completeness of the data, side effects and safety, and differences between the arms.

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 randomized clinical trials.

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), the chair of the HOVON working group involved and the chair of the EMN trialist group. 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 0)
- Early (safety) report, if applicable (as described in 0)

14 Endpoints

14.1 Primary endpoint

- For all registered patients: progression free survival (PFS) as defined by time from registration to progression or death from any cause (whichever occurs first).
- For all patients included in R1; PFS as defined by time from randomization R1 to progression or death from any cause whichever comes first
- For all patients included in R2; PFS as defined by time from randomization R2 to progression or death from any cause whichever comes first

14.2 Secondary endpoints

- Response (PR, VGPR, CR and stringent CR), and improvement of response during the various stages of the treatment
- Overall survival measured from the time of registration/randomization R1/ randomization R2. Patients still alive or lost to follow up are censored at the date they were last known to be alive.
- Toxicity
- Quality of life as defined by the EORTC QLQ-C30 and QLQ-MY20 definitions

15 Registration and Randomization

15.1 Regulatory Documentation

Before shipment of study drug to the investigational site and before enrollment of the first patient the following documents must be provided to HOVON Data Center, unless specified differently in the country/group specific addendum.

By the principal investigator or study coordinator for all sites within their country:

- name and address of the (central) Ethical Committee including a current list of the members and their function;
- any other documentation required by local regulations.

By the local investigator for each investigational site:

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

In addition to this each individual participating center should commit to either a **fixed** 1 HDM or a **random** 1 or 2 HDM policy in all patients.

- In hospitals with a **fixed** HDM policy, all patients will be randomized at R1 between VMP and 1 HDM.
- In hospitals with a **random** policy, all patients will be randomized at R1 between VMP, 1 HDM and 2 HDM.

Every participating center should make their policy clear to the HOVON Data Center before registration of the first patient by that particular center. It is not allowed to follow different policies for different patients in one individual participating center. (see also paragraph 9.3.4).

15.2 Registration and Randomization

15.2.1 Registration

The patient should be registered immediately after diagnosis and before the start of chemotherapy.

Patients will be registered at the EMN Data Center by web http://www.mm-sen.net. Investigators who do not have an account yet should register at this website to obtain an account.

The following information will be requested at registration:

- Institution name
- Name of responsible investigator
- Date of birth
- Date of informed consent
- Date of sample shipment (optional)
- Date of diagnosis of multiple myeloma
- Criteria for measurable disease
- Serum β2-microglobulin
- Serum albumin
- Eligibility criteria

All eligibility criteria will be checked with a checklist. ISS stage will be calculated from the provided serum β2-microglobulin value and serum albumin value.
Each patient will be given a unique patient study number.

15.2.2 Randomization 1

All patients eligible for randomization can be randomized at the EMN Data Center by web http://www.mm-sen.net
The following information will be required:

1. Protocol number
2. Patient's study number
3. Eligibility criteria

The result of randomization will be given immediately.Patients will be randomized, stratified by center and ISS stage (I vs. II vs. III) ensuring balance within each stratum and overall balance. Neither subjects nor treating physicians will be blinded to treatment.

It should be noted that the allocation ratio for R1 depends on the HDM policy, and is 1:1 (VMP vs 1 HDM) for centers with a fixed 1 HDM policy, and 1:1:1 (VMP vs 1 HDM vs 2 HDM) for centers with a random HDM policy.

15.2.3 Randomization 2

All patients eligible for randomization can be randomized at the EMN Data Center by web http://www.mm-sen.net
The following information will be required:

1. Protocol number
2. Patient's study number
3. Eligibility criteria

The result of randomization will be given immediately.
Patients will be randomized stratified by center and randomization 1 arm (VMP vs HDM vs not randomized), ensuring balance within each stratum and overall balance. Neither subjects nor treating physicians will be blinded to treatment.

16 Data collection and quality assurance

16.1 Case Report Forms

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

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

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

- Reason for end of protocol treatment.

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

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

All CRF entries must be based on source documents.

Serious Adverse Event and Pregnancy Notification forms will be sent by fax to EMN Data Center, where they will be entered in the database..

16.2 Reporting of Second Primary Malignancies

Second Primary Malignancies (SPM) should be reported as SAE during treatment and during the Follow Up period. The SAE form must be reported to the EMN Data Center by fax within 24 hours of the initial observation of the Second Primary Malignancy.
For each case of SPM occurring during treatment, contact the Principal Investigator to discuss if treatment needs to be discontinued.

16.3 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.

16.4 Monitoring

This trial is part of the HOVON Site Evaluation Visit program for HOVON sites. For other groups the EMN regulations will apply and monitoring will be described in the addendum. 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.

16.5 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 Statistical considerations

17.1 Patient numbers and power considerations

This study is designed to perform two subsequent randomizations with one main comparison each:

- a 1st randomization after induction, to compare two intensification regimens: VMP vs. HDM, hereafter to be denoted as R1;

- a 2nd randomization, after conclusion of the intensification regimens, to compare VRD consolidation vs. no consolidation, followed by Lenalidomide maintenance in both arms. This randomization will be denoted as R2.

In centers with a **random** HDM policy (see 15.1), all patients will be randomized at R1 between VMP, 1 HDM and 2 HDM, in order also to evaluate 1 HDM vs. 2 HDM. For the primary analysis of R1, patients randomized to 1 HDM and 2 HDM will be combined into the HDM arm.

All patients will be registered upfront. They will then receive 3 induction cycles with VCD, followed by Cyclophosphamide for stem cell mobilization and collection.

It is expected that about 85% of those initially enrolled, will be included in R1; 15% are assumed not to be randomized due to toxicity, early death or progression, or because an upfront allo-SCT is planned. Furthermore, it is assumed that some 30% of the patients in R1 will not fulfill the criteria for R2 due to progression, relapse, severe toxicity or death. This implies that about 60% of all registered patients will be included in both R1 and R2.

The sample size of the study has been calculated in order to have a sufficient number of patients available for R2 who were also randomized in R1; thereafter the statistical power for R1 has been determined.

For all sample size calculations, the same following assumptions have been used:

- Primary endpoint: progression free survival (PFS) from randomization;
- Median PFS in the control arms (VMP for R1, no consolidation for R2): 25 months from randomization;
- Median PFS in the experimental arms (HDM for R1, VRD for R2): 32 months from randomization, which is equivalent to a hazard ratio (HR) = 0.78;
- Significance level α = 0.05 (two-sided);
- The allocation ratio for R2 = 1:1. (Lenalidomide vs VRD followed by Lenalidomide),
- The allocation ratio for R1 depends on the HDM policy, and is 1:1 (VMP vs 1 HDM) for centers with a fixed HDM policy, and 1:1:1 (VMP vs 1 HDM vs 2 HDM) for centers with a random HDM policy,
- Accrual period: 30 months;
- Additional follow up after the last randomized patient: 24 months.

Sample size for R2

The number of events (i.e. progression or death) needed to detect a HR = 0.78 with 80% power (1 - β = 0.8) is 514. Assuming uniform accrual for 30 months and an additional follow up of 24 months, this implies 848 patients to be randomized in R2.

Number of patients to be registered

As we assume that about 60% of the initially registered patients will ultimately be included in both R1 and R2, a total of 848/0.60 = 1414 patients should have to be enrolled in the trial. In order to overcome dropout due to ineligibility, 1500 patients will be registered.

Statistical power for R1

We assume that about 15% of the registered patients will not be included in R1, which implies that 1414×0.85 = 1202 patients will be available for R1.

The power of VMP vs. HDM will depend on the number of patients that will be randomized by centers that participate in the 1 HDM vs. 2 HDM randomization. It is assumed that about 50% of the patients will be randomized by random HDM-policy centers. Consequently, the 1200 patients in R1 may approximately be divided as follows:

a) 300 patients from fixed HDM-policy hospitals randomized to VMP;
b) 300 patients from fixed HDM-policy hospitals randomized to 1 HDM;
c) 200 patients from random HDM-policy hospitals randomized to VMP;
d) 200 patients from random HDM-policy hospitals randomized to 1 HDM;
e) 200 patients from random HDM-policy hospitals randomized to 2 HDM.

In the analysis of VMP vs. HDM, we will in this case compare 500 VMP patients (a. and c.) with 700 HDM patients (b., d. and e.).

