

Randomized phase III trial in elderly patients with previously untreated symptomatic Multiple Myeloma comparing MP-Thalidomide (MP-Thal) followed by thalidomide maintenance versus MP-Lenalidomide (MP-Len) followed by maintenance with lenalidomide

A joint study of the HOVON and the Nordic Myeloma Study Group

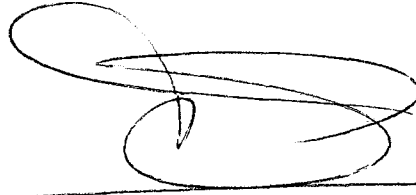
PROTOCOL

| | | |
|------------------------------------|---|--|
| Principal Investigator | : | S. Zweegman (HOVON) |
| Principal Investigator NMSG | : | A. Waage (NMSG) |
| Study Coordinators | : | P. Sonneveld (HOVON) G.M.J. Bos (HOVON) U-H. Mellqvist (NMSG) M. Salomo (NMSG) |
| Sponsor | : | HOVON VU Medical Center, P.O.Box 7057 1007 MB Amsterdam |
| Statistician | : | C. van Montfort |
| Data management | : | HOVON Data Center |
| Registration | : | 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 |
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:



Signature of Investigator

Date 10-11-11

S. ZWEEZMAN
Printed Name of Investigator

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

Local Investigator:

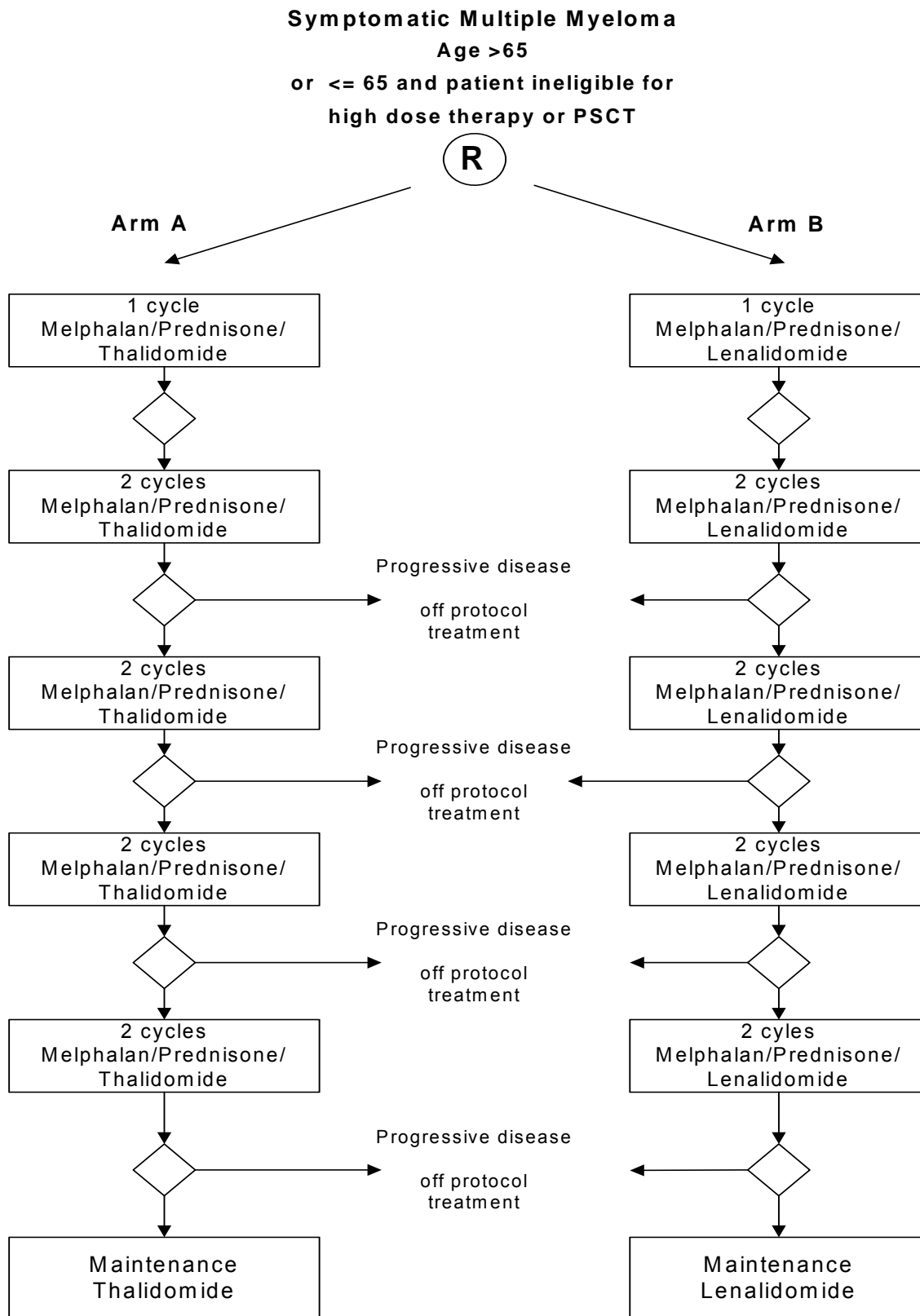
Signature of Investigator

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

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| Study phase | Randomized phase III |
| Study objectives | <ul style="list-style-type: none"> – To compare progression free survival with MP+Thalidomide (MP-Thal) followed by maintenance with thalidomide versus MP+Lenalidomide (MP-Len) followed by maintenance with lenalidomide – To compare (stringent) complete and very good partial response with MP-Thal versus MP-Len – To compare overall survival with MP-Thal versus MP-Len – To assess and compare overall response and time-to-response with MP-Thal versus MP-Len – To assess the effect of maintenance therapy with thalidomide alone following MP-Thal induction or lenalidomide alone following MP-Len induction – To assess and compare the time from relapse/progression (after initial response) to death in patients having been treated with MP-Thal versus MP-Len – To assess the quality of life with these regimens – To assess the safety and toxicity of both regimens |
| Patient population | Previously untreated symptomatic patients with MM Age > 65 or ≤ 65 and patient ineligible for high dose therapy and peripheral stem cell transplantation |
| Study design | Prospective, multicenter, randomized |
| Duration of treatment | Expected duration of induction treatment: 9 months Maintenance therapy with lenalidomide or thalidomide will be given until relapse/progression. All patients will be followed until 10 years after registration |
| Number of patients | 668 eligible patients |
| Adverse events | Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported. |
| Planned start and end of recruitment | Start of recruitment: I 2009 End of recruitment: I 2013 |

4 Investigators and study administrative structure

| Responsibility | Name | Affiliation/Address |
|--|---|---|
| Principal Investigator (HOVON) | S. Zweegman | VU University Medical Center Amsterdam |
| Principal Investigator (NMSG) | A. Waage | University Hospital Trondheim |
| Study Coordinators | P. Sonneveld G.M.J. Bos U-H. Mellqvist M. Salomo | Erasmus Medical Center Rotterdam University Hospital Maastricht Sahlgrenska University Hospital Gothenburg Copenhagen University Hospital Copenhagen |
| Representative of Sponsor (HOVON) | P.C. Huijgens, chairman | VU University Medical Center Amsterdam |
| Representative of Co-Sponsor (NMSG) Registration | P. Gimsing HOVON and NMSG HOVON Data Center | Copenhagen University Hospital Copenhagen Erasmus Medical Center - Daniel den Hoed P.O.Box 5201 3008 AE ROTTERDAM The Netherlands tel. +31.10.7041560 fax +31.10.7041028 https://www.hdc.hovon.nl/top |
| Monitoring | HOVON HOVON Data Center NMSG NMSG | Erasmus Medical Center - Daniel den Hoed NMSG |
| Writing Committee | G.M.J. Bos K.L. Wu P. Gimsing E. Haukås, H.M. Lokhorst U-H. Mellqvist R.A.P. Raymakers M. Salomo R. Schaafsma P. Sonneveld | University Hospital Maastricht ZNA Stuivenberg, Antwerpen Copenhagen University Hospital Copenhagen Stavanger, Norway Utrecht Medical Center Utrecht Sahlgrenska University Hospital Gothenburg UMC St. Radboud Nijmegen Copenhagen University Hospital Copenhagen MST Enschede Erasmus MC Rotterdam |

| | | |
|--|-----------------------|---|
| | E. Vellenga | University Medical Center Groningen |
| | A. Waage | University Hospital Trondheim |
| | J. Westin | Sahlgrenska University Hospital Gothenburg |
| | P.W. Wijermans | Haga Hospital The Hague |
| | S. Zweegman | VU University Medical Center Amsterdam |
| Cytogenetics review | H.B. Beverloo | Erasmus Medical Center, Rotterdam |
| Statistician | C.A.G. van Montfort | HOVON Data Center, Rotterdam |
| Quality of Life | HOVON | |
| | HOVON Data Center | Erasmus Medical Center – Daniel den Hoed Rotterdam |
| | NMSG | |
| | Ullevål Hospital | Oslo |
| CRF collection (including Adverse Events) | HOVON | |
| | HOVON Data Center | Erasmus Medical Center – Daniel den Hoed, Rotterdam |
| | NMSG | |
| | Nordic Study Center | Trondheim |
| Data management | HOVON Data Center | Erasmus Medical Center – Daniel den Hoed |
| Serious Adverse Events (SAEs) notification | HOVON and NMSG | |
| | HOVON Data Center | Erasmus Medical Center – Daniel den Hoed Rotterdam Fax: +31.(0)10.4239094 |

