Ixazomib citrate-thalidomide-low dose dexamethasone induction followed by maintenance therapy with ixazomib citrate or placebo in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplantation; a randomized phase II trial

PROTOCOL

Principal Investigator : S. Zweegman (HOVON)
N. Abildgaard (NMSG)

Sponsor : HOVON

EudraCT number : 2013-003266-14

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Principal Investigator Date

Printed Name of Principal Investigator

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

_____ _____

Signature of Local Investigator Date

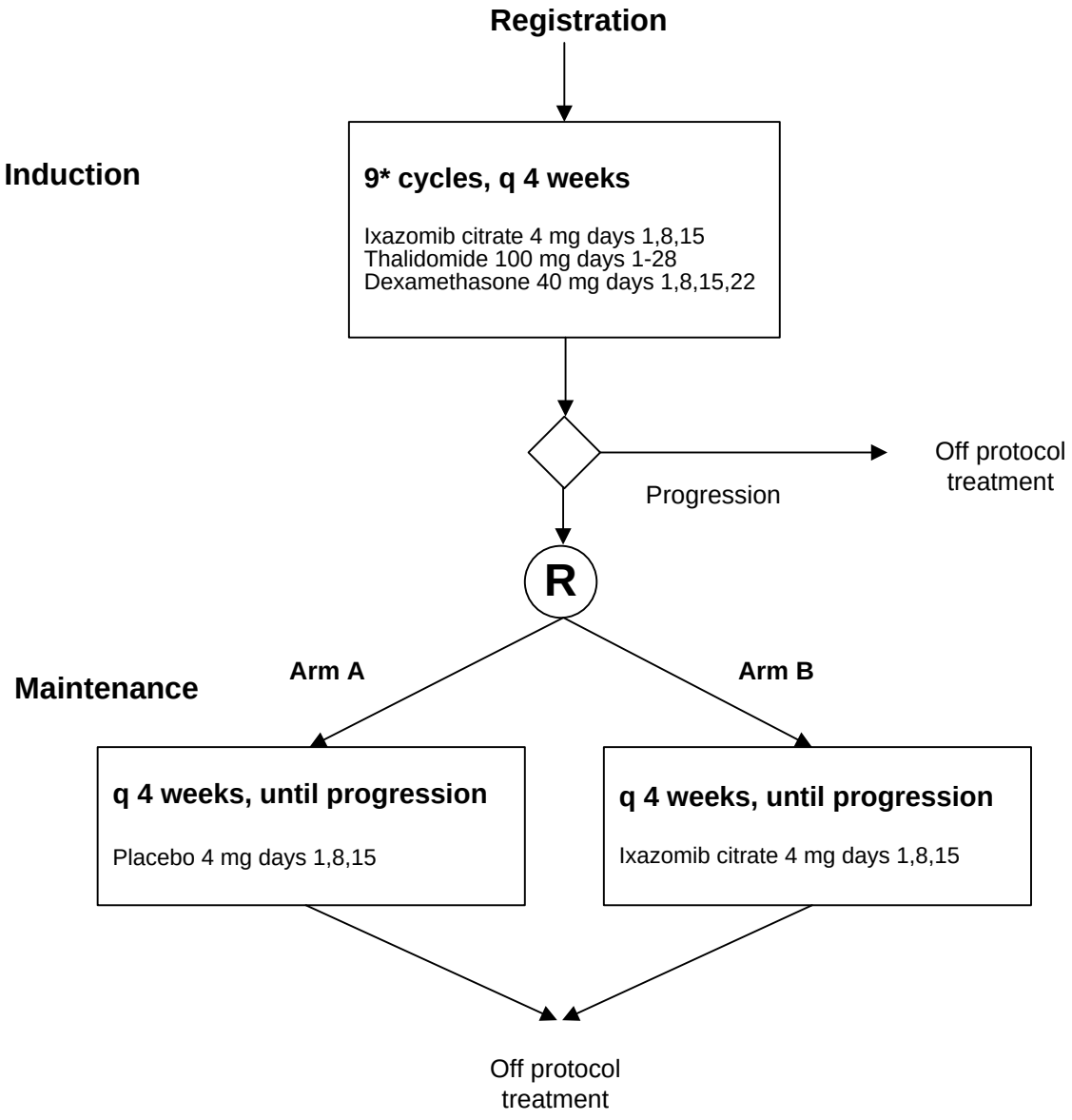
_____

Printed Name of Local Investigator

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

1 Scheme of study

Previously untreated patients with MM
Age ≥ 66 years or patients ≤ 65 years and ineligible for high dose therapy and peripheral stem cell transplantation



* Start of maintenance therapy is allowed after a minimum of 6 induction cycles as described in 8.2.1

2 Table of contents

Page

3 Synopsis

Rationale	Standard of care in Europe for the newly diagnosed elderly MM patient is melphalan-prednisone-bortezomib. Hematological toxicity and increased rate of second primary malignancies with alkylating agents justifies the investigation of a triplet combination therapy ommitting alkylating agents. A triplet combination without alkylating agents combining an IMiD (thalidomide or lenalidomide), a proteasome inhibitor (bortezomib) and corticosteroids have been found to be effective indeed. In view of a high incidence of peripheral neuropathy in the current protocol bortezomib will be replaced with the oral proteasome inhibitor ixazomib citrate. Importantly, this is an oral regimen, especially being convenient in an elderly population. The hypothesis is that the response rate will be superior, with less hematological and a lower incidence of neural toxicity as compared to standard therapy. In addition, a role for maintenance therapy with bortezomib has been suggested in non-head to head comparisons. Therefore, the efficacy of ixazomib citrate maintenance therapy will be investigated by randomizing maintenance treatment with ixazomib citrate versus placebo.
Study objectives	– To compare the efficacy determined as progression free survival between maintenance treatment with ixazomib citrate versus placebo – To determine efficacy of induction therapy determined as stringent CR, CR, VGPR and PR – To determine toxicity, polyneuropathy and hematological toxicity in specific, during induction and maintenance treatment with xazomib citrate or placebo – To determine progression free survival and overall survival from registration – To compare the efficacy between maintenance

	treatment with ixazomib citrate versus placebo determined as overall survival from randomization – To determine the efficacy of maintenance therapy with ixazomib citrate determined as an increase in response during maintenance treatment with ixazomib citrate versus placebo – To determine efficacy of induction therapy determined as time to response – To determine feasibility, defined as discontinuation rate due to toxicity, during induction and maintenance treatment with ixazomib citrate or placebo – To determine time to next treatment – To determine PFS on second line therapy – To determine Quality of Life during induction therapy and maintenance treatment with ixazomib citrate versus placebo – To identify clinical, imaging-related and molecular prognostic markers prognostic and predictive for outcome and toxicity – To determine second primary malignancies (SPM).
Study design	Prospective, multicenter, randomized double blind placebo controlled phase II
Patient population	Previously untreated symptomatic patients with MM age ≥ 66 years or patients ≤ 65 years and ineligible for high dose therapy and peripheral stem cell transplantation
Intervention	Following induction therapy half of the patients will receive 4 mg of ixazomib citrate capsules as a maintenance therapy until progression and the other half of patients will receive placebo capsules as a maintenance therapy until progression
Duration of treatment	Expected duration of induction treatment: 9 months Maintenance therapy with ixazomib citrate or placebo will be given until progression All patients will be followed 8 years after registration