If these patients would be entered in 30 months, then after an additional 2 years of follow up, the power to detect a HR = 0.78 would be 92%, which would require 719 events. For a power of 80%, 507 events should have to be observed, which could theoretically be achieved 9 months after the last patients has been randomized.

Statistical power for 1 HDM vs. 2 HDM

The comparison of 1 HDM vs. 2 HDM will only be based on patients that could actually have been assigned to both 1 HDM or 2 HDM, so this will only be a comparison of d. versus e. in about 200 patients per arm.

If we use the same assumptions as for the other randomizations:

- Primary endpoint: PFS from randomization;
- Median PFS in the control arm (1 HDM): 25 months from randomization;

- Median PFS in the experimental arm (2 HDM): 32 months from randomization, which is equivalent to a hazard ratio (HR) = 0.78;
- Significance level α = 0.05 (two-sided);
- Allocation ratio = 1:1;
- Accrual period: 30 months;
- Additional follow up after the last randomized patient: 24 months.

This would give a power of (only) 49%.

Of course assuming a larger benefit might increase the power (median PFS of 35 months in the 2 HDM arm would imply a HR = 0.71, and a power of 73%). However, it should be stressed that it is not likely that we will have sufficient power to detect superiority of 2 HDM over 1 HDM. Nevertheless this analysis will give an estimate (HR with 95% confidence interval (CI)) of the possible benefit of 2 HDM. And these data might also be used in a meta-analysis should multiple trials pose the same question of 1 HDM vs. 2 HDM.

Expected accrual rate

It should be noted that with an expected accrual of 790 patients/year, the number of 1500 could be reached in about 2 years. However, it will take some time before all centers will be able to include patients into the trial. Therefore it is assumed that the accrual will take some 36 months.

The expected inclusion rates per country are:

Participants	Countries	PI	Recruitment/yr
HOVON	Netherlands, Belgium	Sonneveld	130
NMSG	Norway, Sweden, Finland, Denmark	Waage	150
GIMEMA	Italy	Cavo/Palumbo	240
DSMSG	Germany	Einsele	200
CEMSG	Austria, Hungary	Ludwig	70
Total			790

17.2 Statistical analysis

All analyses will be according the intention to treat principle, i.e. patients will be analyzed according to the treatment arms they were assigned to.

However, patients initially randomized but considered ineligible afterwards based on information that should have been available before randomization, will be excluded from the respective analyses.

17.2.1 Efficacy analysis

The main endpoint for both randomizations R1 and R2 will be PFS from the respective dates of randomization. The formal tests for difference in PFS between the two treatment arms will be done with a multivariate Cox regression analysis with adjustment for the stratification factor (ISS [I vs. II vs. III] for R1; randomization R1 arm [VMP vs HDM] for R2). The primary analysis of R2 will be restricted to patients also randomized in R1. A secondary analysis of R2 will also include those patients not randomized in R1, and then the analysis will be adjusted for R1-VMP vs R1-HDM vs not-randomized-in-R1. The actuarial method of Kaplan and Meier will be used to estimate PFS probabilities at appropriate time points, while the Greenwood estimate will be used to construct corresponding 95% CIs. Competing risk analysis will be used to calculate cumulative incidences of PFS, progression/relapse and death without progression (which add up to 100% at every time point). Kaplan-Meier curves will be generated to illustrate PFS, for all patients as well as by treatment arm. A Cox model will also be used to test for interaction between treatment arms of R1 and R2. Only if the interaction term is statistically significant at a 5% significance level, the comparison of VRD consolidation vs. no consolidation will also be shown separately for R1-VMP patients and R1-HDM patients. However, it should be noted that the study is not powered for this purpose.
PFS will also be the primary endpoint for the comparison 1 HDM vs. 2 HDM, and will be analyzed similar as described for R1. However, due to the probably limited power to detect an improvement of 2 HDM over 1 HDM, the main purpose for this analysis is merely to obtain an estimate of the HR with 95% CI.
The final analyses will not be performed until the required numbers of events have been observed (719 for R1, 514 for R2), and the data have been validated. However, R1 and R2 need not be analyzed at the same time. As there will be two interim analyses for each endpoint, the critical P-value for the final analysis will be 0.045 instead of 0.05, see paragraph 17.3.

Secondary efficacy endpoints are response rate and overall survival from R1 and R2.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events CTCAE grade 2 or more (Appendix C) by treatment arm and cycle. Data from all subjects who receive any study drug will be included in the safety analyses. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE grade. In the case that the adverse events or event frequencies are judged to be clinically important, an exact test will be used to analyze the difference between the treatment groups.

17.2.3 Additional analyses

Additional analyses may involve the analysis of prognostic factors, especially FISH abnormalities, ISS stage and molecular profiles (GWAS, GEP) with respect to PFS, response rate, and OS. Logistic and Cox regression analysis may be used for this purpose. To include all patients in (multivariate) analyses, a multiple imputation algorithm will be used to impute missing covariate values if applicable. In addition, an exploratory analysis evaluating the prognostic value of gene expression profiles on overall response will be performed. At the time of analysis of this microarray data an appropriate tool will be used to overcome the problem of overfitting.
Flow cytometry for detection of neoplastic plasma cells will be performed in patients achieving CR to confirm sCR in patients with normal free light chain. Results will be correlated with PFS and OS.It should be stressed that these additional analyses should be considered as exploratory, and therefore only as hypothesis-generating.

Deviations from the analysis plan will be discussed with the study coordinators and can only affect the additional (exploratory) analyses, but not the primary (confirmatory) analyses on which the sample size is based.

17.3 Interim analysis and safety monitoring

Two interim analyses are planned for each randomization, primarily to guard against unfavorable results in the HDM and in the VRD consolidation arms. Results of the interim analyses will be presented confidentially to an independent data and safety monitoring board (DSMB). Only if the DSMB recommends that the study should be stopped or modified the results will be made public to the principal investigators for further decisions. The interim analyses are planned after 33% and 66% of the events with regard to PFS from R1 and R2 have been observed (240/480 resp. 172/343), which are the primary endpoints for these analyses. It should be noted that at the time of the interim analyses, part of the available data will not yet be reviewed and validated.
The DSMB is free in its public recommendations to the study coordinators and the confidential recommendations to the study statisticians. A benefit in terms of PFS in the experimental arm is in general no reason to recommend early stopping of the study, unless the associated P-value is very extreme. The critical P-values at the interim analyses will be 0.005. Because of the interim analysis, the critical P-value for the final analysis will be 0.045 (J. Crowley et al. Data monitoring committees and early stopping guidelines: the Southwest Oncology Group experience. *Stat.Med.* 1994; 13: 1391-9).

At each interim analysis a detailed report will be generated and presented to the DSMB. The report includes by treatment arm the number of entered patients and at that time evaluable patients, treatment given, response rate, the number of events on the actuarial endpoints, actuarial estimates for those endpoints and incidence of SAE's and other adverse events and infections by grade. Adverse events will be described by summary tables broken by site, CTCAE grade and relation to trial treatment.
The study will be closely and sequentially monitored before the first interim analysis. Monitoring will be based on the reported SAE's, which are not subjected to data delay. The difference in the number of patients with an SAE in both arms and the difference in the number of deaths in both arms are tested using the logrank test. We repeatedly test whether those incidences in the experimental arm are higher at a significance level of 0.05. If one of both incidences is significantly higher in the experimental arm an early report will be presented to the DSMB.
In addition, a separate report on the incidence of SAE's and other adverse events and infections, as described before, will be sent to the DSMB once a year. Again, the DSMB is free in her public recommendations to the study coordinators and the confidential recommendations to the study statisticians.

17.4 Statistical analysis of the quality of life assessment

All patients with the baseline and at least one follow-up QoL questionnaire, separately for QLQ-C30 and QLQ-MY20, will be included in the analysis. To evaluate the difference between two treatment groups with respect to the multi-item scales of the QLQ-C30 and QLQ-MY20, the repeated measures will be analyzed separately using mixed ANOVA models. The single items in the QLQ-C30 and QLQ-MY20 will be analyzed using (ordinal) logistic regression with random effects. The items concerning the diagnosis-specific symptoms will be summarized using the unweighted sumscore. The reliability and validity of the sumscores will be established using baseline data and, when sufficient, the effect of treatment on these sumscores will be evaluated using mixed ANOVA models.

17.5 Data and Safety monitoring board

A data and safety monitoring board will be installed before start of the study.