5 Introduction

5.1 Initial treatment of elderly multiple myeloma patients

Induction therapy

Until recently melphalan/prednisone (MP) has been the standard combination of drug treatment for patients with Multiple Myeloma at an elderly age. With MP the response rate is approximately 50%, of which < 5 % are complete responses (CR). Addition of thalidomide to MP (MP-Thal) increases the overall response (OR), complete response (CR) and event-free survival (EFS) as demonstrated in two recent randomized trials.^{1,2} Despite the lower dose of melphalan used in the study of Palumbo (4 mg/m² for 7 days) compared to 0.25 mg/kg for 4 days used in other protocols, the overall survival (OS) of 64% at 3 years was similar to previously obtained with MP regimens. Addition of thalidomide resulted in a non-significant increase in OS at 3 years to 80%. A significant improvement in median overall survival is now shown by the IFM 99 06 study of the French Myeloma Study Group, using 6-weeks cycles of melphalan (0.25 mg/kg) and prednisone (2 mg/kg) for 4 days either without or with thalidomide²: 52 months in MPT treated patients versus 33 months in MP treated patients. The randomized blinded study on MPT versus MP by the Nordic Myeloma Study Group (NMSG) demonstrated that the improvement in response rate and the quality of response did not translate to improvement in progression free survival (PFS) and OS (Waage et al.³). This might partly have been caused by an increased rate of early deaths in the MPT arm in patients above 75 years of age. A similar tendency was observed in the Italian study¹ and in a randomized study comparing thal-dex versus MP (Ludwig et al. ASH 2008), suggesting a more careful approach to patients above 75 years of age. The data from the Dutch HOVON 49 study, however, do show an improvement in both response, quality of response PFS and OS.⁴ Although the positive effect of MPT on OS has been differently reported, the superior response rates, the quality of response and in most studies the improved PFS reached with MPT versus with MP led to the introduction of MPT as the standard initial treatment of elderly patients with MM in many countries. This is the basis for choosing MPT as a relevant standard against which a new regimen should be compared. This approach was supported by a recent meta analysis of all 6 randomized clinical trials comparing MPT versus MP showed an improvement in all above described outcome parameters including OS.⁵

Lenalidomide has now been tested as single agent in Multiple Myeloma, with clear clinical effects giving response in 25% of patients in heavily pretreated patients, including pretreatment with thalidomide.⁶ Responses up to 60% have been described in combination with dexamethasone or bortezomib in pretreated patients.^{7,8} In previously untreated patients, lenalidomide has demonstrated a response rate of 90% in combination with dexamethason.⁹ In addition, at the ASCO meeting in 2007 the preliminary results of the Eastern Cooperative Oncology Group

comparing high dose dexamethasone (40 mg day 1-4, 9-12, 17-20) in combination with lenalidomide and low dose dexamethasone (40 mg day 1,8,15 and 22) in combination with lenalidomide were presented, showing an OS at 1 year of 86% versus 97% respectively. Therefore, it was decided to prematurely stop the study. In the near future the IFM study group will start a phase III randomized trial comparing MPT with lenalidomide/low dose dexamethason.¹⁰

In analogy to the MP-Thal combination, the Torino group explored the combination of lenalidomide (Revlimid®) combined with MP (MP-Len). It was shown that Melphalan 0.18 mg/kg for 4 days at 4 weeks intervals was at least as effective as melphalan 0.25 mg/kg for 4 days at 4 weeks intervals, giving rise to less toxicity. With this dose, all patients experienced at least minimal response (MR) giving rise to 100% response rate. MP-Len resulted in an at least PR in 81% of patients, with an impressive short time to response exemplified by 53% at least PR after the first cycle, 66% after the third cycle and in 79% after the sixth cycle. The CR and Very Good Partial Response (VGPR) were 48% of which 24% were CRs. These responses compare favorable to their published data on MP-Thal, showing an overall response of 81% and a response of at least PR of 76%. Moreover, the quality of the response obtained with MP-Len is higher compared to MP-Thal: CR+VGPR 48% versus 37%, which is of importance in light of the correlation between high percentages of CR/VGPR and increased EFS and OS.¹ Preliminary data presented at EHA 2010 and ASH 2010 showed improved PFS of MP-Len followed by maintenance therapy compared to MP (28/31 months versus 13 months).¹¹

However, currently no data from randomized studies comparing MP-Thal versus MP-Len are available. Moreover, although from the MP-Len data it seems feasible that a high proportion of patients can achieve a combined complete and partial response rate with a fixed number of MP-Len cycles the optimal number of cycles of induction therapy has still to be determined. Moreover, the suggestion that the number of cycles of MP-Len necessary to obtain a maximum response might be less compared to the number of cycles of MP-Thal has yet to be proven.

Maintenance therapy

Despite the improvement in response rate and EFS with addition of thalidomide to standard treatment, the majority of patients develop a relapse or progressive disease in relatively short time, as indicated by an EFS of 54% at two years in patients treated with MP-Thal. This was observed in both the study of Palumbo and Facon. Palumbo used a lower dose of thalidomide during induction therapy (36 weeks) followed by maintenance therapy (100 mg thalidomide for 9 4-week cycles, followed by 100 mg maintenance) compared to Facon using a higher dose without maintenance therapy, however induction therapy lasted 72 weeks (thalidomide up to 400 mg, with a mean of 200 mg for 12 6-week cycles without maintenance therapy).^{1,2}

Although currently limited experience is available using thalidomide for maintenance treatment, a benefit of maintenance therapy has been observed in MM patients who were treated with autologous stem cell transplantation showing an increase in event free survival, although an increase in overall survival was only reported in the IFM study.^{12,13} Moreover, the Italian MP-Thal trial suggests a role for maintenance therapy as differences in OS and EFS were only observed after 9 months and 6 months respectively.¹ At present several studies investigate the role of maintenance therapy with either thalidomide or lenalidomide. The data of Palumbo support an important role for lenalidomide maintenance following MPR, as MPR without maintenance therapy has not been found to be superior to MP until now.¹¹

Lenalidomide versus thalidomide

In contrast to thalidomide, lenalidomide has a safety profile that does not include central or peripheral neuropathy. Grade 3 and 4 neuropathy and sedation are far less common than with thalidomide. The most frequent toxicity of lenalidomide is hematological toxicity (neutropenia being described in 40% of patients using Melphalan 0.18 mg/kg for 5 days in combination with 10 mg of lenalidomide) and fatigue. An incidence of 15-75% of venous thromboembolic events (VTE) has been observed in both thalidomide and lenalidomide-based regimens during induction therapy. Especially in combination with either dexamethasone, chemotherapeutic agents or both. VTEs can however be prevented by prophylactic LMWH or aspirin.^{9,15} Currently it is not known whether either LMWH or aspirin is superior in preventing VTE. A role for inflammatory and/or treatment-related NFκB activation has been suggested, being the rationale for aspirin as prophylaxis of VTE, as aspirin is known to inhibit NFκB activation.¹⁶ Moreover, the length of thrombosis prophylaxis is not exactly known. It has been suggested that prophylaxis might be necessary during the whole period of induction therapy.¹⁰

5.2 Rationale of the study

In view of the different quality of the response, time to response, overall response and toxicity profiles, it is obvious that the efficacy and safety of a fixed treatment with current standard MP-Thal needs to be compared with MP-Len. It is to be investigated whether the time to response and quality of response is improved indeed and more importantly whether this will be translated in improvement of the progression free survival. Especially in an elderly population it is to be determined whether improvement in response relates to quality of life.

In addition, there is a need to investigate whether maintenance therapy with thalidomide or lenalidomide improves the quality of the response and is feasible in the elderly population.

6 Study objectives

- ◆ To compare progression free survival with MP-Thal followed by thalidomide maintenance versus MP-Len followed by maintenance with lenalidomide
- ◆ To compare (stringent) complete and very good partial response with MP-Thal versus MP-Len
- ◆ To compare overall survival with MP-Thal versus MP-Len
- ◆ To assess and compare overall response* with MP-Thal versus MP-Len
- ◆ To assess time to maximum response with MP-Thal versus MP-Len
- ◆ To assess the effect of maintenance therapy with thalidomide alone following MP-Thal induction or lenalidomide following MP-Len, in terms of improvement of response
- ◆ To assess and compare the time from relapse/progression (after initial response) to death in patients having been treated with MP-Thal versus MP-Len
- ◆ To assess the impact on the quality of life of thalidomide compared with lenalidomide
- ◆ To assess the safety and toxicity of induction of both regimens

* overall response will be defined as (stringent) complete response, very good partial response and partial response (appendix C)

7 Study design

This is an open label, randomized, multicenter, phase III study. Details of all treatments (dose and schedule) are given in section 9. All eligible patients will be registered (see section 8) and randomized between:

Arm A: 9 cycles of MP-Thal, followed by thalidomide maintenance

Arm B: 9 cycles of MP-Len, followed by lenalidomide maintenance

8 Study population

8.1 Eligibility for randomization

All eligible patients have to be registered and randomized before start of treatment

For all patients the ISS stage (appendix B) must be known before randomization for reasons of stratification.