Target number of patients	Approximately 142 patients will be registered in order to randomize 94 patients. See section 14.1 for detailed information.
Expected duration of accrual	18 months
Main study endpoints	Progression free survival from randomization Response rate after induction treatment
Benefit and nature and extent of the burden and isks associated with participation	The benefit will be that patients will be treated with a proteasome inhibitor/IMiD/corticosteroid based induction regimen, that has been shown to result in the highest response rates when non-head to head compared to European standard proteasome inhibitor/alkylating agent/corticosteroid or IMiD/alkylating agent/corticosteroid based regimens. Moreover, the oral proteasome inhibitor ixazomib citrate has been shown to induce considerably less neuropathy as compared to bortezomib. The burden will be that following induction therapy, maintenance therapy will be given until progression. Although a benefit with respect to prolongation of PFS is expected, the extent is currently unknown. Patients may suffer from side effects, although these are generally mild with ixazomib citrate. Moreover, 50% of patients will receive a placebo. There are no additional procedures required as compared to standard care. Patients will only participate in Quality of Life studies.
Planned interim analysis and DSMB	One interim analysis is planned, primarily to describe adverse events observed during the ixazomib citrate-thalidomide - low dose dexamethasone induction therapy. This will be done when of the first 20 registered patients the data regarding cycles 1-4 are available. Results of the interim analysis will be presented confidentially to a DSMB. Only if the DSBM recommends that the study should be stopped or modified, the results will be made public to the principal investigators for further decisions

4 Investigators and study administrative structure

This is an investigator-initiated trial sponsored by HOVON, which means that HOVON holds all sponsor responsibilities unless it is explicitly stated in this protocol that a sponsor responsibility is delegated to another party

Responsibility	Name	Affiliation/Address
Sponsor	HOVON	VU University Medical Center, P.O.Box 7057 1007 MB Amsterdam tel: +31 20 4443797
Co-sponsor	NMSG	
Representative of Sponsor (HOVON)	J.J. Cornelissen, chairman N. Blijlevens, treasurer	Erasmus MC Rotterdam Radboud University Medical Center Nijmegen
Principal Investigator	S. Zweegman (HOVON) N. Abildgaard (NMSG)	VU University Medical Center Amsterdam s.zweegman@vumc.nl, +31204444444, ext 6467 Odense University Hospital Odense
Co-investigators	P. Sonneveld (HOVON) H.M. Lokhorst (HOVON) U-H. Mellqvist (NMSG) A. Waage (NMSG)	Erasmus MC Rotterdam VU University Medical Center Amsterdam Sahlgrenska University Hospital Gothenburg University Hospital Trondheim
Coordinating investigator	**The Netherlands** S. Zweegman (HOVON) **Denmark** N. Abildgaard (NMSG) **Sweden** M. Hansson **Norway** E. Haukås	 VU University Medical Center Amsterdam Odense University Hospital Odense Skåne University Hospital, Lund Stavanger University Hospital Stavanger
HOVON MM working group chair	P.Sonneveld	Erasmus MC Rotterdam
Writing Committee	N.Abildgaard G.M.J. Bos J.Coenen M. Hansson E. Haukås S.K. Klein M-D. Levin M. Minnema U-H. Mellqvist	Odense University Hospital Odense University Medical Center Maastricht Isala Klinieken Zwolle Skåne University Hospital, Lund Stavanger University Hospital Stavanger Meander Medical Center Amersfoort Albert Schweitzer Hospital Dordrecht Utrecht University Medical Center Utrecht Sahlgrenska University Hospital Gothenburg

	M. Salomo	Copenhagen University Hospital Copenhagen
	P. Sonneveld	Erasmus MC Rotterdam
	A. Waage	University Hospital Trondheim
	E. Vellenga	University Medical Center Groningen
	S. Zweegman	VU University Medical Center Amsterdam
Statistician	B. van der Holt	Erasmus MC – Clinical Trial Center, Rotterdam
Registration	HOVON Data Center	Erasmus MC – Clinical Trial Center P.O.Box 2040 3000 CA ROTTERDAM The Netherlands https://www.hdc.hovon.nl/top tel. +31.10.7041560 fax +31.10.7041028
Monitoring	**HOVON**	
	HOVON Data Center	Erasmus MC – Clinical Trial Center
	NMSG	
	Denmark	Danish GCP Units
	Norway and Sweden	Lund University – Clinical Trial Center
Cytogenetics review	M. Stevens-Kroef	University Medical Center Nijmegen
Quality of Life	**HOVON**	
	HOVON Data Center	Erasmus MC – Clinical Trial Center
	NMSG	
	Ullevål Hospital	Oslo
Emergency unblinding	Pharmacist on call	VU University Medical Center Amsterdam 020 4444444
Central Pharmacy	A. Harmsze	VU University Medical Center Amsterdam
Trial management	HOVON Data Center	Erasmus MC – Clinical Trial Center
Data management	HOVON Data Center	Erasmus MC – Clinical Trial Center
Serious Adverse Events (SAEs) notification	HOVON Data Center	Erasmus MC – Clinical Trial Center

5 Introduction and rationale

5.1 Initial treatment of elderly multiple myeloma patients

5.1.1 Induction therapy ommiting alkylating agents

The median age of MM is approximately 65 years indicating that half of the patients with MM will not receive high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). In Europe standard therapy of newly diagnosed patients ineligible for ASCT is an alkylating-based regimen, combined with corticosteroids and a novel agent. Currently, in first line this novel agent is either thalidomide (T) or bortezomib (V). Preliminary results from the MM015 study show that Melphalan (M) Prednison (P) Lenalidomide (R) followed by lenalidomide maintenance therapy is also superior to MP, similar to MPT and MPV.[1] Although these three regimens have greatly improved response rates, PFS and OS, toxicity remains an important issue, especially in this elderly population.
In order to decrease myelotoxicity, the omission of alkylating agents, would be of interest. Moreover, this would diminish the possibility of second primary tumors, now increasingly being described, especially when immunomodulatory agents (ImiDs) are combined with alkylating therapy.[2 3 4] Triplet combination therapy with a proteasome inhibitor (PI), an IMiD and corticosteroids, consisting of bortezomib, thalidomide and dexamethasone (VTD), has been shown to be effective, indicating that alkylating therapy might be omitted indeed. Moreover, hematological toxicity and infectious complications were significantly less frequent as compared to VMP. However, both VMP and VTD give rise to considerable polyneuropathy as up to 10% of patients experience grade 3-4 neuropathy, mostly due to bortezomib.[5]
In view of these considerations it is of great interest to investigate triplet combination therapy omitting alkylating agents and replacing bortezomib with the oral PI MLN9708 (Ixazomib citrate) in newly diagnosed patients, with the hypothesis that response rate will be superior with significantly less hematological and a lower incidence of neural toxicity. In recent studies MLN9708 has shown promising activity, even in patients treated with bortezomib previously.[6 7 8]