18 Ethics

18.1 Accredited ethics committee or Institutional Review Board

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

18.2 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.

18.3 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.

18.4 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.

19 Administrative aspects and publication

19.1 Handling and storage of data and documents

19.1.1 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. 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.

19.1.2 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.

19.1.3 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.

19.1.4 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).

19.2 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.

19.3 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.

19.4 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.

19.5 Publication policy

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-investigator(s) and the trial statisticians on the basis of the statistical analysis performed at the HOVON Data Center by B. van der Holt (HOVON) in close cooperation with G. Ciccone (GIMEMA). 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

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.
The proposed publication policy regarding various manuscripts will be as follows:

Study question	1st author	2nd author	Last author
VMP vs HDM 1 + 2	GIMEMA	DSMSG	HOVON
HDM 1 or 2	DSMSG	GIMEMA	NMSG
VRD vs none	HOVON	NMSG/CEMSG	GIMEMA
Relapse treatment with HDM/ASCT in VMP arm	NMSG	HOVON	DSMSG
Biological and Molecular Prognostice Factors	GIMEMA	HOVON	DSMSG
GEP profiling	HOVON	DSMSG	GIMEMA
QOL	CEMSG	NMSG	To be det.

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

All clinical and study data will be the property of the cooperative tumor groups. Patents and intellectual properties will belong to the cooperative tumor groups or will be subject to a decision made by the prinicipal investigators.

20 Correlative studies

20.1 Validation of the prognostic role of stringent CR and immunophenotype in MM patients undergoing treatment including new drugs

In most hematologic malignancies, response to frontline therapies is a good predictor of prognosis, with the longest survival reported in patients achieving complete response (CR). In this study the prognostic role of minimal residual disease (MDR) detected by free-light chain and by multiparametric flow cytometry (MFC) will be evaluated. Patient with evidence of immunofixation negative CR at a response evaluation moment will be studied. Serum samples will be tested for free-light chain. In addition to measuring the absolute levels of free-light chain, the free-light chain ratio will be considered (normal reference range, 0.26 to 1.65). Patients with a k/l FLC ratio <0.26 are typically

defined as having a monoclonal lambda free light chain and those with ratios >1.65 are defined as having a monoclonal kappa free light chain. Bone marrow samples will be tested by 8-colour flowcytometry for the presence of monoclonal plasma cells according to the methods described in the EMN-02 MRD Protocol. The outcome of patients in stringent CR or MFC remission will be compared with those in immunofixation negative CR or VGPR.

20.2 Substudy: Observation Of Asymptomatic Patients

This is a separate observational study. SAE reporting, monitoring and insurance as described in the main protocol is not applicable for patients in this substudy. Patients wil be registered in a separate database.

Smouldering (asymptomatic) multiple myeloma is an asymptomatic plasma-cell proliferative disorder associated with a high risk of progression to symptomatic myeloma. Prognostic factors for the progression and outcome of this disease are unclear.
To identify specific prognostic factors predicting the risk of progression to symptomatic multiple myeloma is essential to identify the time required to develop symptomatic myeloma.
This substudy is an observational multi-center, international study designed to observe asymptomatic patients excluded to the protocol that in any case could be inserted in the study. The asymptomatic patient is characterized by the absence of end-organ damage or tissue involvement, such as anemia, bone lesions, hypercalcemia, and renal failure, or by other relevant clinical conditions, such as hyperviscosity, amyloidosis, and recurrent infections (CRAB). The definition of smouldering myeloma is according to the publication (myeloma management: guidelines a consensus report from the Scientific advisors of the international myeloma foundation, Durie B et al, Haemat J 2003, 4:379-98).

Eligibility criteria

Inclusion criteria:

- Age 18-65 years inclusive
- monoclonal protein present in the serum or urine, or abnormal free light chain ratio
- monoclonal bone marrow plasma cells > 10% AND/OR serum monoclonal protein ≥ 3 g/dL or urine Bence Jones (K or lambda chain) ≥ 1 g/24 hours
- normal serum calcium, Hb level and serum creatinine
- absence of lytic lesions at X-Rays

Exclusion criteria:

- evidence of presence of myeloma related organ damage

- criteria for diagnosis of MGUS, symptomatic multiple myeloma, or solitary plasmacytoma of bone or soft tissue

Study endpoints

The endpoints of the study are:

- evaluation of time to progression in symptomatic myeloma
- evaluation of prognostic factors that can influence the time to progression
- evaluation of role of MRI to predict time to progression
- evaluation of role of PET-CT to predict time to progression and on skeletal related events (optional)

Screening visits

In the pre-enrolment phase will be performed the following evaluation:

Physical Examination

A complete physical examination and collection of vital signs (blood pressure, pulse) will be conducted during the screening period and during the observation to evaluate any changes from screening. On screening visit measurement of weight will be done.

Comorbidities

All relevant comorbidities that may influence overall survival should be reported, in particular the presence of the following diseases should be reported (Charlson et al): AIDS, Cerebrovascular disease, Chronic pulmonary disease, Congestive heart failure, Connective tissue disease, Dementia, Hemiplegia, Leukemia, Malignant lymphoma, Myocardial infarction, Peripheral vascular disease, Ulcer disease, Diabetes mellitus, Liver disease, Renal disease, Malignant solid tumor.

Karnofsky Assessment

Karnofsky performance status scores are to be determined during the screening period.

Clinical Laboratory Evaluations at the start of the study

The following clinical laboratory evaluations will be performed:

- Serum Chemistry: Sodium, potassium, creatinine, glucose, total protein, 24 hours urine proteine, creatinine clearance, total bilirubin, AST, ALT, β2-microglobulin, albumin, LDH
- Hematology: Hemoglobin, white blood cell (WBC) count and differential, absolute neutrophil count (ANC) and platelets

- Immunochemistry: Quantitative Ig, Serum protein electrophoresis (SPEP), urine Bence Jones quantitation, 24-hr protein electrophoresis (UPEP), Free kappa/lambda light chain and ratio

Radiology evaluation

- skeletal survey
- MRI
- CT-scan, if clinically indicated
- PET-CT (optional)

Bone marrow evalutions

Cytogenetic samples will be collected and shipped to the centralized laboratory of each country.

-Cytogenetic evaluations by FISH (Fluorescent in situ hybridization)

- Bone marrow aspiration

Molecular side-studies

In order to characterise the molecular changes that occur between asymptomatic and symptomatic MM, gene expression profiling and paired-end whole exome sequencing will be performed. For these substudies bone marrow, peripheral blood and saliva samples are collected at the time of diagnosis and if progression to symptomatic MM occurs.

Study assessments

Every 3 to 6 months the following clinical laboratory evaluations will be performed:

- Serum Chemistry: Sodium, potassium, creatinine, glucose, total protein, 24 hours urine proteine, creatinine clearance, total bilirubin, AST, ALT, β2-microglobulin, albumin, LDH
- Hematology: Hemoglobin, white blood cell (WBC) count and differential, absolute neutrophil count (ANC) and platelets
- Immunochemistry: Quantitative Ig, Serum protein electrophoresis (SPEP), urine Bence Jones quantitation, 24-hr protein electrophoresis (UPEP), Free kappa/lambda light chain and ratio

The following clinical laboratory evaluations will be performed if clinically indicated and/or if progression to symptomatic myeloma is suspected:

- skeletal survey
- MRI
- PET-CT

If progression to symptomatic myeloma occurs and the study enrolment is still active the physician can decide to enrol the patient in the protocol, according to the inclusion criteria and the patient's willingness. At any case the participation is not mandatory.

Flow chart Asymptomatic Study

	At entry	After 3 months	After 6 months	After 9 months	After 12 months	After 15 months	After 18 months	After 21 months	After 24 months	t =symptomatic MM
Medical history	X									X
Physical examination	X	X	X	X	X	X	X	X	X	X
Comorbidities evaluation	X									X
Karnofsky Assessment	X	X	X	X	X	X	X	X	X	X
Hematology[1)]	X	X	X	X	X	X	X	X	X	X
Blood chemistry[2)]	X	X	X	X	X	X	X	X	X	X
Immunochemistry[3)]	X	X	X	X	X	X	X	X	X	X
Bone marrow aspirate	X									X
Skeletal survey	X									X
MRI[4)]	X									X
PET-CT[4,5)]	X									
Cytogenetic evaluation	X									X
Molecular side-studies[6)]	X									X

1) Hematology: hemoglobin, white blood cell (WBC) count, differential, absolute neutrophil count (ANC) and platelets.