8.1.1 Inclusion criteria

- ◆ Previously untreated patients with a confirmed diagnosis of symptomatic multiple myeloma according to IMWG criteria (see appendix A)
- ◆ Age > 65 years or patients ≤ 65 not eligible for high dose chemotherapy and peripheral stem cell transplantation
- ◆ WHO performance status 0-3 for patients <75 years and WHO performance status 0-2 for patients ≥ 75 years (see appendix E)
- ◆ Measurable disease as defined by the presence of M-protein in serum or urine or proven plasmacytoma by biopsy (see appendix A for definitions)
- ◆ Written informed consent

8.1.2 Exclusion criteria

- ◆ Non-secretory MM
- ◆ Known hypersensitivity to thalidomide
- ◆ Systemic AL amyloidosis
- ◆ Polyneuropathy, grade 2 or higher
- ◆ Severe cardiac dysfunction (NYHA classification II-IV, appendix F)
- ◆ Severe pulmonary dysfunction
- ◆ Significant hepatic dysfunction (total bilirubin ≥ 30 µmol/l or transaminases ≥ 3 times normal level), unless related to myeloma
- ◆ Creatinine clearance <30 ml/min
- ◆ Patients with active, uncontrolled infections
- ◆ Pre-treatment with cytostatic drug, IMiDs or proteasome inhibitors. Radiotherapy or a short course of steroids (e.g. 4 day treatment of dexamethasone 40 mg/day or equivalent) are allowed.
- ◆ Patients known to be HIV-positive
- ◆ History of active malignancy during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma
- ◆ Not able and/or not willing to use adequate contraception
- ◆ Pregnancy

9 Treatment

9.1 Treatment with melphalan/prednisone/thalidomide (Arm A)

9.1.1 Treatment schedule

All patients will receive a fixed number of 9 cycles of melphalan 0.18 mg/kg per day for 4 days, prednisone 2 mg/kg per day for 4 days and thalidomide 200 mg from day 1 until 4 weeks after the last cycle of MPT, irrespective existing pancytopenia. Therapy cycles will be given every 4 weeks. Maintenance treatment with thalidomide 100 mg will start 4 weeks after start of the last cycle of MP-Thal.

Start of maintenance therapy is allowed after a minimum of 6 induction cycles, in case

- 1) after dose reductions according to the flow sheet in appendix G there is ongoing hematological toxicity at dose level -3 (melphalan and prednisone only) requiring discontinuation of MP AND subsequent recovery to ANC $\geq 1.0 \times 10^9$ /L and platelets $\geq 75 \times 10^9$ /L occurs within 6 weeks,
- 2) there is non-hematological toxicity NOT related to thalidomide.

Maintenance cycles will be repeated at 28-days intervals until relapse, progression or when a medical condition occurs that requires stopping the treatment.

| Agent | Dose/day | Route of administration | Days |
|---------------------------------------|------------|-------------------------|---|
| Melphalan | 0.18 mg/kg | p.o | 1 - 4 |
| Prednisone | 2 mg/kg | p.o | 1 - 4 |
| Thalidomide in conjunction with MP | 200 mg | p.o | Until 4 weeks after last cycle of MP |
| Thalidomide maintenance | 100 mg | p.o | Until disease progression |

After cycle 1, 3, 5, 7 and 9 evaluation will take place. In case of progressive disease after cycle 3, 5, 7 or 9 patients will go off study.

All patients will receive thrombosis prophylaxis with "aspirin" (acetylsalicylic acid 75 or 80 mg or carbasalate calcium 100 mg) during the entire period of induction therapy. Patients with a positive history of a venous thrombosis event will receive thrombosis prophylaxis with low molecular heparin. The treating physician might prefer LMWH instead of aspirin, also in patients other than with a positive history of venous thrombosis, which is allowed. Both aspirin and LMWH will be discontinued if platelets fall below 50×10^9 /L. Patients will receive prophylactic therapy with

antibiotics at the discretion of the treating physician. In case the patient experiences an infectious event requiring admission during induction therapy, prophylactic antibiotics (type of antibiotics according to local protocols; e.g. quinolone, trimethoprim-sulfamethoxazole or penicillin) are mandatory during the following courses of induction therapy. Patients will receive biphosphonates therapy at the discretion of the treating physician.

9.1.2 Dose adjustments during treatment with melphalan/prednisone/thalidomide in arm A

During the first cycle, melphalan will always be administered in a 100% dose, independently of blood cell counts. Dose reduction instructions for melphalan and thalidomide are given appendix G. If after 2 dose reductions no recovery is observed bone marrow investigation (both aspirate and biopsy) will be performed to exclude disease progression and myelodysplasia, in which case patients will go off protocol.

If the dose of prednisone 2 mg/kg leads to toxicity the dose reduction instruction for prednisone in appendix I should be applied.

9.1.3 Dose adjustments during maintenance treatment with thalidomide

Dose reduction instructions for thalidomide are given in appendix H.

Attention: Dose reduction in maintenance (appendix H) differs from dose reduction schemes during induction (appendix G).

9.1.4 Special precautions during treatment with thalidomide

Thalidomide is known to be teratogenic. In order to prevent pregnancies during the use of thalidomide, both patient information, patient registration and patient counseling will occur as defined in the Risk Management Programmes running in each separate country.

9.2 Treatment with melphalan/prednisone/lenalidomide (Arm B)

9.2.1 Treatment schedule

All patients will receive a fixed number of 9 cycles of melphalan 0.18 mg/kg per day for 4 days, prednisone 2 mg/kg per day for 4 days and lenalidomide 10 mg, irrespective of existing pancytopenia at the start of treatment. Lenalidomide will be given on day 1-21 followed by a 1 week interval. Therapy cycles will be given every 4 weeks.

Maintenance treatment with lenalidomide will be started 4 weeks after start of the last MP-Len cycle, at a dose of 10 mg days 1-21.

Start of maintenance therapy is allowed after a minimum of 6 induction cycles, in case

- 1) after dose reductions according to the flow sheet in appendix G there is ongoing hematological toxicity at dose level -3 (melphalan and prednisone only) requiring discontinuation of MP AND subsequent recovery to ANC $\geq 1.0 \times 10^9$ /L and platelets $\geq 75 \times 10^9$ /L occurs within 6 weeks,
- 2) there is non-hematological toxicity NOT related to lenalidomide.

Maintenance cycles will be repeated at 28-days intervals until relapse, progression or when a medical condition occurs that requires stopping the treatment.

| Agent | Dose/day | Route | Days |
|--|------------------|-------|--|
| Melphalan | 0.18 mg/kg | p.o | 1 - 4 |
| Prednisone | 2 mg/kg | p.o | 1 - 4 |
| Lenalidomide in conjunction with MP | 10 mg once a day | p.o | 1 - 21 |
| Lenalidomide maintenance | 10 mg once a day | p.o | 1-21 of every 28 day cycle until disease progression |

After cycle 1, 3, 5, 7 and 9 evaluation will take place. In case of progressive disease after cycle 3, 5, 7 or 9 patients will go off study.

All patients will receive thrombosis prophylaxis with "aspirin" (acetylsalicylic acid 75 or 80 mg or carbasalate calcium 100 mg) during the entire period of induction therapy. Patients with a positive history of a venous thrombosis event will receive thrombosis prophylaxis with low molecular heparin. The treating physician might prefer LMWH instead of aspirin, also in patients other than with a positive history of venous thrombosis, which is allowed. Both aspirin and LMWH will be discontinued if platelets fall below 50×10^9 /L. Patients will receive prophylactic therapy with antibiotics at the discretion of the treating physician. In case the patient experiences an infectious event requiring admission during induction therapy, prophylactic antibiotics (type of antibiotics according to local protocols; e.g. quinolone, trimethoprim-sulfamethoxazole or penicillin) are mandatory during the following courses of induction therapy. Patients will receive biphosphonates therapy at the discretion of the treating physician.

9.2.2 Dose adjustments during treatment with melphalan/prednisone/lenalidomide in arm B

During the first cycle, melphalan will always be administered in a 100% dose, independently of blood cell counts. Dose reduction instructions for melphalan and lenalidomide are given in appendix G.

If after 2 dose reductions no recovery is observed bone marrow investigation (both aspirate and biopsy) will be performed to exclude disease progression and myelodysplasia, in which case patients will go off protocol.

If the dose of prednisone 2 mg/kg leads to toxicity the dose reduction instruction for prednisone in appendix I should be applied.

9.2.3 Dose adjustments during maintenance treatment with lenalidomide

Dose reduction instructions for lenalidomide are given in appendix H.

Attention: Dose reduction in maintenance (appendix H) differs from dose reduction schemes during induction (appendix G).

9.2.4 Special precautions during treatment with lenalidomide

Lenalidomide might be teratogenic. In order to prevent pregnancies during the use of lenalidomide, both patient information, patient registration and patient counseling will occur as defined in the Risk Management Programmes running in each separate country.

9.3 Drug supply

Thalidomide will be provided by Celgene. In the Netherlands and Belgium the drug will be shipped from the VU University Medical Center Pharmacy to the pharmacy at the study sites. In case thalidomide is registered and reimbursed, commercially available drug will be prescribed. In the Nordic countries commercially available drug will be prescribed.

Lenalidomide will be supplied as 5 mg capsules for oral administration by Celgene. The drug will be shipped from the VU University Medical Center Pharmacy to the pharmacy at the study sites in the Netherlands and in Belgium, and from the central pharmacy in each individual country of the NMSG to the pharmacy at the study sites in that specific country in individual wallets with multi-language tear-off labels. Two wallets will contain a sufficient number of capsules to last for 21 days of dosing.