5.1.2 Maintenance therapy

In general maintenance therapy with IMiDs or PIs have been found to increase response rates and PFS, however the impact on OS is less clear. Therefore, future clinical trials should aim to define the need, the optimum period and the type of maintenance therapy. There seems to be an improvement in outcome due to maintenance therapy with bortezomib with respect to PFS. However, this concerns a non head-to-head comparison of VMP with a once-weekly administration during 6 cycles followed by 3 years of maintenance therapy with either VP or VT with the historical data from the VISTA trial. Median PFS is longer (31 versus 24 months) indeed.[5 9] Accordingly an increase in response was

observed during maintenance therapy. In addition, the Italian GIMEMA study showed that VT maintenance was feasible and resulted in an improved PFS and OS compared to no maintenance, however induction therapy was different in both arms; VMPT in the maintenance arm versus VMP in the non-maintenance arm. Therefore, the improvement in PFS and OS might not be solely due to maintenance therapy, although the difference in PFS and OS occurred during maintenance only. Moreover, it is currently unknown whether a treatment-free interval followed by re-treatment at relapse would at least equal the outcome compared to maintenance treatment until relapse. And the evolvement of therapy-resistant clones remains a concern. When taking thalidomide maintenance in account, subgroup analyses highly suggest a patient-tailored approach is necessary. This is exemplified by the fact that maintenance therapy with thalidomide was shown to result in an inferior outcome in patients with high risk cytogenetics. [10 11] This suggests the evolution of therapy-resistant clones indeed. Whether this holds true for proteasome inhibitor therapy is currently unknown. Especially long term treatment might induce therapy resistance. Therefore, correlative studies aiming at characterizing biological subgroups in more depth will be of critical importance in order to guide the duration and type of maintenance therapy.

5.2 Ixazomib citrate

Bortezomib, the first-in-class, small-molecule proteasome inhibitor, validated the proteasome as a therapeutic target. Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Ixazomib citrate (formerly known as MLN9708) has been developed with the aim of improving the pharmacology of the agent, building on the efficacy seen with bortezomib in MM and other hematologic malignancies, and improving safety and convenience of drug administration. Ixazomib citrate is the first oral proteasome inhibitor undergoing clinical investigation in humans.

5.2.1 Ixazomib citrate (MLN9708): pharmacology, pharmacokinetics and pharmacodynamics

Like bortezomib, ixazomib citrate is a modified peptide boronic acid analog. Ixazomib citrate is the citrate ester of the biologically active dipeptide boronic acid, MLN2238. Ixazomib citrate was formulated to improve the chemical properties of MLN2238 for clinical delivery. Ixazomib citrate rapidly hydrolyzes to MLN2238 upon contact with either plasma or aqueous solutions. MLN2238 is the active form that potently, reversibly, and selectively inhibits the proteasome. In contrast to bortezomib, MLN2238 demonstrates a faster dissociation rate from the proteasome that may result in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration. MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 was selective for the proteasome over a panel of several proteases (IC_{50} values between 20 and100 μM),

103 kinases (IC_{50} values > 10 µM), and receptors (IC_{50} values > 10 µM). MLN2238 and bortezomib have different β5 proteasome dissociation half-lives ($t_{1/2}$), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation [$t_{1/2}$] for MLN2238 and bortezomib are 18 and 110 minutes, respectively).

5.2.2 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days.[12] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[13] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

5.2.3 Preclinical experience

Please be refered to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

5.2.4 Clinical Experience

As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 IB.

5.2.5 Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 5-1.

Table 5-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO, W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008	PO, TW, combination with LenDex 21	3.0-3.7 mg fixed dose* W

Table 5-1 Ongoing Studies of Oral MLN9708

NDMM N=11	day cycle	MTD: 4 mg DLT:
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies (C16003, C16004, C16007, and C16009) is shown in Table 5-2.

Table 5-2 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N=146 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anaemia 30 (21);

	Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: MLN9708 Investigator's Brochure Edition 6
Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 daysafter the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 5-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

Table 5-3 Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);

Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: MLN9708 Investigator's Brochure Edition 6.
Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

The clinical experience with MLN9708 also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors[14], non-Hodgkin's disease, Hodgkin's disease[15], relapsed and/or refractory multiple myeloma [RRMM; [8 16]], relapsed or refractory systemic light chain amyloidosis [RRAL], and newly diagnosed multiple myeloma [NDMM; [17 18 19]]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

5.2.6 Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m^2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m^2.
Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety,

tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];
2. Carfilzomib expansion cohort
3. Proteasome Inhibitor-Naïve expansion cohort
4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[20 21]

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1- 11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 5-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 5-4 Study C16004, Oral MLN9708, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%) Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: MLN9708 Investigator's Brochure Edition 6

*** Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic,** pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and not related Grade 4 elevation in creatinine (1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly , Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38% and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 5-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 5-5 Study C16007, Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30 April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased Appetite (21%) Peripheral Edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in more than 3 Patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

Source: MLN9708 Investigator's Brochure Edition 6

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB, SMA, and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and standard medical interventions, which may include dose reductions and supportive care. Please refer to the MLN9708 IB and SMA for further information.

5.2.7 Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been

translated into a fixed dose of 4.0 mg based on the results from the population PK analysis.
Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.
In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.
A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 5-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 5-6 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (37%) Nausea (34%) Constipation (31%) Vomiting (28%) Diarrhoea (26%) Thrombocytopenia (23%) Upper respiratory tract infection (22%) Anaemia and oedema peripheral (20% each)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Nausea, vomiting (n=3 each) Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: MLN9708 Investigator's Brochure Edition 6.
a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.
As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia.