2) Chemistry: Sodium, potassium, creatinine, glucose, total protein, 24 hours urine proteine, creatinine clearance, total bilirubin, AST, ALT, B2-microglobulin, albumin, LDH.

3) Immunochemistry: quantitative Ig, serum protein electrophoresis (SPEP), urine Bence Jones quantitation, 24-hr protein electrophoresis (UPEP), Free kappa/lambda light chain and ratio.

4) Skeletal survey, MRI and PET-CT at the screening and then if clinically indicated or in case of suspected progression.

5) PET-CT is optional

6) Samples to be drawn for molecular side-studies include ≥10 mL bone marrow, 2 x 6 mL EDTA peripheral blood (PB), 1 x 6 mL heparin PB, 1 x 6 mL citrate PB, 1 x 6 mL serum PB & 2 mL saliva in an Oragene® OG-500 collection tube

20.3 Substudy: Non-Myeloablative/Reduced-Intensity Allogeneic Stem Cell Transplantation Followed By Maintenance Therapy In Untreated Myeloma

This substudy is optional. Patients with an HLA-identical sibling or unrelated donor are eligible for a non-myelo-ablative allogeneic stemcell transplantation Details are given in appendix H.

20.4 Iron deficiency sub study: Randomized prospective open label phase III study comparing single dose Ferric Carboxymaltose (FCM) with control in patients undergoing VCD induction therapy followed by stem cell collection and either ASCT or VMP chemotherapy

This substudy is not applicable to all HOVON investigators in the Netherlands. They can not participate in this sub study. This sub study is optional for other collaborative groups.

Anaemia is frequently observed in patients with multiple myeloma. It may be hypothesized that these high rates of anaemia may be, at least partially, due to iron deficiency (either functional or absolute) either at baseline or during the treatment period.
Options for correction of iron deficiency include both oral and parenteral preparations. In myeloma patients serum levels of hepcidin are upregulated and correlate with the degree of anemia. Oral iron is poorly absorbed in patients with elevated hepcidin levels. As such, the effectiveness of oral iron may be reduced or ineffective in myeloma patients. Per the EORTC guidelines, the use of oral iron is not recommended when combined with ESA.
Ferric carboxymaltose (FCM) is a relatively new preparation of intravenous iron that is a more stable complex that is non-dextran based and permits higher single doses in short periods of time.
It is the aim of this randomised, 2 arm open-label sub study to assess the incidence of iron deficiency in previously untreated patients with MM at start of and during 4 cycles of induction therapy and to evaluate whether iv iron (ferric carboxymaltose, FCM) can correct iron deficiency and improve quality of life in both anaemic and non-anaemic patients with newly diagnosed MM undergoing induction chemotherapy with VCD.
Further information is given in appendix I

20.5 Substudy: Prognostic role of 18F-FDG PET/CT in young MM patients receiving up-front novel agents and ASCT

This is a separate optional substudy. Patients wil be registered in a separate database, using a centralization of imaging.
Further information is given in appendix K.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
BMT	Bone Marrow Transplant
BRDU	Bromo Deoxy Uridine
BUN	Blood Urea Nitrogen
Ca	Calcium
VCD	Cyclophosphamide, Bortezomib, Dexamethasone
CR	Complete Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
EORTC	European Organization for Research and Treatment of Cancer
FISH	Fluorescence In Situ Hybridisation
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastro-intestinal
HB	Hemoglobin
HDM	High Dose Melphalan
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HZ	Herpes Zoster
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFM	Intergroup Français de Myelom

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
NaCl	Sodium Chloride
NCI	National Cancer Institute
NMSG	Nordic Myeloma Study group
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cell(s)
PD	Progressive Disease
PO	Per Os
PR	Partial Response
SPM	Second Primary Malignancies
SAE	Serious Adverse Event
SC	Subcutaneous
SCT	Stem Cell Transplantation
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
SPEP	Serum protein electrophoresis
ULN	Upper Limit of Normal
UPEP	Urine protein electrophoresis
VMP	Bortezomib, Melphalan, Prednisone
VRD	Bortezomib, Lenalidomide, Dexamethasone
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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A. Criteria for diagnosis

Criteria for symptomatic MM and measurable disease

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

Criteria for symptomatic MM

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

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

AND

Clonal plasmacells in bone marrow or plasmocytoma

AND

More than 1 myeloma-related dysfunction* (CRAB criteria):

- calcium > 2.65 mmol/l
- renal insufficiency (creatinin > 177umol/l)
- anemia (Hb < 6.2 mmol/l or 10 g/dl)
- bone disease (lytic lesions or osteopenia)

* must be attributable to the underlying plasma cell disorder

Criteria for measurable disease

Serum M-protein > 10 g/l

OR

Urine M-protein > 200 mg/24 hours

OR

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

OR

Proven plasmacytoma by biopsy

Staging according to ISS criteria

Stage I:	Serum β_2-microglobulin < 3.5 mg/l AND Serum albumin ≥ 3.5 g/dl (≥ 35 g/l)
Stage II:	Patients who qualify for neither Stage I nor III
Stage III:	Serum β_2-microglobulin ≥ 5.5 mg/l

B. Response criteria

Based on IMWG criteria [28]

RESPONSE CRITERIA

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

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

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

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

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

[d] Refer to Appendix A for definitions of measurable disease.

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

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

RELAPSE CRITERIA

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

Abbreviations: CR, complete response; DFS, disease-free survival.

[a] All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

[b] For progressive disease, serum M-component increases of ≥ 1 g/dl (10 g/l) are sufficient to define relapse if starting M-component is ≥ 5 g/dl (50 g/l).

[c] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[d] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

PRACTICAL DETAILS OF RESPONSE EVALUATION

Laboratory tests for measurement of M-protein

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

Definitions of measurable disease

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

Follow-up to meet criteria for PR or SD

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

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

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

C. Common Terminology Criteria for Adverse Events

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 'Studies' > 'Algemene studie-informatie'

'Trials' -> 'General information about studies'

D. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

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

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

4 Unable to get out of bed

E. NYHA* scoring list

Grade 1 No breathlessness

Grade 2 Breathlessness on severe exertion

Grade 3 Breathlessness on mild exertion

Grade 4 Breathlessness at rest

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

F. 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	Reduce to once weekly or 25% dose reduction	Hold; 50% dose reduction; Schedule Δ required	Discontinue Bortezomib
	1	Mild pain not interfering with function	No action	Reduce to once weekly	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 better.

25% Dose reduction: Bortezomib dose reduction from 1.3 to 1.0 mg/m^2/dose.

50% Dose reduction: Bortezomib dose reduction from 1.3 to 0.7 mg/m^2/dose.

Schedule Δ required: Schedule change from Bortezomib twice per week (days 1, 4, 8 and 11) to once per week (days 1, 8, 15, and 22) required. If the patient is already on a once weekly schedule, then the drug will be given every other week (e.g. day 1, day 15)

G. Management and handling of myeloma samples for micro-array

Bone marrow and plasma cryopreservation

EMN-02 biobank laboratories will collect bone marrow cells, peripheral blood cells and saliva which are stored according to biobank laws in the separate countries. This material will be used for additional investigations in order to determine prognostic factors.

These will include:

A. Cytogenetic analysis

In case FISH analysis has not been performed at entry, FISH analysis will be either performed on cryopreserved bone marrow samples or bone marrow slides for del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p

B. Whole genome gene expression profiling

Whole genome transcriptional profiling will be used to establish the level of over 47,000 transcripts, representing 38,500 genes. Aim of this exploratory analysis is to further develop a molecular classification of multiple myeloma patients, validation of prognostic markers identified in previous studies and identification of novel candidate markers that predict patients response to the specific treatment used in the current study by correlations with clinical outcome.

Bone marrow samples for gene expression profiling will be collected centrally at the EMN-02 biobank laboratories, where plasma cells will be purified within 24 hours after sampling using a CD138 positive selection kit. Performance of the purification will be monitored using FACS analysis of the original bone marrow sample and the final purified plasma cell fraction with CD38, CD138 and CD45 antibodies. The viability of the cells will be measured using annexin and 7AAD.