10 End of protocol treatment

- ◆ Progression/relapse during treatment
- ◆ Excessive toxicity (including toxic death)
- ◆ Intercurrent death
- ◆ No compliance of the patient (especially refusal to continue treatment)

11 Required clinical evaluations

11.1 Time of clinical evaluations

- ◆ At entry: before start of treatment
- ◆ During induction therapy after 1, 3, 5, 7 and 9 cycles
- ◆ During maintenance therapy every 4 weeks

11.2 Required investigations

- ◆ Disease related symptoms and WHO staging.
- ◆ Physical examination at entry of the study and during follow up
- ◆ Quantitative M-protein in serum and urine by gel electrophoresis preferably. Nephelometry or turbidometry are allowed, see appendix C for instructions..
- ◆ Qualitative M-protein in serum and urine by immunofixation.
- ◆ Immunofixation and Free Light Chain ratio to determine the achievement of CR and sCR respectively.
- ◆ Bone marrow aspiration (obligatory) and biopsy (optional) at entry, including (molecular) cytogenetic evaluation
- ◆ Repeated bone marrow aspiration (biopsy is optional) in case the decline in M-protein suggest achievement of CR or sCR (see appendix C for response criteria). In case no BM biopsy is performed a stringent CR can be confirmed by kappa/lambda labeling using immunophenotyping of the BM aspirate.
- ◆ Radiographic assessment of lytic bone lesion at entry, after completion of induction therapy and in case of confirming (s)CR and VGPR
If an MRI is performed at entry and found positive it should be repeated after induction chemotherapy and in case CR is suggested.

Required investigations at entry, during treatment and during follow up

| | At entry | 4 weeks after start of cycles 1,3,5,7,9 | During maintenance every 4 weeks and during follow up every 8 weeks ²⁾ |
|---|------------------|---|---|
| Medical history | x | x | x |
| Physical examination | x | x | x |
| Hematology | x | x ¹⁾ | x |
| Blood chemistry | x | x | x |
| Immunochemistry | x | x | x |
| Bone marrow | | | |
| Bone marrow aspirate | x | x ³⁾ | x ³⁾ |
| Bone marrow biopsy | x ⁴⁾ | x ⁴⁾ | x ⁴⁾ |
| Cytogenetic analysis (karyotyping/FISH) ⁵⁾ | x | | |
| BM cryopreservation⁶⁾ | x | | |
| Specific investigations | | | |
| ISS β_2 -microglobulin and albumin | x | | |
| Creatinine clearance | x | o.i | o.i |
| Skeletal survey | x ⁷⁾ | x ⁸⁾ | x ⁸⁾ |
| MRI or CT ⁹⁾ | o.i. | o.i. | o.i. |
| X-thorax | x | | |
| ECG | x | | |
| Additional investigations | o.i. | o.i. | o.i. |
| PB cryopreservation ¹⁰⁾ | x ¹⁰⁾ | o.i. ¹⁰⁾ | o.i. ¹⁰⁾ |
| Quality of Life | x | x ¹¹⁾ | x ¹¹⁾ |

o.i. on indication

- 1) Hematology every 2 weeks. In case no hematological toxicity occurs in the cycles 1, 2 and 3 every 4 weeks is allowed. As soon as in the following cycles hematological toxicity occurs, the interval will be shortened to 2 weeks.
- 2) During maintenance therapy out clinic visits haematology, blood chemistry and immunochemistry will be performed every four weeks. After discontinuation of maintenance therapy follow up visits haematology, blood chemistry and immunochemistry will be performed every eight weeks or at shorter intervals at the discretion of the treating physician until progression. These visits in follow up may be conducted alternately via telephone and in the clinic, blood sampling should be performed every 8 weeks.
- 3) In case of confirming CR, at the moment of complete disappearance of serum/urine M-component by immunofixation, a bone marrow aspirate is indicated. After a confirmed CR repeated sampling of bone marrow aspirate is no longer necessary. To confirm stringent CR, either kappa/lambda labeling of a bone marrow biopsy or immunophenotyping of the BM aspirate has to be performed.
- 4) A bone marrow biopsy is optional. In case of confirming stringent CR at the moment of complete disappearance of serum/urine M-component by immunofixation, either a kappa/lambda labeling of a bone marrow biopsy or immunophenotyping of a BM aspirate has to be performed.
- 5) See below under bone marrow.
- 6) Will be performed at entry in every patient for future biological studies (see appendix J for procedures for collecting and handling samples)
- 7) Only osteolytic lesions observed at total body X-ray will be criterium for symptomatic MM only (see appendix A), abnormalities at MRI or CT will be monitored in order to determine response
- 8) After completion of induction therapy, in case of confirming (s)CR and VGPR and when clinically indicated

- 9) In case of (extramedullary) plasmacytoma, the MRI or CT should be repeated after cycle 9 of induction treatment and yearly thereafter or in case CR is suggested
- 10) Will be performed at entry in every patient and during treatment / follow up in patients if disease progression / relapse occurs for SNP analysis and future biological studies see appendix J for procedures for collecting and handling samples
- 11) Quality of life after cycle 3 and 9 (or earlier in case of prematurely discontinuation of induction treatment), and after 6 and 12 months of maintenance

Medical history

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

Only at entry:

- Occupational history
- Prior and present other diseases
- Antecedent hematological or oncological diseases
- Previous chemotherapy or radiotherapy

Physical examination

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

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

Hematology

- Hemoglobin
- Leukocyte count, Neutrophil count
- Platelets
- At entry: PB cryopreservation

Blood chemistry

- Creatinine
- Liver enzymes

- Total bilirubin
- Alkaline phosphatase
- Total proteins
- Albumin
- LDH
- Calcium

Immunochemistry

- At entry: Qualitative and Quantitative serum and urine (24 hrs urine) M-protein, including immunofixation.
- Evaluation: Qualitative and Quantitative serum and urine (24 hrs urine) M-protein, including immunofixation to confirm CR. FLC ratio only to confirm (s)CR.

Bone marrow

Bone marrow aspirate at entry for:

- Morphology
- Conventional cytogenetic analysis will be performed in all Dutch centers and in Nordic countries where available. Each cytogeneticist, responsible for the cytogenetic analysis of the patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study. A filled out cytogenetic form together with 2 representative karyotypes and a copy of the original cytogenetic report is requested to be sent within 3 months to the HOVON Data Center for central review.
- FISH analysis will be performed for chromosome 13q deletions, the presence of 14q32 abnormalities (t(4;14)(p16;q32) and t(14;16)(q32;q23)) and deletion of p53 (17p13). Conditions for FISH will be standardized by the HOVON Cytogenetic Working Party. In case FISH analysis has not been performed at entry, it will be performed either on cryopreserved bone marrow or bone marrow slides (see appendix J).

Bone marrow aspirate at response evaluation for confirmation of CR.

Bone marrow biopsy at entry (optional) and to confirm (stringent) complete response, including kappa lambda labeling. In case no BM biopsy is performed a stringent CR can be confirmed by kappa/lambda labeling using immunophenotyping of the BM aspirate. After a confirmed CR repeated sampling of bone marrow aspirate is no longer necessary.

Specific investigations

- Serum β 2-microglobulin
- Creatinine clearance if increased serum creatinine
- Radiographic skeletal survey including skull, pelvis, vertebral column and long bones
- X-Thorax
- ECG

Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis
- Bleeding time, aPTT, PT(INR).
In case of prolonged aPTT and/or PT(INR) a factor X activity has to be determined
- Cryoglobulins, cold agglutinins
- Fundoscopy

- Spirometry

Quality of Life

See chapter 11.4

11.3 Response evaluation

The response will be evaluated after cycle 1, 3, 5, 7 and 9 and at 2 months intervals during maintenance treatment. Response will be evaluated according to appendix C.

11.4 Quality of Life assessment

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

- ◆ EORTC QLQ-C30 questionnaire

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

- ◆ EORTC QLQ-MY20

This questionnaire measures specific aspects of multiple myeloma, i.e. specific pain complaints.

In a number of hospitals HO 87 MM patients will be asked to participate in an extensive Quality of Life study. Participants will be asked also to fill out the questionnaires EQ-5D; NTx subscale of FACT/GOG-NTx; EORTC-QLQ-info26 and SF-HLQ. All questionnaires will be reviewed by the Ethics Committee.

- ◆ EuroQol 5 Dimensions (EQ-5D) questionnaire measures generic quality of life and can be converted into a 'health utility' score, ranging from 0.0 (death) to 1.0 ('perfect health'). The 5 dimensions of the self-classifier are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with 3 levels of severity.
- ◆ The NTx subscale of the Functional Assessment of cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire (FACT/GOG-NTx) is internationally validated and comprises 11 items that specifically deal with neuropathy. This questionnaire is a reliable instrument for assessing the impact of neuropathy on HRQoL.
- ◆ The EORTC-QLQ-INFO25 questionnaire will be used to assess cancer patients' perception of the information received during different phases of the care.
- ◆ The SF-HLQ questionnaire will be used to assess the societal costs.

HOVON participants

Collection of the QoL questionnaires will be performed in the following manner:

A QoL coordinator will be assigned in each participating center. During informed consent the patient will be asked to participate in the quality of life part of this study. As soon as a patient is randomized at the HOVON Data Center (HDC), the QoL coordinator is notified by e-mail. Patient subject number, date of birth, date of randomization are mentioned in this e-mail. The baseline questionnaire will be handed over to the patient by the QoL coordinator/local investigator. The completed questionnaire should be sent to HOVON Data Center.

The following QoL questionnaires will be presented to the patient by the QoL coordinator/local investigator at the appropriate time points (see below), and sent to the HOVON Data Center. The coordinator will be reminded in time to hand over the questionnaire at the correct date. If a QoL questionnaire has not been received by HOVON Data Center within 14 days of the expected date, a reminder/request will be sent to the local QoL coordinator to collect and send in the questionnaire.

NMSG participants

The patients are randomized at the HOVON center. If the patient has signed the consent to participate in the QoL study, he/she will be asked to fill in the baseline questionnaire which is sent to QoL center at Ullevål Hospital, Oslo. All centers will be provided with questionnaires and prestamped reply envelopes. When the first questionnaire is received at the QoL center, new questionnaires with prestamped envelopes will be sent out at regular intervals. The procedure in the Dutch and NMSG branch is similar except that Ullevål Hospital will be the Nordic QoL center.