One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

5.3 Rationale of the study

In view of the considerations described in the introduction, a triple combination induction regimen with an oral PI, an IMiD and a corticosteroid preferably should be oral and with a low risk for the development of painful neuropathy. In addition, the costs of therapy should be taken into account. These requirements are met by a triple combination induction therapy with ixazomib citrate as a proteasome inhibitor, thalidomide as an IMiD and low dose dexamethasone. Besides an effective induction regimen, especially in the elderly in whom induction therapy might be less dose intense and of shorter duration due to toxicity, the role of maintenance therapy has to be defined.[22] Thalidomide maintenance has shown not to be effective given a limited improvement in PFS only, without improving OS in the elderly population.[10] Although lenalidomide has been shown to considerably increase PFS, improvement in OS has to be shown yet in 2 out of 3 studies. Moreover, the increased incidence of SPM is a concern during maintenance.[1 2 3 4] The non head–to-head comparison of maintenance with VP or VT following MPV or MPT with the classical VISTA without maintenance suggest a role for maintenance therapy with a PI.[5 9] Therefore, we aim to assess the efficacy and feasibility of this triple combination induction therapy with Ixazomib as a PI, Thalidomide as an IMiD and low dose Dexamethasone. Moreover, the merits and feasibility of MLN9708 (Ixazomib) maintenance will be determined. The data from this study may allow to design a future randomized phase III clinical trial comparing ixazomib citrate-thalidomide-low dose dexmethasone either with or without maintenance therapy with ixazomib citrate with an alkylating based regimen.

6 Study objectives

In newly diagnosed patients with MM who are not eligible for ASCT:

Primary objectives

Maintenance treatment

- To compare progression free survival between maintenance therapy with Ixazomib versus placebo, both following induction therapy with ixazomib citrate – thalidomide – low dose dexamethasone

Induction treatment

- To determine overall response* rate of induction therapy with ixazomib citrate – thalidomide – low dose dexamethasone
  - * overall response will be defined as (stringent) complete response, very good partial response and partial response (appendix C)

Secondary objectives

- To determine toxicity, polyneuropathy in specific, during induction treatment and maintenance treatment with ixazomib citrate or placebo
- To determine progression free survival and overall survival from registration
- To compare the efficacy between maintenance treatment with ixazomib citrate versus placebo determined as overall survival from randomization
- To determine the efficacy of maintenance therapy determined as an improvement in response during maintenance treatment with ixazomib citrate or placebo
- To determine efficacy of induction therapy determined as time to response
- To determine feasibility, defined as discontinuation rate due to toxicity, during induction treatment and maintenance treatment with ixazomib citrate or placebo
- To determine time to next treatment
- To determine PFS on second line therapy
- To determine Quality of Life during induction treatment and maintenance therapy with Ixazomib or placebo
- To identify clinical, imaging-related and molecular markers prognostic and predictive for outcome and toxicity
- To establish second primary malignancies (SPM)

7 Study design

This is a multicenter phase II clinical trial, with upfront registration and late double-blind, placebo-controlled, maintenance randomization. Details of all treatments (dose and schedule) are given in section 9 and appendix F, G and H.

1. Patients will be registered, and then they will be treated with 9 cycles of induction therapy* with ixazomib citrate– thalidomide – low dose dexamethasone;
2. After induction, patients eligible for randomization will be randomized double-blind between maintenance treatment with ixazomib citrate versus placebo.

The primary objective of this trial is to assess whether maintenance with ixazomib citrate improves PFS (calculated from date of randomization) as compared to placebo. This is used for the sample size calculation. This trial is therefore a superiority trial.

** Randomization and subsequent start of maintenance therapy is allowed after a minimum of 6 induction cycles as described in 8.2.1.*

8 Study population

All eligible patients have to be registered before start of treatment. After the induction treatment patients will be randomized.

8.1 Eligibility for registration

All patients must meet all of the following eligibility criteria.

8.1.1 Inclusion criteria

- Previously untreated patients with a confirmed diagnosis of symptomatic multiple myeloma according to IMWG criteria (see appendix A)
- Measurable disease according to the IMWG criteria (see appendix A)
  (If plasmacytoma is the only measurable parameter, the patient is not allowed to be included in the study, because of difficult response evaluation)
- Age ≥ 66 years or patients ≤ 65 years not eligible for ASCT
- WHO performance status 0-3 for patients <75 years and WHO performance status 0-2 for patients ≥ 75 years (see appendix D)
- Absolute neutrophil count (ANC) ≥ 1.0 x10^9/l and platelet count ≥ 75x10^9/l , unless related to bone marrow infiltration by malignant plasmacells
  Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment
- Written informed consent
- Patient gives consent for extra bone marrow and blood sampling
- Negative pregnancy test at study entry or at least 1 year post-menopausal or surgically sterile before study entry
- A female patient of childbearing potential, agrees to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program (**for thalidomide**) OR agrees to completely abstain from heterosexual intercourse. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)

- Male patients, even if surgically sterilized, (i.e., status post vasectomy) must agree to practice effective barrier contraception during the entire study period and through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program **(for thalidomide),** OR agrees to completely abstain from heterosexual intercourse (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

8.1.2 Exclusion criteria

- Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent
- Systemic AL amyloidosis
- Polyneuropathy, grade 3 or higher or grade 2 with pain on clinical examination during the screening period
- Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months
- Severe pulmonary dysfunction (Modified Medical Research Counsil dyspnea scale classification III-IV)
- Significant hepatic dysfunction (total bilirubin ≥ 1.5 x ULN or transaminases ≥ 3 times normal level) except patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin
- Creatinine clearance <30 ml/min or Calculated Glomerular Filtration Rate [ml/min/1.73m^2] <30.
- Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.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. Radiotherapy should not be given within 14 days before enrollment. In case of palliative radiotherapy for pain control and if the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib citrate
- Not able and/or not willing to use adequate contraception
- Female patients who are lactating or have a positive serum pregnancy test during the screening period
- Major surgery within 14 days before enrollment
- Central nervous system involvement
- Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive

- Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib citrate including difficulty swallowing
- Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection
- Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21 days of the start of this trial and throughout the duration of this trial
- Any serious medical or psychiatric illness, or familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

8.2 Randomization after induction treatment.

Patients should be randomized and start maintenance treatment after induction treatment, at least 12 weeks after the start of the last cycle.

8.2.1 Inclusion criteria for randomization

- At least partial response on induction treatment
- Hematological recovery defined as ANC ≥ 1.0 x 10^9 /L and platelets ≥ 75 x 10^9 /L
- Completion of 9 cycles of induction treatment ***OR*** a minimum of 6 cycles in case there is non-hematological toxicity NOT related to ixazomib citrate, requiring discontinuation of induction therapy (for definitions of non-hematological toxicity requiring discontinuation see appendix G for thalidomide and appendix H for dexamethasone)

8.2.2 Exclusion criteria for randomization

- Non-hematological toxicity grade 2 or more related to ixazomib citrate at time of randomization.
- Significant hepatic dysfunction (total bilirubin ≥ 1.5 x ULN µmol/l or transaminases ≥ 3 times normal level) except patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin.
- Creatinine clearance <30 ml/min or Calculated Glomerular Filtration Rate [ml/min/1.73m^2] <30.

- Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction after registration.
- Severe pulmonary dysfunction (Modified Medical Research Counsil dyspnea scale classification III-IV).
- Uncontrolled infection at time of randomization.

9 Treatment

9.1 Induction treatment with ixazomib citrate/thalidomide/low dose dexamethasone

9.1.1 Treatment schedule

Induction therapy should start within 4 weeks after patient registration. Patients will receive 9 cycles of ixazomib citrate (4 mg) on days 1, 8, 15 of a 28-day cycle and a daily dose of thalidomide (100 mg) continuously plus dexamethasone (40 mg) on days 1, 8, 15 and 22.

Agent	Dose/day	Route of administration	Days
Ixazomib citrate	4 mg	p.o	1,8 and 15
Thalidomide	100 mg	p.o	1 - 28
Dexamethasone	40 mg	p.o.	1, 8, 15 and 22

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 protocol treatment.

9.1.2 Dose adjustments during treatment with ixazomib citrate/thalidomide/low dose dexamethasone

During the first cycle, the first dose of ixazomib citrate will always be administered in a 100% dose, independently of blood cell counts. At day 8 and 15 doses will be adjusted according to the tables and the flow sheet in appendix F (in case platelets are ≤ $30x10^9$/L and or neutrophils are ≤$0.5x10^9$/L).
For next cycles to begin the patient must meet the following criteria:

- ANC ≥ $1.0x10^9$/L
- platetelets ≥ $75x10^9$/L
- other non-hematological toxicities (except alopecia) ≤ CTCAE grade 1 or the patient's baseline condition.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 6 weeks. See the tables and the flow chart in appendix F.

Instructions for intake and dose reduction for ixazomib citrate, thalidomide and dexamethasone are given appendix F, G, and H respectively.

9.1.3 Supportive care

- 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 intolerance to “aspirin” or a positive history of a venous thrombosis event will receive thrombosis prophylaxis with low molecular weight heparin (LMWH). The treating physician might prefer LMWH instead of aspirin, also in patients other than with intolerance to “aspirin” or a positive history of venous thrombosis, which is allowed. Both aspirin and LMWH will be discontinued if platelets fall below 50 x 10^9/L.
- All patients will receive Herpes Zoster prophylaxis with valacyclovir at a dose of 500 mg two times daily during the induction and maintenance treatment until 1 month after the last administration of ixazomib citrate.
- 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) are mandatory during the following courses of induction therapy. Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John’s wort.. In addition, cotrimoxazole is allowed. For further details also see paragraph 9.3.
- Treatment with bisphosphonates, either pamidronate 30 mg/month or zoledronate 4 mg/month is advised and will be continued for at least 2 years or longer at the discretion of the treating physician.
- Myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) are permitted, according to institutional practice

9.2 Maintenance treatment with ixazomib citrate or Placebo maintenance

9.2.1 Treatment schedule

After the response evaluation of the last ixazomib citrate -thalidomide-low dose dexamethasone cycle patients will be randomized. In randomized patients, maintenance treatment with either ixazomib citrate or placebo will be started within a maximum of 12 weeks after start of the last ixazomib citrate -thalidomide-low dose dexamethasone cycle, at a dose of 4 mg on days 1, 8, and 15 of a 28-day cycle.

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

Agent	Dose/day	Route	Days
Ixazomib citrate or placebo	4 mg*	p.o	1, 8 and 15

*or at the dose level during induction therapy in case dose reductions were required during induction therapy

Response evaluation will take place as described in chapter 10.

9.2.2 Dose adjustments during maintenance treatment with ixazomib citrate

Dose reduction instructions for ixazomib citrate are given in appendix F.

9.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:
Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib exposure would be decreased):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The following medicinal products and procedures are prohibited during the study:

- Excluded foods and dietaty supplement include Sr. John’s wort and Ginkgo biloba
- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).

- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.

9.4 Precautions and Restrictions

- Fluid deficits should be corrected before and throughout treatment.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

Thalidomide is known to be teratogenic.

It is not known what effects ixazomib citrate has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR

- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

9.5 Investigational Medicinal Product ixazomib citrate.

9.5.1 Summary of known and potential risks

The emerging safety profile indicates that ixazomib citrate is generally well tolerated with manageable and reversible AEs with both the IV and PO formulations
The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials irrespective of the combination and irrespective of causality to ixazomib citrate, include fatigue (39%), nausea (33%), constipation (30%), thrombocytopenia (29%), vomiting (26%), diarrhea (23%), anemia (23%), peripheral edema (21%), fever (20%), and neutropenia (20%).

Ixazomib citrate may be harmful to the unborn child.

For al full overview of toxicity reported with ixazomib citrate treatment we refer to the Investigator's Brochure.

9.5.2 Preparation and labeling

Ixazomib citrate will be labeled as an Investigational Medicinal Product.
The ixazomib citrate capsules will be provided by Millennium. The study drug will be labeled.
Packaging labels will fulfill all requirements specified by governing regulations.
The ixazomib citrate capsule formulation consists of drug substance, microcrystalline cellulose, talc, and magnesium stearate. The capsules are individually packaged in cold form foil-foil blisters. The 2.3-, 3.0-, and 4.0 mg capsules used in this trial are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet. Each capsule strength has a unique color. Dosage strength is stated as the active boronic acid.

.

Capsules should be stored unopened at 2-8ºC (36-46ºF) and must be administered as intact capsules and are not intended to be opened or manipulated in any way.

9.5.3 Storage and handling

Ixazomib citrate is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib citrate capsules.
Upon receipt at the investigative site, ixazomib citrate should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.
In countries where local regulations permit, ixazomib citrate capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.
Because ixazomib citrate is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.
The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.
In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of Ixazomib, including that ixazomib citrate is to be taken as intact capsules.

9.5.4 Study drug supply

The sponsor will arrange delivery of ixazomib citrate to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.
Ixazomib citrate will be provided as unlabeled bulk drug by Millennium The Takeda Oncology Company to the central pharmacy in the VU University Medical Center Amsterdam, where the drug

will be labeled. From the central pharmacy in the VU University Medical Center Amsterdam the drug will be shipped refrigerated to the pharmacy at the study sites.

9.5.5 Drug accountability

When ixazomib citrate capsules are dispensed to the patient for take-home dosing, patients should be instructed to return their empty blister packs to the trial site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication.
The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

9.5.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
At the end of the trial or after expiry of the product unused investigational medicinal product should be destroyed by the trial site according to site's standard procedures. Destruction should be documented.