Purified plasma cells will be stored in RLT Plus buffer with β-mercaptoethanol at -80°C and shipped to the laboratory of the Erasmus MC EMN-02 biobank laboratory badgewise, where these will be further processed and analyzed as outlined below.

Total RNA will be isolated using the RNeasy kit (Qiagen). RNA levels and quality will be assessed with the RNA6000 Nano assay on the Agilent 2100 Bioanalyzer. Samples of which the 28S/18S ratio is <1,7 or with a RIN number <7.0 will be excluded from further analysis.

Total RNA will be used to prepare antisense biotinylated RNA using the genechip ® 3"IVT express kit (Affymetrix). The biotinylated RNA will be hybridized to the Affymetrix U133 Plus 2.0 array. Staining, washing and scanning procedures, as well as hybridization controls provided by Affymetrix will be used and GeneChips will be visually inspected for irregularities.

The global method of normalization will be used and the mean difference between all GeneChips will be used as indicator of assay-quality. In addition, the variations in percentage of genes present, the 3'/5' ratio of Actine and the 3'/5' ratio of GAPH will be assessed to verify the quality of the array.

The Omniviz package will be used to perform and visualize the results of unsupervised cluster analysis, whereas all supervised analyses will be performed using SAM software. For supervised class-prediction analyses, PAM software in R will be applied

C. Single Nucleotide Polymorphisme (SNP) analysis in MM patients

Anti-cancer treatment is associated with a wide variety of side effects, which also vary considerably between patients. Bortezomib induces painful neuropathy, thrombocytopenia and gastro-intestinal symptoms. Lenalidomide induces neutropenia and thrombocytopenia. The proportion of patients experiencing these side effects in trials ranges from 10 to 50%. The most likely explanation for the inter-individual variation in response and toxicity may be found in the genetic heterogeneity of genes involved in detoxification processes, DNA repair, myeloma biology and neuropathy.

It is known that such single nucleotide polymorphisms (SNPs) are observed in many genes that are important for multiple myeloma biology and/or are involved in metabolism of anti-cancer drugs. Furthermore, it is anticipated that these SNP's play an important role in outcome (OS and DFS) and toxicity in patients treated with conventional agents, while little is known about their relevance for the effects of novel agents.

The novel agents Bortezomib and Lenalidomide are now moving to up-front therapy of multiple myeloma. Therefore it is of critical importance to investigate which gene(s) are involved in the drug metabolism and anti-tumor effect of these agents.

The involvement of inherited genetic polymorphisms will be investigated prospectively in this trial, using in a high through-put system with a Genome-Wide Human SNP array 6.0 (Affymetrix) platform of DNA isolated from white blood cells. The presence of inherited genotype polymorphisms will be correlated to response, progression-free survival and toxicity.

Blood samples will be taken before start of treatment. About 6 ml of EDTA blood divided over two tubes, is needed to obtain a reasonable amount of DNA, necessary for the analyses.

Blood samples will be stored at room temperature immediately after collection. The samples should be sent to the central laboratory at room temperature by overnight mail within one day after sampling to maintain a good quality of DNA. The centers will be provided with special envelopes for the sending of diagnostic samples. The central laboratories for participating countries will contact the hospitals for instructions and to make arrangements for shipping of samples.

D. Additional molecular analyses of MM samples

Other analyses may appear to be relevant at a later stage and the EMN-02 biobank is left open to interested groups. The procedure and what analyses to be performed will be decided later. In addition to cryopreserved bone marrow cells and DNA of peripheral blood cells, peripheral blood plasma and saliva will be stored.

Required bone marrow and peripheral blood and logistics

Note 1: This section is discussed in the lab manual.

H. Non-Myeloablative/Reduced-Intensity Allogeneic Stem Cell Transplantation Followed By Maintenance Therapy In Untreated Myeloma with high risk features

Design and Rationale:

Multiple myeloma remains an incurable disease despite the development of new therapies. Allografting is considered the only potentially curative treatment for its well-documented graft-vs.-myeloma effect. The unacceptably high transplant related mortality described with conventional myeloablative conditioning regimens, has led to the development of new conditionings characterised by low toxicity profiles. So called non-myeloablative or reduced-intensity conditionings (originally described by Maloney et al, Blood 2003, and Kroger et al, Blood 2002 respectively) in newly diagnosed patients showed a significantly reduced toxicity with encouraging overall and event free survivals. Importantly, the achievement of at least very good partial remission at the time of allografting conferred a significant advantage in both event-free-survival and overall survival. Unfortunately, disease relapse remains an issue and mainly occurs in patients not achieving complete remission after allografting. The aim of this study is to combine the pre-transplant efficacy of new drugs in reducing the disease and the graft-vs.-myeloma effect of allografting followed by post-transplant maintenance/consolidation treatment. Furthermore, an important objective is to collect data from transplant centers that employ the two most commonly used conditionings.

Due to the current excellent survival of patients with standard risk features treated with novel anti-myeloma agents it is strongly recommended to restrict Allo-SCT to patients with high risk features including 17P-, (t) 4/14, (t) 14/16, and 1p/q abnormalities as determined by FISH in combination with ISS II/III. Centers with an Allo-SCT policy for high risk myeloma will be identified and are requested to perform HLA-typing of all potential patients and sibs.

Objectives:

Primary endpoints:

a) To evaluate toxicity and tolerability of new drugs pre/after allografting for high risk myeloma

b) To evaluate efficacy of new drugs in reducing tumor burden before and in inducing complete remission (immunofixation negative) after allografting for high risk myeloma

Secondary endpoints:

a) To evaluate overall-survival for high risk myeloma

b) To evaluate progression free survival for high risk myeloma

c) To evaluate event-free survival for high risk myeloma

d) To monitor minimal residual disease in patients achieving CR with Lenalidomide

Eligibility criteria

Inclusion Criteria

- Newly diagnosed multiple myeloma patients with an HLA-identical sibling or an unrelated donor (at least 9/10 allele-matched donor) enrolled in the EMN trial for patients < 65 years.
- Being high risk as defined by 17P-, (t) 4/14, (t) 14/16, and 1p/q abnormalities as determined by FISH in combination with ISS II/III

Exclusion Criteria

- Patients with deep vein thrombosis or any other thrombotic event in the 3 months prior to Lenalidomide therapy.
- Patients with rapidly progressive disease
- Life expectancy severely limited by diseases other than malignancy.
- Any current CNS involvement with disease refractory to intrathecal chemotherapy.
- Fertile men or women unwilling to use contraceptives during and for up to 12 months post treatment.
- Female patients who are pregnant or breast feeding.
- HIV positive patients.
- Patients with active non-hematological malignancies (except localized non-melanoma skin malignancies).
- Fungal pneumonia with radiological progression after receipt of amphotericin formulation or mold-active azoles for longer than 1 month.
- Karnofsky score < 50% .
- Patients with the following organ dysfunction:
- Symptomatic coronary artery disease or ejection fraction <35% or other cardiac failure requiring therapy.
- Poorly controlled hypertension.
- Poorly controlled diabetes
- DLCO <30%, TLC <30%, FEV1 <30% and/or receiving supplementary continuous oxygen.
- Liver function abnormalities: Patients with clinical or laboratory evidence of liver disease would be evaluated for the cause of liver disease, its clinical severity in terms of liver function, and the degree of portal hypertension. Patients will be excluded if they are found to have fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, alcoholic hepatitis, esophageal varices, a history of bleeding esophageal varices, hepatic

encephalopathy, uncorrectable hepatic synthetic dysfunction evinced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal liver abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin >3 mg/dL, and symptomatic biliary disease.

Treatment plan:

Patients with an HLA-identical sibling or a suitable unrelated donor allocated to a planned non-myeloablative/reduced-intensity allograft will receive 4 courses of VCD, Cyclophosphamide/G-CSF mobilised PBSC collection and standard autologous transplant with Melphalan at 200 mg/m^2

Allogeneic Transplant phase

Conditioning

The conditioning regimen consists of the combination of busulfan and fludarabine i.v. Recommendations for the scheme are given below. Slight variations may be possible according to local protocols.

Agent	Dose/day	Route	Days
Busulfan	3.2 mg/kg/day	i.v.	Day-5,-4,-3,-2
Fludarabine	40 mg/m²/day	i.v.	Day-5,-4,-3,-2

Graft versus Host Disease Prophylaxis

GvHD prophylaxis consists of Cyclopsporin-A combined with Mycophenolate Mofetil (MMF). In patients with an 9/10 sibling donor or an unrelated donor Anti-Human Thymocyte Globulin (ATG) is added to the conditioning regimen. Recommendations for the prophylaxis scheme are given below. Slight variations may be possible according to local protocols.