Quality of life will be measured:

- at entry
- after cycle 3, approx. at 3 months after start cycle 1
- after cycle 9, approx. at 9 months after start cycle 1 or earlier in case of prematurely discontinuation of induction treatment
- at 6 months after start of maintenance therapy
- at 12 months after start of maintenance therapy

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

12 Toxicity assessment

Thalidomide

Most frequently reported adverse events are constipation, neuropathy, rash, weakness and fatigue. Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

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.

Thalidomide and Lenalidomide may increase the risk on Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE). DVT and PE are serious adverse events (SAE).

Any suspected foetal exposure to lenalidomide or thalidomide must be reported within 24 hours of being made aware of the event.

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

13 Reporting serious adverse events and SUSARS

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 a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse reaction (AR)

Adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected.

Serious adverse event (SAE)

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

- ◆ death
- ◆ a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- ◆ hospitalization or prolongation of hospitalization
- ◆ deep venous thrombosis (DVT)
- ◆ pulmonary embolism (PE)
- ◆ significant / persistent disability
- ◆ a congenital anomaly / birth defect
- ◆ any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

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

Unexpected SAE

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

Suspected unexpected serious adverse reaction (SUSAR)

All suspected ARs which occur in the trial and that are both unexpected and serious.

Protocol treatment period

The protocol treatment period is defined as the period from registration until 30 days after stopping of the protocol treatment.

13.2 Reporting of (serious) adverse events**Adverse event**

All AEs CTCAE grade ≥ 2 and polyneuropathy grade ≥ 1 have to be reported on the CRF.

All adverse events, with the exception of progression of multiple myeloma, will be reported from the first study-related procedure until 30 days following the last dose of study drug or until the start of subsequent systemic antimyeloma therapy, if earlier. Resolution information after 30 days should also be provided. Adverse events occurring after 30 days should also be reported if considered related to study drug.

SAE and Unexpected serious adverse event

During protocol treatment **HOVON and NMSG participants** must report all SAEs directly to the HOVON Data Center by fax **within 24 hours of the initial observation of the event**, except hospitalizations for:

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

complication considered to be at least possibly related to the study drug remains a reportable serious adverse event.

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

At any time after the protocol treatment period, Serious Adverse Events that are considered to be at least **suspected** to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, within 24 hours after the SAE was known to the investigator.

Foetal exposure to lenalidomide or thalidomide

Female of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 28 days of the subject's last dose of study drug, are considered events to be reported immediately to the Sponsor.

If the subject is on study drug, the study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor who will inform the manufacturer immediately by facsimile using an SAE Report Form. All details should be documented on the pregnancy form CRF. The patient should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counseling. 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 [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted foetus]), the Investigator should follow the procedures for reporting SAEs. In the case of a live "normal" birth, the Sponsor should be advised as soon as the information is available. All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported.

Male Subject:

Female partners of males taking investigational product should be advised to call their healthcare provider immediately if they get pregnant and male subjects should notify their doctors as well. The pregnancy should be reported to the Sponsor. All details should be documented on the pregnancy form CRF.

Causality assessment

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following:

| 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. |

13.3 Processing of serious adverse events reports

The HOVON Data Center will forward all reports within 24 hours of receipt to the principal investigator and the product manufacturer. The HOVON Data Center will assess all SAE reports for SUSAR criteria.

Suspected unexpected serious adverse reactions (SUSARs) will be reported by HOVON Data Center to the investigators, to the Ethics Committees that approved the study and to applicable Health Authorities within required timelines. The manufacturer will receive a copy.

The HOVON Data Center will ensure that a six-monthly line listing of all reported SAE's is provided to the Ethics Committee(s) if this is required by national laws or regulations or by the procedures of the Ethics Committee.

13.4 Annual safety reporting

The HOVON Data Center will provide an annual safety report to the Ethics Committees that approved the study and to applicable Health Authorities within required timelines. The manufacturer will receive a copy.

14 Endpoints

14.1 Primary endpoint

- ◆ Progression free survival, defined as time from registration to progression or death from any cause
- ◆ Response rate defined as sCR, CR or VGPR

14.2 Secondary endpoints

- ◆ Overall response rate defined as sCR, CR, VGPR or PR
- ◆ Overall survival, measured from time of registration
- ◆ Quality of response during maintenance, measured as improvement of response (from start maintenance till progression)
- ◆ Time to maximum response, defined as time from registration to maximum response
- ◆ Time to death from relapse/progression (after initial response), measured from time of first relapse/progression
- ◆ Safety and toxicity as defined by type, frequency and severity of adverse events as defined by the National Cancer Institute (NCI) Common Terminology Criteria (CTC), version 3.0
- ◆ Quality of life as defined by the EORTC QLQ-C30 definitions.

15 Randomization

15.1 Regulatory Documentation

The following documents must be provided to the HOVON Data Center before enrollment of the first patient.

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:

- ◆ HDC 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 (dated and signed if not recently provided);
- ◆ signed local investigator signature page ;
- ◆ local lab accreditation and list of local lab normal values (if not recently provided);
- ◆ any other documentation required by local regulations.

15.2 Randomization

Eligible patients should be randomized before start of treatment. Patients need to be registered at the HOVON Data Center of the Erasmus MC Rotterdam – location Daniel via the Internet via TOP (Trial Online Process; <https://www.hdc.hovon.nl/top>) or by phone call: +31.10.7041560 or fax +31.10.7041028 Monday through Friday, from 09:00 to 17:00 CET. A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

Protocol number

Institution name

Name of caller/responsible investigator

Sex

Date of birth

Date written informed consent

ISS stage

Will patient participate in the quality of life study

'Risk Management Program' discussed with patient

Approval for blood storage for scientific research

Approval for bone marrow storage for scientific research

Eligibility criteria

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

Each patient will be given a unique patient study number. Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

16 Data collection

16.1 CRFs

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

- ◆ inclusion and exclusion criteria;
- ◆ baseline status of patient including medical history and stage of disease;
- ◆ timing and dosage of protocol treatment;
- ◆ adverse events;
- ◆ parameters for response evaluation;
- ◆ any other parameters necessary to evaluate the study endpoints;
- ◆ survival status of patient;
- ◆ reason for end of protocol treatment.
- ◆ Second primary malignancy report form

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient name code (as documented at registration) to be filled out before completing the form.

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

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

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

NMSG participants

NMSG will elaborate a web-based CRF version of the CRF. CRFs are stored at the Nordic Study Center and will be transmitted to HOVON Data Center at regular intervals.

16.2 Monitoring

Sites participating in this trial will be subject to Site Evaluation Visits on behalf of the sponsor to verify that trial conduct at the site is in compliance with GCP and the applicable regulatory requirements.

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

16.3 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 and associated personnel before the study, and monitoring visits by the sponsor. CRF completion guidelines will be provided. The data will be entered into the clinical study database and verified for accuracy.

16.4 On-site audits

The local investigator/institution 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. Subject privacy must, however, be respected.

Similar auditing procedures may also be conducted by agents of any regulatory body. 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

After entry of the last patient an additional follow up of one year is planned before the first analysis. Based on previous studies, the expected accrual rate is 155 patients per year.

For the detection of a relative hazard ratio of 0.714 for the MP-Len arm and with an expected median PFS time in the MP-Thal arm of 20 months (as in Fayers et.al.), with $\alpha=0.05$ (two-sided) and 90% power, 377 events have to be observed. This number of events is expected to be reached after the recruitment of 668 patients with an average accrual rate of 155 patients per year. A relative hazard ratio of 0.714 corresponds to an increase of median PFS to 28 months in the MP-Len arm.

17.2 Statistical analysis

All main analyses will be according the intention to treat principle, restricted to eligible patients.

17.2.1 Efficacy analysis

Main endpoint for the comparison of the two treatment arms will be PFS defined as time from registration to progression or death from any cause, with adjustment for the stratification factors. Secondary endpoints are response rate (sCR, CR, VGPR or PR), overall survival and quality of response during maintenance and time to maximum response.

Formal tests for the difference in PFS between the two treatment arms will be done with Cox regression analysis. Actuarial estimates of competing risks of failure (progression or death without progression) will be made for each treatment arm.

A preliminary efficacy analysis on response (CR or VGPR) is planned immediately after end of recruitment. This analysis will be restricted to the first 300 patients, because not all responses will be available at that moment. No conclusions will be drawn based on this analysis.

In addition to the first analysis for the main endpoint and the preliminary analysis, a third analysis is planned after an additional follow up of two years after inclusion of the last patient.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be mainly done primarily by tabulation of the incidence of side effects and infections with CTCAE grade 3 or more (see Appendix D) by treatment arm and cycle.

17.2.3 Additional analyses

Additional analysis involve the analysis of prognostic factors, including ISS stage and cytogenetics (e.g. t(4;14)), with respect to response rate, PFS and OS from registration. Logistic and Cox regression will be used for this purpose.

17.3 Interim analysis

One interim analysis is planned primarily to guard against unfavorable results in the Lenalidomide arm. Results of this interim analysis 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 discussions. The interim analysis is planned after 50 events with regard to PFS, which is the primary endpoint for this analysis.

At this 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 and the incidence of SAEs and other adverse events and infections. Special attention will be paid to thrombosis, if the incidence of thrombosis is higher than 10% in one of the treatment arms, modifications of prophylaxis therapy is recommended.