9.6 Investigational Medicinal Product: Placebo

9.6.1 Summary of known and potential risks

The emerging safety profile indicates that the placebo capsules consisting of microcrystalline cellulose, talc, and magnesium stearate is generably well tolerated with manageable and reversible AEs.

9.6.2 Preparation and labeling

Placebo will be labeled as an Investigational Medicinal Product.
The placebo capsules will be provided by Millennium. The placebo will be labeled. Packaging labels will fulfill all requirements specified by governing regulations. The placebo capsules consists of microcrystalline cellulose, talc, and magnesium stearate.
Capsules should be stored unopened at 2-8ºC (36-46ºF) and must be administered as intact capsules and are not intended to be opened or manipulated in any way.

9.6.3 Storage and handling

Similar to section 9.5.3

9.6.4 Study drug supply

The sponsor will arrange delivery of placebo to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.
Placebo will be provided by Millennium The Takeda Oncology Company as described for ixazomib citrate in section 9.5.4.

9.6.5 Drug accountability

Similar to section 9.5.5.

9.6.6 Study drug return and destruction

Similar to section 9.5.6.

10 Study procedures

10.1 Time of clinical evaluations

- At entry: before start of treatment (periperheral blood and urine lab values within 6 weeks prior to start, bone marrow and skeletal survey within 8 weeks).
- During induction therapy after 1, 3, 5 ,7 and 9 cycles (just before start of the next cycle).
- Before start of maintenance treatment (periperheral blood and urine lab values within 4 weeks prior to start),

- During maintenance therapy after every maintenance cycle during the first year, thereafter every 8 weeks.
- When patient is taken off protocol treatment.
- During follow up every 8 weeks untill *second* progression and every 6 months thereafter.

All patients will be followed until 8 years after registration.

10.2 Required investigations

Required investigations at entry, during treatment and during follow up

	At entry	After cycles 1,3,5,7,9 (just before start next cycle)	During maintenance after every cycle during the first 12 months, thereafter and during follow up every 8 weeks[2)]	When going off protocol treatment
Medical history	x	x	x	x
Physical examination	x	x	x	x
Hematology	x	x[1)]	x	x
Blood chemistry	x	x	x	x
Immunochemistry	x	x	x	x
Bone marrow				
Bone marrow aspirate	x	x[3)]	x[3)]	x
Bone marrow biopsy	x[4)]	x[4)]	x[4)]	x
Cytogenetic analysis[5)]	x			x
BM cryopreservation	x[6)]	x[6)]	x[6)]	x
Specific investigations				
ISS β_2-microglobulin and albumin	x			
Creatinine clearance	x	o.i	o.i	
Skeletal survey or CT	X[7)]	X[8,9)]	X[8,9)]	
MRI[9)]	o.i.	o.i.	o.i.	
X-thorax	x			
ECG	x			
Additional investigations	o.i.	o.i.	o.i.	
PB cryopreservation	X[10)]	X[10)]	X[10)]	
Quality of Life	x	X[11)]	X[11)]	
FDG-PET[12]	x	X[12]		

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, hematology, blood chemistry and immunochemistry will be performed every cycle during the first 12 months, thereafter every 8 weeks. After discontinuation of maintenance therapy during follow up visits hematology, blood chemistry and immunochemistry will be performed every eight weeks or at shorter intervals at the discretion of the treating physician until second progression and every 6 months thereafter. During maintenance therapy physical examination will done every 2 cycles.

3) In case of confirming CR, at the moment of complete disappearance of serum/urine M-component by immunofixation, or at progression, a bone marrow aspirate and/or bone marrow biopsy is indicated. To confirm stringent CR, either kappa/lambda labeling of a bone marrow biopsy or immunophenotyping of the BM aspirate has to be performed. **Moreover, the first time of confirming CR, bone marrow has to be send to the central laboratory to determine the MRD status by use of flow cytometry. Please also send material for biological studies to the central laboratory at the time of progression.** See appendix I for procedures for collecting and handling of the samples. After a confirmed CR repeated sampling of bone marrow aspirate is no longer necessary. In case the hematologist decides to send a second sample to the central laboratory for MRD analysis and the patient is participating in the PET-CT study, with a positive PET at the first MRD analysis, a PET-CT scan will be repeated at the second MRD analysis. See 12).
4) A bone marrow biopsy is optional. In case of first diagnosis or 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) Cytogenetic analysis will be performed in the cytogenetic reference labs for each local site
6) Will be performed at entry, at confirmation of a (s)CR and at progressive disease. See appendix I for procedures for collecting and handling of the samples. The samples have to be sent to the central lab of Erasmus MC.
7) Osteolytic lesions observed at total body X-ray or CT (≥1 osteolytic lesion and focal lesions at MRI (at least 2 focal lesions must be 5 mm or more in size) will be criteria for symptomatic MM (see appendix A).
8) After completion of induction therapy, in case of confirming (s)CR and when clinically indicated
9) In case of (extramedullary) plasmacytoma on MRI or CT, this examination should be repeated at least after cycle 9 of induction treatment and yearly thereafter or in case (s)CR is suggested
10) Will be performed at entry and at progressive disease in every patient for future biological studies (during follow up). See appendix I for procedures for collecting and handling of the samples.
11) Quality of life at entry, after cycle 3, 6 and 9 (or earlier in case of prematurely discontinuation of induction treatment), after 6 and 12 months of maintenance and at discontinuation of maintenance therapy.
12) In patients who gave permission to participate in the FDG-PET study a FDG-PET CT scan will be performed at the following study time points:

A) At entry and before randomization of maintenance therapy after completion of 9 cycles of induction treatment or after a minimum of 6 cycles in case there is non-hematological toxicity not related to ixazomib citrate, requiring discontinuation of induction therapy;
B) At the time CR* is reached and MRD assessment in bone marrow by MFC is performed;
C) in case a second MRD assessment will be performed and FDG-PET negativity (PET-CR or complete metabolic response (CMR)) has not been reached yet, an additional FDG-PET-CT will be performed.

* In case CR/sCR are reached before the end of induction therapy and FDG-PET negativity (CMR) has been reached already, no FDG-PET-CT will be performed before randomization of maintenance therapy in case there is no loss of CR/sCR

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

Blood chemistry

Creatinine, ASAT, ALAT, Total bilirubin, Total proteins, Albumin, LDH, Calcium

Immunochemistry

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

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

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 ciriteria) or at progressive disease/relapse.