Agent	Dose/day	Route	Days
Cyclosporine	5 mg/kg q12hrs	i.v.	From day -3 to +80 then tapered. STOP at day +180
Mycophenolate Mofetil			
Sibling donor	15 mg/ kg q12hrs	p.o. (or i.v).	From day 0 to +27
Unrelated donor	15 mg/ kg q8hrs	p.o. (or i.v)	From day 0 to +40 then tapered. STOP at +96
Anti-Human Thymocyte Globulin			
Unrelated donor only	2.5 mg/ kg	i.v.	Day -3 and day -2

Maintenance

Lenalidomide will be started at a minimum of 6 months post-allotransplant in patients (unless in molecular CR), if the following conditions are present:

- No immune suppressive drugs for at least 4 weeks;
- No signs of any grade of acute GvHD or extensive GVHD with the exception of oral GvHD that is manageable with local therapy;
- Absolute neutrophil count >1 x 10^9/L without the use of growth factors;
- Platelet count > 75 x 10^9/L without transfusion support;
- Calculated or measured creatinine clearance: ≥ 20 mL/minute;
- Total bilirubin < 2 x the upper limit of normal;
- AST (SGOT) and ALT (SGPT) < 2.5 x upper limit of normal;

~Treatment dosing and schedule

- Lenalidomide 5 mg/day will be given every other day for 21 consecutive days of a 28 day cycle in the first 2 cycles in the absence of WHO grade 3 toxicity and any grade acute GvHD or extensive GvHD with the exception of oral GvHD that is manageable with local therapy.
- Lenalidomide 5 mg once daily will be given in the next cycles for 21 consecutive days of a 28 day cycle.
- Lenalidomide will be stopped immediately at any sign of acute GVHD or chronic GvHD with the exception of oral GvHD that is manageable with local therapy.
- In patients treated with 5 mg Lenalidomide may be restarted with 5 mg every other day after complete disappearance (minimal 1 month) of GvHD.
- Lenalidomide will be given for a maximum of 2 years.
- Lenalidomide will be discontinued in patients who achieve and maintain molecular remission for 2 consecutive controls at least 6 weeks apart.
- Molecular remission may be determined by patient specific PCR or based on plasma cell chimerism in purified bone marrow plasmacells.

I. Randomized prospective open label phase III study comparing single dose Ferric Carboxymaltose with control in patients undergoing VCD induction therapy followed by stem cell collection and either ASCT or VMP chemotherapy

Steering Committee: Heinz Ludwig, Wilhelminenspital, Vienna, Austria
Tim Cushway, Vifor Pharma, Glattbrugg, Switzerland
Brigitte Klement, Vifor Pharma, Glattbrugg, Switzerland

Contents

List of abbreviations

ADR	Adverse Drug Reaction
EORTC	European Organisation for Research and Treatment of Cancer
ESA	Erythropoiesis stimulating agent
FCM	Ferric Carboxymaltose
Hb	Hemoglobin
HDM	High Dose Melphalan
ID	Iron deficiency
IDA	Iron deficiency anaemia
IV	Intra venous
PS	Performance Status
QoL	Quality of Life
SAE	Serious Adverse Event
TSAT	Transferrin saturation
VCD	Bortezomib-Cyclophosphamide-Dexamethasone
VMP	Bortezomib-Melphalan-Prednisone

Rationale

Iron is essential for all functions of the body, with important roles including, but not limited to, oxygen uptake and transport (central ion of the haem of haemoglobin), oxygen supply of muscles (component of myoglobin) and metabolism. Additionally, as a component of oxidative enzymes and respiratory chain proteins it is crucial for energy production. High amounts of iron are required for erythropoiesis (approximately 500 mg per litre of blood) and when iron supply is restricted it may lead to iron deficiency anaemia (IDA)[1, 2]. Based on the above biology, in addition to IDA, iron deficiency (ID) alone has been associated with reduced functional capacity and/or patient reported poor physical condition[3, 4]. Recently, the correction of ID (anaemic and non-anaemic) in patients with chronic heart failure with IV iron showed significant improvements in patient and physician assessed quality of life (QoL), symptoms and exercise performance[5].

In anaemic patients with cancer IV iron in conjunction with ESA has been shown to shorten time to response, improve response rate, and quality of life[6, 7, 8, 9]. These benefits may be hypothesised to include improved iron replenishment in iron restricted erythropoiesis due to increased requirements on iron stores from ESA use, as well as iron deficiency correction alone. Indeed the benefit of

each treatment is still open and recent observational data suggest a role for iron alone in correction of anaemia due to iron restricted erythropoiesis. Improvements in Hb levels of up to 3g/dL were reported for 80% of all patients when up to 4,000mg of iron was administered in single doses of up to 1,000mg[10]. Interim data of a second observational study showed an increase in haemoglobin of approximately 1.0-1.5 g/dL over 12 weeks.[11] On average, 1008 mg of IV iron as FCM was administered with similar effectiveness for single doses of greater than 500 mg iron compared to more frequent individual lower doses.

The incidence and clinical consequences of ID in oncology is still largely unknown and definitions of iron deficiency are not uniformly accepted. However, TSAT is widely accepted as a marker of circulating iron and may be used in combination with other iron parameters to define absolute iron deficiency or functional iron deficiency (where iron stores appear to have iron but due to the underlying disease this is not available for use within the body).

Anaemia is frequently observed in patients with multiple myeloma. At start of therapy about 60% of patients present with haemoglobin levels below 12g/dl, and the prevalence may increase to up to 80% with active myeloma therapy. Regarding iron parameters only few data have been reported as yet. A recent retrospective survey conducted at the Center of Oncology and Hematology, Wilhelminenspital, Vienna revealed a prevalence of functional iron deficiency (defined by a TSAT <20%) of 36% in patients seen either during routine follow up examinations or during periods of active therapy.[12] It may be hypothesized that these high rates of anaemia may be, at least partially, due to iron deficiency (either functional or absolute) either at baseline or during the treatment period.

Options for correction of iron deficiency include both oral and parenteral preparations. In myeloma patients serum levels of hepcidin are upregulated and correlate with the degree of anemia.[13] Oral iron is poorly absorbed in patients with elevated hepcidin levels. As such, the effectiveness of oral iron may be reduced or ineffective in myeloma patients. This was shown in two trials in combination with ESA.[8,9] Per the EORTC guidelines, the use of oral iron is not recommended when combined with ESA.[14]

Ferric carboxymaltose (FCM) is a relatively new preparation of intravenous iron that is a more stable complex that is non-dextran based and permits higher single doses in short periods of time. This preparation has been approved in 2007 (with marketing authorisation in 19 countries across Europe) for use in patients with iron deficiency where oral iron preparations are ineffective or cannot be used. In this study, FCM will be administered as a single infusion of 1,000mg iron over

15 minutes (per label) to replenish iron stores in iron deficient patients (defined as TSAT <20%). A second dose will be administered, if indicated, on the day of stem cell priming if TSAT <20%.

Aims

To assess the incidence of iron deficiency in previously untreated patients with MM at start of and during 4 cycles of induction therapy and to evaluate the role of iv iron (ferric carboxymaltose, FCM) in correcting iron deficiency in both anaemic and non-anaemic patients with newly diagnosed MM undergoing induction chemotherapy with VCD.

Study objectives

This study will aim to assess the efficacy and safety of FCM in ID MM patients. Additionally, the study will explore the impact of the correction of iron deficiency on QoL measurements and the impact on treatment outcomes.