The DSMB is free in her public recommendations to the principal investigators and the confidential recommendations to the trial statistician, but the following guidelines apply:

- Primary purpose of the interim analysis is to guard against a lower PFS in the MP-Len arm. A lower PFS in the MP-Len arm with a P-value < 0.1 (logrank test) is a good reason to recommend stopping of the trial or recommendations for modifications.
- A benefit in terms of PFS in the MP-Len arm is in general no good reason to recommend early stopping of the study, unless the associated P-value is very extreme (P < 0.001, logrank)

The study will be closely and sequentially monitored before the interim analysis. Monitoring will be based on the reported SAEs which are not subjected to data delay.

17.4 Data and Safety monitoring board

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

17.5 Statistical analysis of the quality of life assessment

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

18 Ethics

18.1 Accredited ethics committee or Institutional review board

The study protocol and any substantial amendment will be approved by an accredited Ethics Committee or Institutional Review Board. The principal investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subject's health. The investigator will take care that all subjects are kept informed.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Tokyo 2004), the ICH-GCP Guidelines, the EU directive for Good Clinical Practice (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study.

18.3 Patient information and consent

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

19 Trial insurance

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

Patients entered by NMSG participants will be insured according to the procedures in the individual countries.

20 Publication policy

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

Authors of the manuscript will include the study coordinator(s), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the HOVON data manager in charge of the trial, and others who have made significant scientific contributions. There will be a reasonable distribution of authors between the HOVON and the NMSG.

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

Any publication, abstract or presentation based on patients included in this study must be approved by the Principal Investigator and Study Coordinator(s). 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 end-points unless the final results of the trial have already been published.

Glossary of abbreviations
(in alphabetical order)

| | |
|-------|---|
| AE | Adverse Event |
| AL | Amyloid Light-chain |
| ANC | Absolute Neutrophil Count |
| BJ | Bence Jones |
| BM | Bone Marrow |
| Ca | Calcium |
| CKTO | Commissie voor Klinisch Toegepast Onderzoek' |
| CR | Complete Remission |
| CRAB | Calcium elevation, Renal insufficiency, Anemia and Bone abnormalities |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CTC | Common Toxicity Criteria |
| DLT | Dose Limiting toxicity |
| DVT | Deep Venous Thrombosis |
| ECG | Electrocardiogram |
| EBMT | European Group for Blood and Marrow Transplantation |
| FISH | Fluorescence In Situ Hybridization |
| FLC | Free Light Chain |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte-Colony Stimulating Factor |
| GI | Gastro-intestinal |
| HB | Hemoglobin |
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leukocyte histocompatibility Antigen |
| HOVON | Dutch-Belgian Hematology-Oncology Cooperative Group |
| ICH | International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use |
| IFM | Intergroup Français de Myelome |
| 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 |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PO | Per Os |
| PR | Partial Response |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |
| SD | Stable Disease |
| SPEP | Serum protein electro-phoresis |
| ULN | Upper Limit of Normal |
| UPEP | Urine protein electro-phoresis |
| WHO | World Health Organization |
| WMO | Wet Medisch-Wetenschappelijk Onderzoek met mensen |

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A. Criteria for symptomatic MM and measurable disease

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

Criteria for symptomatic MM

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

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

AND

Clonal plasma cells in bone marrow or plasmacytoma

AND

At least 1 myeloma-related dysfunction*:

calcium > 2.65 mmol/l

renal insufficiency (creatinine > 177 μ mol/l)

anemia (Hb < 6.2 mmol/l or > 1.25 mmol/l below normal limit)

bone disease (lytic lesions or osteopenia)[^]

* must be attributable to the underlying plasma cell disorder

[^] as observed at whole body X-ray

Criteria for measurable disease

Serum M-protein \geq 10 g/l or

Urine M-protein \geq 200 mg/24 hours or

Proven plasmacytoma by biopsy

B. International Staging System for Multiple Myeloma (ISS stage)

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

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

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

C. Response criteria for Multiple Myeloma

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

RESPONSE CRITERIA

| <i>Response subcategory</i> | <i>Response criteria^a</i> |
|-----------------------------|---|
| sCR* | CR as defined below plus <ul style="list-style-type: none"> ▪ Normal FLC ratio and ▪ Absence of clonal cells in bone marrow^b by immunohistochemistry or immunophenotyping^c |
| CR | <ul style="list-style-type: none"> ▪ 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 | <ul style="list-style-type: none"> ▪ ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h ▪ In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required |
| SD ^d | Not meeting criteria for CR, VGPR, PR or progressive disease |

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

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

^a All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

^b Confirmation with repeat bone marrow examination not needed.

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

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

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

RELAPSE CRITERIA

| <i>Relapse subcategory</i> | <i>Relapse criteria</i> |
|--|--|
| <p>Progressive disease^a</p> <p>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)</p> | <p>Progressive Disease: requires any one or more of the following:</p> <ul style="list-style-type: none"> ▪ Increase of $\geq 25\%$ from lowest response level in serum M-component (the absolute increase must be ≥ 0.5 g/dl)^b and/or ▪ Increase of $\geq 25\%$ from lowest response level in urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or ▪ Increase of $\geq 25\%$ from lowest response level in bone marrow plasma cell percentage: the absolute % must be $\geq 10\%$^c ▪ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas ▪ Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder |
| <p>Clinical relapse^a</p> | <p>Clinical relapse requires one or more of:</p> <p>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</p> <ol style="list-style-type: none"> 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcaemia (> 2.65 mmol/l) [11.5 mg/dl] 4. Decrease in hemoglobin of ≥ 1.25 mmol/l [2 g/dl] 5. Rise in serum creatinine by 177 μmol/l or more [2 mg/dl or more] |
| <p>Relapse from CR^a</p> <p>(To be used only if the end point studied is DFS)^d</p> | <p>Any one or more of the following:</p> <ul style="list-style-type: none"> ▪ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ▪ Development of $\geq 5\%$ plasma cells in the bone marrow^c ▪ Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypocalcaemia see above) |

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

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

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

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

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

PRACTICAL DETAILS OF RESPONSE EVALUATION

Laboratory tests for measurement of M-protein

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

Follow-up to meet criteria for PR or SD

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

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

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

D. Common Toxicity Criteria

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

<http://ctep.cancer.gov/reporting/ctc.html>

<http://www.eortc.be/Services/Doc/CTC>

<http://www.hovon.nl>

E. 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

F. 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

G. Management of toxicity during a cycle**Dose levels****Dose Levels for Melphalan during Induction Therapy**

| Dose Levels | Melphalan* |
|---------------|---|
| Starting Dose | 0.18 mg/kg once daily on days 1-4 every 28 days |
| Dose Level -1 | 0.14 mg/kg once daily on days 1-4 every 28 days |
| Dose Level -2 | 0.10 mg/kg once daily on days 1-4 every 28 days |
| Dose Level -3 | 0.10 mg/kg once daily on days 1-4 every 28 days |

Dose Levels for Thalidomide / Lenalidomide during Induction Therapy

| Dose Levels | Thalidomide | Lenalidomide |
|---------------|------------------|---|
| Starting Dose | 200 mg every day | 10 mg once daily on days 1-21 every 28 days |
| Dose Level -1 | 100 mg every day | 7.5 mg once daily on days 1-21 every 28 days* |
| Dose Level -2 | 50 mg every day | 5.0 mg once daily on days 1-21 every 28 days |
| Dose Level -3 | no thalidomide | no lenalidomide |

* alternately 10 and 5 mg.

Dose reduction instructions

Arm A: Dose Modification Instructions for Thalidomide and Melphalan for Haematologic Toxicity during a Cycle

| Toxicity | Dose Modification | |
|--|----------------------|--|
| | Thalidomide | Melphalan |
| Grade 4 Neutropenia (ANC < 0.5 x 10 ⁹ /L) or Febrile neutropenia (fever ≥ 38.5 °C and ANC < 1 x 10 ⁹ /L) | no dose modification | If the subject was not receiving GCSF therapy, initiate GCSF therapy on Day 5 of next cycle ¹ and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle ² . |
| Grade 4 Thrombocytopenia (Platelets < 25 x 10 ⁹ /L) | no dose modification | Decrease by one dose level when dosing restarted at next cycle ² . |

¹ Pegylated G-CSF (Neulasta[®] 6 mg) on day 5.