- Bone marrow **aspirate at entry** for:
  - Morphology
  - FISH analysis: see section 10.5
  - Immunophenotyping has to be performed at entry in case no BM biopsy is performed in order to determine the presence of monoclonal plasmacells.
- Bone marrow **aspirate at response evaluation** for confirmation of CR, flowcytometry analysis to determine MRD and molecular studies.
- Bone marrow **aspirate at progressive disease** for confirmation of progression and molecular studies.
- Bone marrow **biopsy at entry** and **to confirm (stringent) complete response**, including kappa lambda labeling.In case no BM biopsy is performed the presence of monoclonal plasmacells at entry or a stringent CR has to 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.

Radiographic assessment of lytic bone lesions (either X-ray or whole body CT) at entry, after completion of induction therapy and in case of confirming (s)CR

If an MRI is performed at entry and found positive it should be repeated after induction chemotherapy and in case CR is suggested

Additional investigations

Only on clinical indication:

- Survey for exclusion of AL amyloidosis
- 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

10.3 Response evaluation

The response will be evaluated after the induction cycles 1, 3, 5, 7 and 9; after every maintenance cycle during the first year and thereafter every 2 maintenance cycles. Response evaluation should also be done when taken off protocol treatment and during follow up every 8 weeks untill *second* progression and every 6 months thereafter. Response will be evaluated according to appendix C.

10.4 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.

HOVON participants

Collection of the QoL questionnaires will be performed in the following manner:
A QoL coordinator will be assigned in each participating center. The QoL questionnaire collection is left to the responsibility of the QoL coordinator.
During informed consent the patient will be asked to participate in the quality of life part of this study. If the patient gives consent, the QoL coordinator is notified by e-mail as soon as a patient is registered at the HOVON Data Center (HDC). Patient study number, date of birth and date of registration are mentioned in this e-mail. The baseline questionnaire will be handed to the patient by the QoL coordinator. At subsequent time points the coordinator will be reminded in time to hand over the questionnaire at the correct date. The QoL coordinator will collect the questionnaire from the patient and send it to HDC. 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 registered at the HOVON data 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
- after cycle 6
- after cycle 9 or earlier in case of premature discontinuation of induction treatment
- at 6 months after start of maintenance therapy
- at 12 months after start of maintenance therapy
- at discontinuation of maintenance therapy

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

10.5 Central review

10.5.1 Cytogenetic review

FISH analysis is required in all patients at diagnosis/start of study. The following cytogenetic abnormalities will be evaluated as prognostic variables del1p, gain 1q, t(4;14)(p16;q32), t(14;16)(q32;q23), t(11;14)(q13;q32), del13q/13-, del17p and hyperdiploidy (at least 2 of the chromosomes 5, 9, 11 and 15 should be analyzed). Conditions for FISH will be according to the EMN guidelines (Ross et al., Haematologica 97, 1272-1277 (2012))

The cytogenetic review concerns a review of the original FISH data, cross checking original FISH data, data on CRF and data in the database

10.6 Side studies

Genomic profiling, β5 subunit mutation analysis & single nucleotide polymorphism (SNP) analysis

Gene expression profiling, miRNA profiling, sequencing, β5 subunit mutation analysis and SNP analysis will be performed to further characterize MM subgroups at the molecular level, to find new

biomarkers with prognostic value, to elucidate mechanisms of drug resistance & disease progression and identify SNPs related to treatment outcome and side-effects. Bone marrow samples and peripheral blood will be drawn before start and during treatment. Samples will be sent to the Erasmus MC as per instructions in Appendix I. In addition, we aim to include additional studies aimed at elucidating aberrancies on DNA, RNA and protein level, including copy number analysis and transcription factor binding studies. Optional studies of peripheral blood include in depth analysis of immunoglobulins as well as cytokines.

Minimal Residual Disease

In this trial the importance of flowcytometric Minimal Residual Disease (MRD) negativity will be investigated in a correlative study. Patients who are immunofixation negative in serum and urine need to undergo a bone marrow aspirate in order to confirm flowcytometric MRD negativity. A bone marrow puncture needs to be performed at the first response evaluation moment at which there is immunofixation negativity. Material for MRD has to be obtained only once, at the first immunofixation negative result; there is no sequential analysis of MRD status in this trial.Also see appendix I.

FDG-PET study

Recently it was found that the extent of the disease as defined by FluoroDeoxyGlucose - Positron Emission Tomography (FDG-PET) was correlated with clinical outcome of transplant-eligible patients. However, data in non-transplant eligible patients are lacking. Therefor, the prognostic value of FDG-PET at diagnosis and following induction therapy will be determined. To this end the extent of bone disease (number of lesions) and several Standard Uptake Value (SUV) metrics reflecting FDG uptake at diagnosis will be related to PFS and OS. In addition, the prognostic value of normalisation of FDG uptake after induction therapy will be determined.

11 Withdrawal of patients or premature termination of the study

11.1 Specific criteria for withdrawal of individual patients

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

- Death
- Excessive toxicity
- Progression during treatment
- No compliance of the patient
- Refusal to continue protocol treatment

11.2 Follow up of patients withdrawn from treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in 10.2 for follow up.
For patients who are withdrawn from treatment because in hindsight they did not fulfil the eligibility criteria (at time of enrolment (see 8.1) or at time of randomization (see 8.2)), data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in 12.3. At the time of withdrawal, all study procedures outlined for the *off protocol treatment* visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.
No further information will be collected for patients who have withdrawn their consent. If a patient withdraws consent please consult HOVON Data Center.
Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

11.3 Premature termination of the study

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

- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.
- The DSMB recommends to end the trial based on viable arguments other than described above

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

12 Safety

12.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study administered a medicinal product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Serious adverse event (SAE)

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

- Death
- A life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed) It does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Significant / persistent disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- 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, including suspected transmission of infectious agents by a medicinal product). Examples of such medical events include second primary malignancies, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

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 and must be reported as described in 12.3.1.

Suspected unexpected serious adverse reaction (SUSAR)

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

12.2 Adverse event

12.2.1 Reporting of adverse events

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.
Adverse Events have to be reported on the Adverse Events CRF. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4.0 (see appendix E).
The investigator must determine both the intensity of the event and the relationship of the event to study drug administration.
Pre-existing conditions will be collected on the baseline concomitant diseases CRF, i.e. active (symptomatic) diseases of *CTCAE grade* $\geq$ *2* diseases under treatment, chronic diseases and long term effects of past events as present at the time of baseline assessment.

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

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AE's of CTCAE grade 1, however **polyneuropathy grade 1 has to be reported**
- An abnormal laboratory value that does not lead to discontinuation or delay in treatment, or dose modification, or therapeutic intervention, and is not considered by the investigator to be a clinically significant change from baseline
- Relapse/progression of the disease under study; complications as a result of disease progression remain reportable Adverse Events

12.2.2 Follow up of adverse events

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

Follow up information for all other adverse events should be reported on the AE CRF until recovery or until 30 days after the last dose of any drug from the protocol treatment schedule, whichever comes first.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

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

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

Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE (also see 12.1 and 12.2.1)

The following events are not considered to be a Serious Adverse Event:

- Relapse/progression of the disease under study; complications as a result of disease progression remain reportable Serious Adverse Events
- Hospitalization for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an adverse event. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.