Primary

- Efficacy of FCM in correction of ID (TSAT >=20%)
- Impact of FCM on quality of life (EORTC QLQ-C30)

Secondary

Impact of FCM on:

- Haemoglobin levels during induction therapy
- Number of stem cells collected
- Transfusion rate during induction
- Transfusion rate after stem cell transplantation (<21 days)
- Response to VCD induction chemotherapy
- Toxicity

Endpoints

Laboratory

- Percentage of iron deficient patients (TSAT) at week 3, 6, 9, 14(+/-1), 21(+/-2), and 27(+/-4)
- Percentage of patients with Hb >10g/dL at week 3, 6, 9, 14(+/-1), 21(+/-2), and 27(+/-4)

Assessments

- Quality of Life (EORTC QLQ-C30)
- Performance Status

Adverse Events

- Assessment of adverse events (related and not-related to iron): grade 2-5
- Number and duration of hospital or other clinic visit(s)
- Summary of SAE's

Other

- Summary of ESA use (number patients requiring ESA, total dose required)
- Summary of transfusion requirements during induction chemotherapy (number of patients requiring a transfusion, total units transfused)
- Summary of transfusion requirements in patients undergoing stem cell transplantation (number of patients requiring a transfusion, total units transfused)
- Response to VCD induction chemotherapy
- Number of stem cells collected
- Toxicity (number of adverse events, related adverse events and SAE's)

Patient Population (Inclusion / Exclusion)

Patients must meet all criteria for inclusion in protocol "*A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma*". For eligibility to the sub-study, patients must meet following criteria:

Inclusion:

- Written informed consent
- Screening TSAT value <20%
- Screening serum ferritin < 800ng/mL

Exclusion:

- prior iv iron use in 4 weeks prior to planned date of FCM administration
- oral iron in past 10 days prior to planned date of FCM administration
- previous or known hypersensitivity to FCM. Previous (or known) hypersensitivity to other iron preparations permitted.
- history of acquired iron overload or haemochromatosis.

Study Design

Multi-centre, randomised, controlled, 2 arm open-label prospective study to evaluate efficacy and safety of FCM in correcting iron deficiency in young multiple myeloma patients with iron deficiency and undergoing VCD induction chemotherapy.
Patients will be stratified according to iron status (absolute versus functional iron deficiency).

Treatment

Arm A: Standard of care, patients will be treated per institutional practice

Arm B: 1000 mg iron as FCM on the first day of induction chemotherapy (VCD). *Patients with haemoglobin>14g/dL should receive 500mg iron as FCM.*

Study Drugs Description

All manufacturing operations, including packaging and labelling, will be performed according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines. The study drug will be labelled in accordance with local study site regulations for investigational products.

Ferric Carboxymaltose

Ferric carboxymaltose will be provided by Vifor Pharma for this study.

Strength:	5% w/v iron containing 50 mg iron per ml, as sterile solution of FCM in water for injection.
Excipients:	Sodium hydroxide, hydrochloric acid, water for injection.
Appearance:	Dark brown, non-transparent aqueous solution.
Dosage Form:	10 mL vials containing 500 mg iron per vial
Manufacturer:	Vifor Pharma – Vifor (International) Inc., Switzerland.

Note: For drip infusions, FCM must be diluted only in sterile 0.9% sodium chloride.

Ferric carboxymaltose storage requirements: Do not store above 30°C. Do not freeze.

Administration of FCM as an IV Drip Infusion

Ferric carboxymaltose will be administered via IV drip infusion by designated staff at each site. Ferric carboxymaltose must be diluted only in sterile 0.9% sodium chloride solution as per table below:

Dilution of FCM as an IV Drip Infusion

FCM	Amount of Iron	Dilution - Amount of Sterile 0.9% Sodium Chloride Solution	Administration Time
10-20 mL	500-1,000 mg	250 mL	At least 15 minutes

Note: FCM = Ferric carboxymaltose.

Supply to Site, Storage, Compliance, and Accountability

Site Supply

Once a site has been approved to receive study drug, the site will be supplied with an initial stock of FCM. The need for drug resupply will be assessed on a regular basis taking into account the number of subjects enrolled, and the number of subjects in screening, at the site.

Storage

Ferric carboxymaltose storage requirements: Do not store above 30°C. Do not freeze.

Accountability

The investigator at each site is responsible for study drug supplies. The Investigator will ensure that adequate records of the receipt, preparation, administration and return of the study drug are kept and that the study drug is used only for subjects enrolled in the study. All data regarding the study drug must be recorded on the relevant forms provided.

Potential Adverse Events and Complications

The most commonly reported ADR is headache, occurring in 3.3% of the patients. The following additional events may also occur:

- *Immune system disorders:* Uncommon (>1/1,000, <1/100): Hypersensitivity including anaphylactoid reactions
- *Nervous system disorders:* Common (>1/100, <1/10): Headache, dizziness; Uncommon (>1/1,000, <1/100): Paraesthesia
- *Vascular disorders:* Uncommon (>1/1,000, <1/100): Hypotension, flushing

- *Respiratory, thoracic and mediastinal disorders:* Rare (>1/10,000, <1/1,000): Dyspnoea
- *Gastrointestinal disorders:* Common (>1/100, <1/10): Nausea, abdominal pain, constipation, diarrhoea; Uncommon (>1/1,000, <1/100): Dysgeusia, vomiting, dyspepsia, flatulence
- *Skin and subcutaneous tissue disorders:* Common (>1/100, <1/10): Rash; Uncommon >1/1,000, <1/100): Pruritus, urticaria
- *Musculoskeletal and connective tissue disorders:* Uncommon (>1/1,000, <1/100): Myalgia, back pain, arthralgia
- *General disorders and administration site conditions:* Common (>1/100, <1/10): Injection site reactions; Uncommon (>1/1,000, <1/100): Pyrexia, fatigue, chest pain, rigors, malaise, oedema peripheral
- *Laboratory:* Common (>1/100, <1/10): Transient blood phosphorus decreased, alanine aminotransferase increased; Uncommon (>1/1,000, <1/100): Aspartate aminostransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased

Prohibited Therapy and Concomitant Treatment

All medications may be prescribed at discretion of the treating physician. As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.

Assessments and Study Drug Dosing

Screening

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required*
- QoL assessment (between screening and prior to cycle 1 VCD treatment)

Day 1, Cycle 1 VCD Induction Chemotherapy (Week 0)

- 1,000mg iron as FCM immediately post VCD chemotherapy*
- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required. Screening values may be used if sample not older than 4 weeks.*

Day 1, Cycle 2 VCD Induction Chemotherapy (Week 3)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*

Day 1, Cycle 3 VCD Induction Chemotherapy (Week 6)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*

Day 1, Cycle 4 VCD Induction Chemotherapy (Week 9)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*
- QoL assessment

Day of Cyclophosphamide Priming (Week 13-15)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*
- QoL assessment (before FCM dosing, if applicable)
- 1,000mg iron as FCM immediately after Cyclophosphamide infusion (if TSAT at previous visit <20%)*

Day 1 of HDM or VMP (Week 19-23)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*
- QoL assessment

After 1st cycle of HDM (Week 27-31) or VMP (Week 25-29)

- Blood collected for local lab should have the following parameters assessed: Hb, TSAT & serum ferritin. *Additional sampling is not required.*
- QoL assessment

* iron dosing only in eligible patients randomised to FCM arm. Patients with Hb>14g/dL should receive 500mg iron as FCM.

Duration of Treatment:

FCM will be administered once on day 1 of start of chemotherapy and will be repeated in patients with TSAT <20% (and serum ferritin < 800ng/mL) on the day of cyclophosphamide priming

Safety

(Serious) adverse event reporting will occur within the scope of protocol "*A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma*".

Number of Patients

Study will be open to all subjects participating in parent study. Approximately 300 - 500 patients are expected based on rate of iron deficiency in this patient population and anticipated site involvement.

Statistics

Endpoints	Type	Control Response	SD	FCM response (for significance)		
				n=100	n=300	n=500
Percentage TSAT > 20%	Binary	10%	NA	35.1%*	22.6%	19.2%
Percentage Hb > 10 g/dL	Binary	40%	NA	69.5%	56.8%	52.9%

*Required % FCM responders needed for 80% power (i.e. 0.351*50~18 responders in FCM group)

The above tests are calculated with a 5% 2-sided alpha and 80% power. The sample size quoted is total sample size (i.e. 100= 2*50 patients per group). The TSAT and Hb calculations are based on control group treatment response estimates from FCM registrational program and clinical experience.