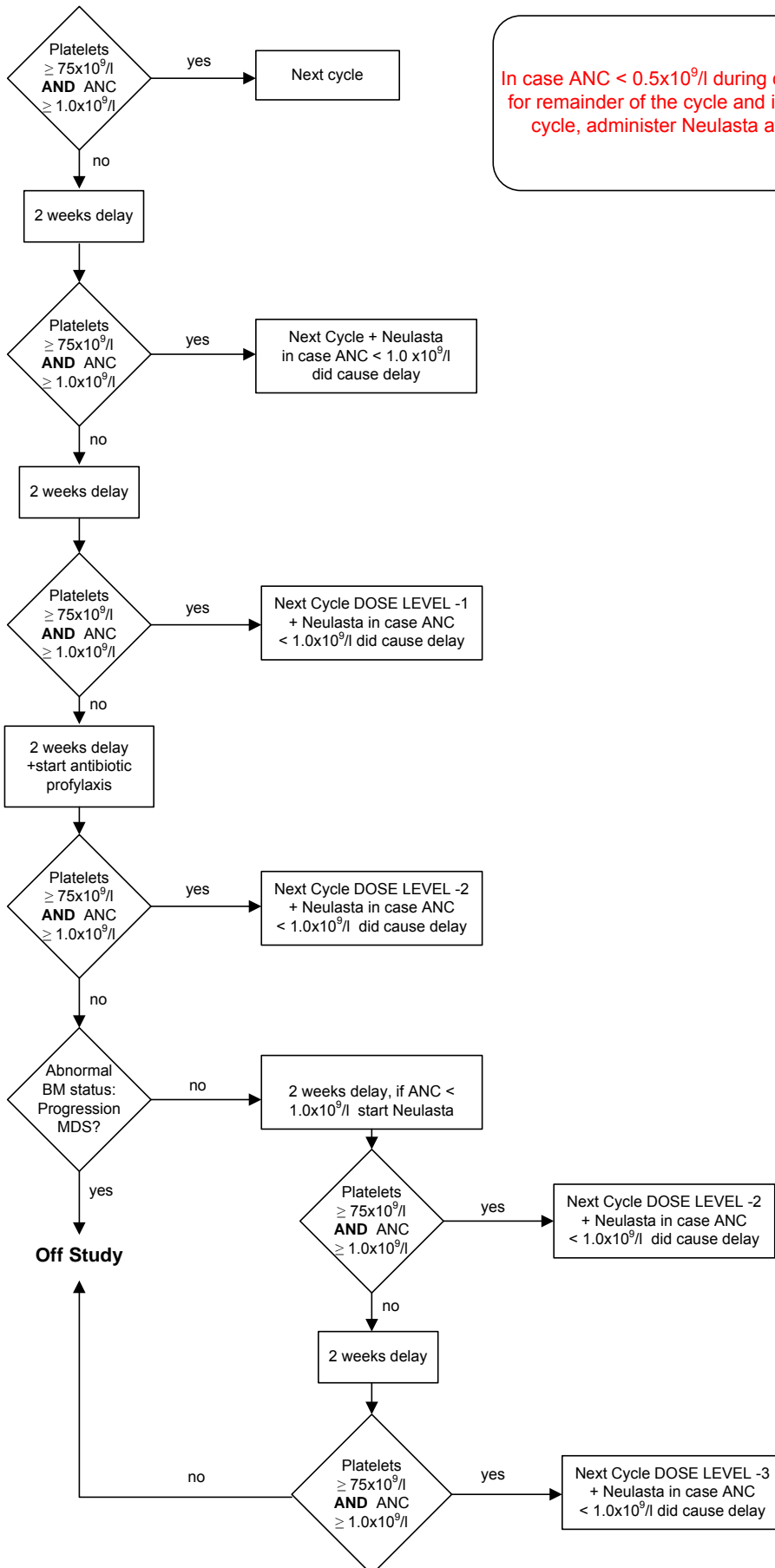
² The next cycle is allowed if ANC ≥ 1.0 x 10⁹ /L and platelets ≥ 75 x 10⁹ /L. For dose reductions see flow chart (next page). A delay of 2 weeks is allowed. If recovery occurs after a 4 week delay only, decrease by an additional dose level. After 2 dose reductions bone marrow examination has to be performed in order to exclude progression of disease or myelodysplasia. In case ANC < 1.0 x 10⁹ /L start pegylated G-CSF. In case recovery (ANC ≥ 1.0 x 10⁹ /L and platelets ≥ 75 x 10⁹ /L) occurs within 2 weeks, continue therapy at dose level -2. In case no recovery occurs, a delay of an additional 2 weeks is allowed. In case recovery after 2 weeks continue therapy at dose level -3.

Arm B: Dose Modification Instructions for Lenalidomide and Melphalan for Haematologic Toxicity during a Cycle

| Toxicity | Dose Modification | |
|--|--|--|
| | Lenalidomide | Melphalan |
| 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 the subject was not receiving GCSF therapy, initiate GCSF therapy ¹ on day 5 of next cycle and maintain dose of lenalidomide if neutropenia was the only DLT. Otherwise decrease by one dose level at start of next cycle. | If the subject was not receiving GCSF therapy, initiate GCSF therapy ¹ on day 5 of next cycle and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle ² . |
| Grade 4 Thrombocytopenia (Platelets < 25 x 10 ⁹ /L) | Stop the dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle. | Decrease by one dose level when dosing restarted at next cycle ² . |

¹ Pegylated G-CSF (Neulasta[®] 6 mg) on day 5.

² The next cycle is allowed if ANC ≥ 1.0 x 10⁹ /L and platelets ≥ 75 x 10⁹ /L. For dose reductions see flow chart (next page). A delay of 2 weeks is allowed. If recovery occurs after a 4 week delay only, decrease by an additional dose level. After 2 dose reductions bone marrow examination has to be performed in order to exclude progression of disease or myelodysplasia. In case ANC < 1.0 x 10⁹ /L start pegylated G-CSF. In case recovery (ANC ≥ 1.0 x 10⁹ /L and platelets ≥ 75 x 10⁹ /L) occurs within 2 weeks, continue therapy at dose level -2. In case no recovery occurs, a delay of an additional 2 weeks is allowed. In case recovery after 2 weeks continue therapy at dose level -3.



In case ANC < 0.5x10⁹/l during courses, stop Lenalidomide for remainder of the cycle and irrespective of ANC at next cycle, administer Neulasta at day 5 of the next cycle

Dose Modification Instructions for Thalidomide and Lenalidomide for Polyneuropathy during a Cycle

| Toxicity | Action Thalidomide/Lenalidomide |
|-------------------|---|
| Grade 1 | no dose adjustment |
| Grade 2 | reduction of daily dose by one dose level per cycle until toxicity resolved to grade ≤ 1 , remain at reduced dose. Minimum doses as indicated above. |
| Grade 3 | withhold thalidomide/lenalidomide until toxicity resolved to grade ≤ 1 , resume at one dose level below the latest use daily dose. Minimum doses as indicated above. |
| Grade 3 recurring | withhold thalidomide/lenalidomide until toxicity resolved to grade ≤ 1 , resume at one dose level below the latest use daily dose. Minimum doses as indicated above. |
| Grade 4 | End treatment with thalidomide/lenalidomide |

Dose Modification Instructions for Thalidomide and Lenalidomide for other Non-Haematologic Toxicity during a Cycle

| Toxicity | Dose modification Thalidomide/Lenalidomide |
|---|--|
| Rash = Grade 1 or 2 (= limited localized rash) | Continue Thalidomide/Lenalidomide, start antihistaminics and topical corticosteroid treatment. |
| Rash = Grade 3 | Hold dose for remainder of cycle. Start antihistaminics and topical corticosteroid treatment, consider a short course of low dose corticosteroids in case of extensive rash. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to \leq Grade 1). |
| Rash = Grade 4 or Blistering | Discontinue Thalidomide/Lenalidomide |
| Constipation \geq 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 \leq Grade 2). |
| Thrombosis/embolism \geq 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 \geq 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. |

H. Management of toxicity during maintenance treatment

Dose levels

Dose Levels for Thalidomide and Lenalidomide during Maintenance Therapy

| Dose Levels | Thalidomide | Lenalidomide |
|---------------|-------------------|---|
| Starting Dose | 100* mg every day | 10** mg once daily on days 1-21 every 28 days |
| Dose Level -1 | 50 mg every day | 5 mg once daily on days 1-21 every 28 days |
| Dose Level -2 | no thalidomide | no lenalidomide |
| Dose Level -3 | no thalidomide | no lenalidomide |

* If during induction therapy last dose Thalidomide was 50 mg daily the starting dose of maintenance therapy should be 50 mg daily instead of 100 mg.

** If during induction therapy last dose Lenalidomide was 7.5 mg daily the starting dose of maintenance therapy should be 7.5 mg daily instead of 10 mg.

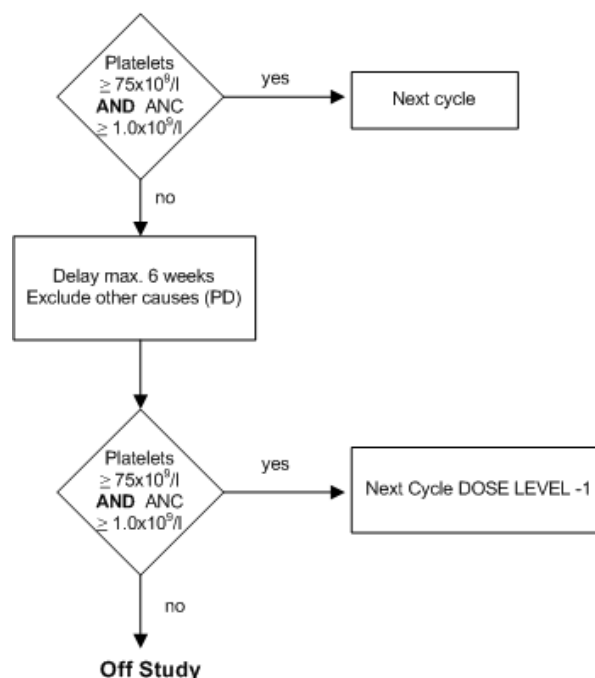
Dose reduction instructions

Dose Modification Instructions for Thalidomide and Lenalidomide for Haematologic Toxicity* during Maintenance

| Toxicity | Thalidomide/Lenalidomide Dose Modification |
|---|---|
| Neutropenia (Neutrophil < 0.5×10^9 /L) | Stop the dose for remainder of cycle **. Decrease by 1 dose level when dosing restarted at next cycle ** |
| Grade 4 neutropenia (ANC < 0.5×10^9 /L) or Febrile neutropenia (fever $\geq 38.5^\circ\text{C}$ and ANC < 1×10^9 /L) | Stop the dose for remainder of cycle **. Decrease by one dose level when dosing restarted at next cycle **. |
| Grade 4 Thrombocytopenia (Platelets < 25×10^9 /L) | Stop the dose for remainder of cycle **. Decrease by one dose level when dosing restarted at next cycle **. |

*Exclude other causes, especially progressive disease. Especially in case of thalidomide another cause should be searched for as hematological toxicity of thalidomide is rare.