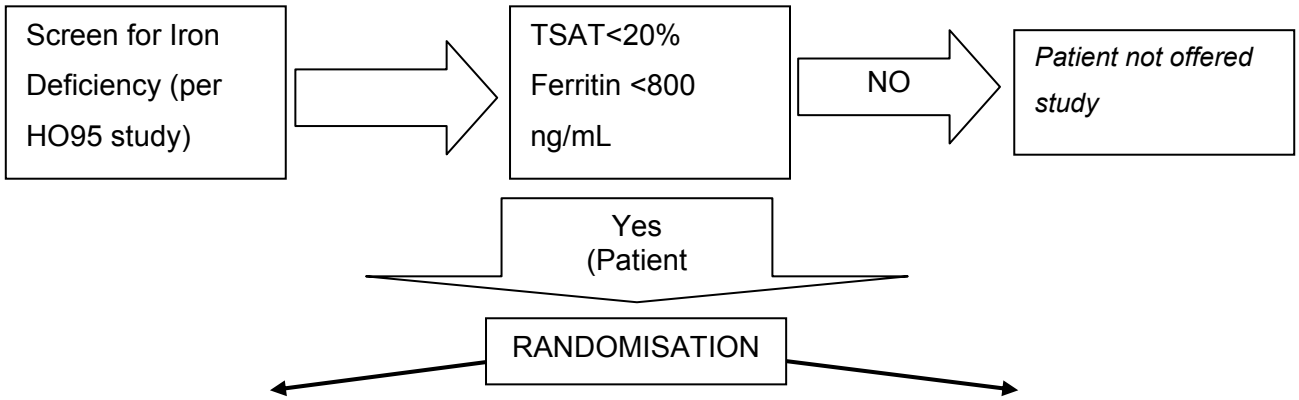
Statistical analysis for all 3 endpoints should include baseline score as a covariate.

Important covariates will include:

- Hb (<10g/dl vs. ≥ 10g/dl)
- Age (<60 vs. ≥ 60 years)
- Disease Stage (ISS stage I, vs. II, vs. III)
- Performance Status (PS (WHO) 0-I, vs. ≥ II)

Expected patient numbers approximately 300-500 patients.

Flow chart



FCM	Control
Day 1 of 1st cycle VCD (wk 0) Iron status/Hb/ QoL FCM 1000mg*	Day 1 of 1st cycle VCD (wk 0) Iron status/Hb/QoL Standard of care
Day 1 of 2nd cycle VCD (wk 3) Iron status/Hb/RBC use	Day 1 of 2nd cycle VCD (wk 3) Iron status/Hb/RBC use
Day 1 of 3rd cycle VCD (wk 6) Iron status/Hb/RBC use	Day 1 of 3rd cycle VCD (wk 6) Iron status/Hb/RBC use
Day 1 of 4th cycle VCD (wk 9) Iron status/Hb/RBC use/QoL	Day 1 of 4th cycle VCD (wk 9) Iron status/Hb/RBC use/QoL
Day of stem cell priming (wk 13-15) Iron status/Hb/RBC use/QoL If TSAT <20% (ferritin < 800ng/mL) ⇒ 1000mg FCM*	Day of stem cell priming (wk 13-15) Iron status/Hb/RBC use/QoL
Start of High dose melphalan or of VMP (wk 19-23) Iron parameter/Hb/QoL	Start of High dose melphalan or of VMP (wk 19-23) Iron parameter/Hb/QoL
After 1st HDM or 1st VMP (wk 25-29) Iron parameters/Hb/RBC use/QoL	After 1st HDM or 1st VMP (wk 25-29) Iron parameters/Hb/RBC use/QoL
End of follow up	

***** *Patients with Hb>14g/dL should receive 500mg iron as FCM*

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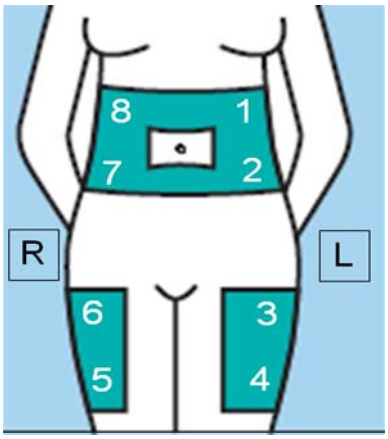
J. Guidelines for Bortezomib subcutaneous injection

The following SC injection guidelines will be observed:

- Each SC dose will be given as a single injection.
- Anatomical sites of SC administration are thighs (right or left) or abdomen (right or left).
- The SC injection site will be rotated for successive injections.
- Within the same cycle, injections at the same site should be avoided; it is recommended to alternate between right and left abdomen, upper and lower quadrant, or between right and left thigh, proximal and distal sites.
- The selected SC injection site should be free from any skin condition that might interfere with the assessment of injection site reactions.



It is very important to rotate sites

Potential injection sites

1. left abdomen upper quadrant
2. left abdomen lower quadrant
3. left thigh proximal site
4. left thigh distal site
5. right thigh distal site
6. right thigh proximal site
7. right abdomen lower quadrant
8. right abdomen upper quadrant

K. Substudy: Prognostic role of 18F-FDG PET/CT in young MM patients receiving up-front novel agents and ASCT

This is a separate optional substudy. Patients will be registered in a separate database, using a centralization of imaging.

Rationale of the sub-study

Incorporation of novel agents into autologous stem-cell transplantation (ASCT) for multiple myeloma (MM) has affected unprecedented rates of complete response (CR). As a result, interest in the evaluation of the depth of response has progressively grown. Highly sensitive techniques, such as multiparametric flow cytometry (MFC) and polymerase chain reaction (PCR), can carefully detect the presence or absence of minimal residual disease (MRD) at the bone marrow level, thus allowing to identify subgroups of patients with conventionally defined CR who are at different risk of progression or death. However, both MFC and PCR fail to identify the possible persistence of bone focal lesions (FLs) potentially harbouring non secretory MM cells or of sites of active disease outside of the medullary cavity of the bone.

FDG-PET/CT detects with high sensitivity and specificity the presence of myeloma bone lesions and/or bone marrow involvement at the onset of the disease and has the additional advantage to assess whether residual disease after treatment is active or inactive. PET/CT has been explored as a means to monitor response and to predict the outcome in various tumours, most extensively in lymphoma. Several experiences on the prognostic relevance of this imaging technique are now emerging also in MM. In particular, PET/CT involvement in terms of number of FLs and SUVmax at diagnosis was shown to be closely associated with different outcomes in two independent series of patients. In both these studies, the extremely poor prognosis of patients with extramedullary disease (EMD) at diagnosis was highlighted. In addition, PET/CT appeared also as a reliable tool for predicting the outcomes (PFS and OS) after both induction and high-dose therapy. In particular, PET-CT negativity after ASCT identified a subgroup of patients with conventionally defined CR whose outcome was significantly better in comparison with that of patients with PET-CT positivity.

Objectives

-**Primary end-points**

-To confirm the impact of PET/CT involvement at baseline on clinical outcomes of young MM patients treated up-front with novel agents and ASCT, particularly on CR duration, TTP, PFS, TFI, TTNT and OS

- To evaluate whether PET/CT involvement at baseline correlates with other prognostic factors, in particular cytogenetic and molecular abnormalities

-To assess the impact of PET/CT negativity after induction therapy and ASCT(s) or consolidation therapy on TTP, PFS, TFI, TTNT and OS

-**Secondary end-points**

-To evaluate the correlation between PET-CT changes and response after induction, ASCT(s) or consolidation therapy according to conventional criteria

-To evaluate the prognostic role of PET/CT changes after treatment in the sub-group of patients with immunophenotypic CR

Design of the sub-study

All patients will be studied at baseline with whole body X Ray (WBXR) and 18F-FDG PET-CT. PET/CT will be repeated after induction treatment (10 days after completion of therapy), at 3 months from the last ASCT (either single or double according to the policy of different centers) for those not randomized to consolidation or after 3 months from the end of consolidation therapy for those patients randomized to receive consolidation. These time-points will allow to evaluate the role of ASCT(s) and of consolidation with respect to the imaging PET-CR. MRI of the spine and pelvis will be performed at physician's discretion or upon clinical need at baseline and during follow-up.

Eligibility criteria

Newly diagnosed MM patients enrolled in the EMN02 trial for whom PET-CT study can be planned and who provide written informed consent to receive PET scans at appropriate timelines.

PET/CT Imaging protocol

Whole-body (including skull, superior limbs and femurs) PET/CT will be carried out using standard procedures in each participating centre. In order to avoid heterogeneity in the interpretation of the results, PET/CT images will be centralized and read independently by two nuclear medicine physicians, with a previous common agreement on the criteria to define PET/CT positivity and PET/CT response