** The next cycle is allowed if ANC $\geq 1.0 \times 10^9$ /L and platelets $\geq 75 \times 10^9$ /L. A delay of 6 weeks is allowed before dose level -1 or before going off protocol if already at dose level -1.



Dose Modification Instructions for Thalidomide and Lenalidomide for Polyneuropathy during Maintenance

| Toxicity | Action Thalidomide/Lenalidomide |
|-------------------|---|
| Grade 1 | no dose adjustment |
| Grade 2 | Decrease daily dose by one dose level every 4 weeks until toxicity resolved to grade \leq 1. Remain at last reduced dose. Minimum doses as indicated above. |
| Grade 3 | End treatment with thalidomide/lenalidomide |
| Grade 3 recurring | End treatment with thalidomide/lenalidomide |
| Grade 4 | End treatment with thalidomide/lenalidomide |

Dose Modification Instructions for Thalidomide and Lenalidomide for other Non-Haematologic Toxicity during Maintenance

| Toxicity | Dose modification Thalidomide/Lenalidomide |
|---|--|
| Rash = Grade 1 or 2 (= limited localized rash) | Continue Thalidomide/Lenalidomide, start antihistaminics and topical corticosteroid treatment. |
| Rash = Grade 3 | Hold dose for remainder of cycle. Start antihistaminics and topical corticosteroid treatment, consider a short course of low dose corticosteroids in case of extensive rash. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to \leq Grade 1). |
| Rash = Grade 4 or Blistering | Discontinue Thalidomide/Lenalidomide and discontinue subject from study. |
| Constipation \geq 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 \leq Grade 2). |
| Thrombosis/embolism \geq 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 \geq 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. |

I. Management of prednisone related toxicity

Dose Levels for Prednisone during Induction Therapy

| Dose Level | Prednisone |
|---------------|--------------------------|
| Starting Dose | 2 mg/kg/d on Days 1-4 |
| Dose Level -1 | 1 mg/kg/d on Days 1-4 |
| Dose Level -2 | 0.5 mg/kg/d on Days 1-4 |
| Dose Level -3 | 0.25 mg/kg/d on Days 1-4 |

Dose Modification Instructions for Prednisone during a Cycle

| Toxicity | Prednisone Dose Modification |
|---|--|
| Dyspepsia = Grade 1-2 | Maintain dose and treat with histamine (H2) blockers or proton pump inhibitors. Decrease by one dose level if symptoms persist. |
| Dyspepsia \geq Grade 3 | Hold dose until symptoms are controlled. Add H2 blocker or proton pump inhibitors and decrease one dose level when dose restarted. |
| Edema \geq Grade 3 | Use diuretics as needed and decrease dose by one dose level. |
| Confusion or mood alteration \geq Grade 2 | Hold dose until symptoms resolve. When dose restarted decrease dose by one dose level. |
| Muscle weakness (steroid myopathy) \geq Grade 2 | Hold dose until muscle weakness \leq Grade 1. When dose restarted decrease dose by one dose level. |
| Hyperglycaemia \geq Grade 3 | Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed. |
| Acute pancreatitis | Discontinue prednisone and discontinue subject from the study. |

J. Bone marrow and plasma cryopreservation (See lab manual at HOVON 87 website)

A biobank including bone marrow cells and peripheral blood cells, bone marrow slides and peripheral plasma which is frozen and stored according to biobank laws in the separate countries. This material will be used for additional investigations in order to determine prognostic factors. This will include:

A. FISH 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 chromosome 13q deletions, the presence of 14q32 abnormalities (t(4;14)(p16;q32) and t(14;16)(q32;q23)) and deletion of p53 (17p13). Conditions for FISH will be standardized by the HOVON Cytogenetic Working Party.

B. 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 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 whole genome transcriptional profiling will be collected at entry and during treatment and follow up if disease progression / relapse occurs (section 11.2.10). Plasma cells collected in the Netherlands and Belgium will be purified at the Erasmus Medical Center using the positive selection kit (StemCell technologies). Performance of the purification will be monitored using FACS analysis of the original bone marrow sample and the final plasma cell fraction with CD38 and CD138 antibodies.

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.

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 ratio of action 3' to 5' and the ratio of GAPH 3' to 5' will be assessed to monitor sample and assay quality.

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. SNP analysis

The involvement of specific genes in the drug metabolism and anti-tumor effect of Lenalidomide and Thalidomide will be investigated, using the Genome-Wide Human SNP 6.0 array (Affymetrix). The presence of inherited genotype polymorphisms will be correlated to response and toxicity.

Thalidomide and Lenalidomide have a remarkable effect in patients with relapsed or refractory multiple myeloma with 30-40% response rates. However, 15-30% of the patients have to stop prematurely because of intolerable side effects. The toxicity profile consists of neutropenia (Lenalidomide), thrombocytopenia (Lenalidomide), neuropathy (Thalidomide) and venous thromboembolic events (Thalidomide and Lenalidomide). The proportion of patients experiencing these side effects in trials ranged 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, inflammatory pathways and coagulation pathways.

This explanation is substantiated by retrospective analysis that has been done in the Erasmus MC. It was observed that patients with multiple myeloma who were treated in a phase III trial with conventional vs. high-dose regimens and who have a variant polymorphism genotype of a gene involved in drug metabolism, CypP450 3A5, have a better overall survival compared to patients with a wild-type genotype of this gene. It is known that such single nucleotide polymorphisms are observed in many genes that are important for multiple myeloma biology and/or are involved in metabolism of anti-cancer drugs, thereby affecting both outcome and side effects. It is anticipated that these SNPs also play an important role in outcome (OS and DFS) and toxicity in patients treated with novel agents.

The novel agents Lenalidomide and Thalidomide are now moving from relapse treatment to up-front therapy of multiple myeloma. Therefore it is of critical importance to investigate which gene(s) are involved in drug metabolism, thereby affecting the anti-tumor effect and side effects of these agents.

The presence and involvement of these genes will be investigated, using DNA isolated from blood on the Genome-Wide Human SNP 6.0 array (Affymetrix). The presence of inherited genotype polymorphisms will be correlated to response and toxicity.

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.

D. Future analyses to be determined

Other analyses may appear to be relevant at a later stage and the biobank is left open to interested groups related to HOVON and NMSG. 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 will be stored.

Required bone marrow and peripheral blood and logistics

For further details on logistics and laboratory procedures see lab manual at HOVON 87 website (Lab manual HOVON-87)

Ad A FISH analysis

FISH analysis will be performed in all participating centers at entry. In case FISH analysis has not been performed directly, FISH will be performed at a later time point either on the cryopreserved buffy coat of bone marrow or bone marrow slides. For FISH analysis and analyses as mentioned under C 14 ml Heparin Bone Marrow will be taken at entry.

Ad B Gene Expression Profiling

At least one day before the bone marrow aspiration will take place, it is preferred to give notice of this to the laboratory of the Erasmus Medical Center. Inform the laboratory either by email or by phone. (see address below)

Plasma cell purification of Histopaque separated bone marrow (at least 10 ml of heparin bone marrow divided over two tubes should be aspirated), by using a CD138 positive selection kit (StemCell technologies), will occur before cryopreservation. This will enable future analyses like Gene Expression Profiling for which a pure fraction of plasma cells is required.

On the day of sampling the samples should be sent to the laboratory of the Erasmus Medical Center at room temperature by overnight express mail. For further details on logistics and laboratory procedures see lab manual at HOVON 87 website (Lab manual HOVON-87)

Attention! When the bone marrow aspiration occurs on Friday, the bone marrow transport will take place by taxi. It is important that the driver delivers the sample personally to room Ee1314 of the laboratory of the Erasmus Medical Center before 2 o'clock p.m.

The centers in the Netherlands will be provided with special envelopes (according to Dutch post office directives) for the sending of diagnostic samples.

Contact information:

Contact person: Yvonne de Knegt or Martijn Schoester
Adress: Department of Hematologie,
Roomnumber Ee1330
(faculty building),
Dr. Molewaterplein 50,
3015 GD Rotterdam
Telephone number: +31 (0)10 704 36 09 or +31 (0)6 14802999
Fax number: +31 (0)10 70 44 745
Email: y.deknegt@erasmusmc.nl AND m.schoester@erasmumc.nl
myeloma.hematology@erasmusmc.nl

Ad C SNP analysis

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

On the day of sampling the samples should be sent to the laboratory of the Erasmus Medical Center laboratory at room temperature (for contact information see address above). The centers in the Netherlands will be provided with special envelopes (according to Dutch post office directives) for the sending of diagnostic samples. Centers from other participating countries will be contacted directly by the Erasmus Medical Center laboratory to make arrangements for shipping of samples.

Ad D Future analyses

Plasma cell purification of Ficoll separated bone marrow (about 10 ml of heparin bone marrow should be aspirated), by using a CD138 magnetic cell sorting selection, will occur before cryopreservation. This will enable future analyses like Gene Expression Profiling for which a pure fraction of plasma cells is required. The centers in the Netherlands will be provided with special envelopes (according to Dutch post office directives) for the sending of diagnostic samples. Centers from other participating countries will be contacted directly by the Erasmus Medical Center laboratory to make arrangements for shipping of samples.

In all participating centers blood samples will be taken before start of treatment in order to store peripheral blood plasma and serum. About 6 ml of Citrate blood and 6 ml of blood, both divided over 2 tubes, will be needed for plasma cryopreservation. At least 3,5 ml serum collected in a serum gel tube will be needed for cryopreservation. This can be sent to the Erasmus Medical Center laboratory together with material for SNP analysis in the especially provided envelopes (see above). Alternatively plasma and serum will be stored at -80 °C in the institute where the patient is under treatment after which it will be shipped deep frozen to the reference laboratories in each country at a later time point.