- Hospitalization for a procedure that was planned prior to study participation (i.e. prior to registration or randomization). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.2 Causality assessment of Serious Adverse Events

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

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

12.3.3 Follow up of Serious Adverse Events

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

12.3.4 Processing of serious adverse event reports

The HOVON Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator, and the manufacturer of the investigational medicinal product Millennium The Takeda Oncology Company
The HDC safety desk will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR). The causality assessment made by the investigator will be used to determine reasonable causality. 'Unrelated' and 'unlikely' will qualify as 'no' and 'possible', 'probable', 'definitely' and 'not assessable' will qualify as 'yes'.
The IB *w*ill be used as a reference document for expectedness assessment.
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.

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

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

12.5 Pregnancies

Pregnancies of a female subject or the female partner of a male subject, occurring while the subject is on protocol treatment or within 90 days following the last dose of any drug from the protocol treatment schedule, should be reported to the sponsor. Pregnancies must be reported to the HOVON Data Center by fax within 24 hours after the event was known to the investigator, using the pregnancy report form provided.
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. 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 classification as a SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly - including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live “normal” birth, the sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects is related to the in utero exposure to the investigational medicinal product(s) should also be reported.
The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission. The HOVON Data Center will forward all pregnancy reports within 24 hours of receipt to the Principal Investigator and the manufacturer of the investigational medicinal product Millennium The Takeda Oncology Company.

12.6 Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to any study drug, occurring at any time for the duration of the study, from the time of signing informed consent until 8 years after registration in the trial or until completion of maintenance therapy for patients who are stil on maintenance at 8 years after registration.
Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g. pathology report).
The incidence of second primary malignancies is also monitored via a separate form (Second Primary Malignancy Report Form). This form should be filled out, dated and signed by the responsible investigator and returned to the HOVON Data Center by fax within 14 days after establishment of a second primary malignancy.
SPM must also be documented in the other appropriate page(s) of the CRF (e.g. Adverse Event Form and Follow up Form).

For each case of SPM occurring during treatment, contact the Principal Investigator to discuss if treatment needs to be discontinued.

12.7 Reporting of safety issues

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

12.8 Annual safety report

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

12.9 Data Safety and Monitoring Board

A data and safety monitoring board will be installed before start of the study.
The DSMB will advise the Principal Investigator, co-investigators and the chair of the working group in writing about the continuation of the trial. The DSMB will review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events and safety. The DSMB will consider if there is any concern regarding the safety and well-being of trial subjects or regarding the scientific validity of the trial results. The DSMB will base its advice on the reports provided by the statistician. The DSMB is free to take into consideration external information, such as the (interim) results of other trials or literature reports.
The DSMB consists of at least three members, with at least one statistician and two physicians. Details of the DSMB constitution and tasks are documented in the trial specific DSMB charter.

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

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

12.10 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Please also inform the HOVON Data Center of your complaint by fax (+31 (0)10 704 1028) or email (hdc@erasmusmc.nl). Note that product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to HOVON Data Center see section 12.3.1).

13 Endpoints

13.1 Primary endpoint

Maintenance treatment

- Progression free survival (PFS) from randomization, defined as time from randomization to progression or death from any cause, whichever comes first

Induction treatment

- Response rate defined as sCR, CR, VGPR or PR

13.2 Secondary endpoints

- Safety and toxicity as defined by type, frequency and severity of adverse events as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4
- PFS from registration
- Overall survival (OS) from registration, measured until death from any cause. Patients alive will be censored at the date of last contact
- OS from randomization.
- 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 progression (after initial response), measured from time of first relapse/progression
- Time to next treatment
- PFS from the start of second line therapy
- Quality of life as defined by the EORTC QLQ-C30 and QLQ-MY20 definitions.
- Second Primary Malignancies

14 Statistical considerations

14.1 Patient numbers and power considerations

There are no data yet on PFS after 9 cycles of ixazomib citrate – thalidomide – dexamethasone induction chemotherapy. However, in the recently published MPR-R trial (Palumbo et al, NEJM. 2012; 366: 1759-69), median PFS for no-maintenance *after MPR* was 7 months. If ixazomib citrate - thalidomide – low dose dexamethasone is a more effective induction regimen, median PFS after randomization in the no-maintenance arm may be 10 months. Median PFS for lenalidomide maintenance *after MPR* was 26 months. An improvement of median PFS from 10 to 26 months with ixazomib citrate-maintenance equals a hazard ratio of 0.39. For the current sample size calculation the following assumptions have been used:

- uniform accrual for 18 months; additional follow up of 12 months after the last patient has been randomized;
- two-sided significance level a = 0.05;
- power 1 – ß = 0.90;
- median PFS in the no-maintenance arm = 10 months;
- HR = 0.39.

This results in a total number of patients to be randomized of 94 (= 47 per arm), and the final analysis will be performed when 55 events after randomization have been reported (using the Freedman-Peto method). If we assume that 66% (based on the 34% discontinuation rate in the VISTA trial) of the patients will be randomized, then 94/0.66 = 142 patients have to be registered. However, in case the randomization rate is lower then expected, we will recalculate the number of patients that have to be registered, in order to achieve 94 randomized patients required for the primary endpoint. An estimate of the randomization rate will be performed in the first 50 patients.
Assuming a response rate of about 80% after induction chemotherapy, the 142 registered patients will enable to estimate the response rate with a standard error of about 3%.

14.2 Statistical analysis

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

14.2.1 Efficacy analysis

The main endpoint will be PFS from the date of randomization. The formal test for difference in PFS between the two treatment arms will be done with a multivariate Cox regression analysis with adjustment for International Scoring System (ISS, I vs II and III), age (<75 vs ≥ 75 years) and response after induction treatment ((s)CR vs VGPR and PR). An estimate of the HR with corresponding 95% CI will be obtained. The actuarial Kaplan-Meier method will be used to estimate PFS probabilities at appropriate time points, while the Greenwood estimate will be used to construct corresponding 95% CIs. Competing risk analysis will be used to calculate cumulative incidences of PFS, progression/relapse, and death without progression (which add up to 100% at every time point). A Kaplan-Meier curve will be generated to illustrate PFS in each arm. In case the accrual will be 18 months, randomization will take place 9 months after registration of the last patient, and if 12 months of follow up after the last patient is required, then the final analysis may be performed after 18 + 9 + 12 = 39 months after start of the trial, if the complete and validated data including 55 events are available. The response rate after induction chemotherapy will be summarized as the proportion of patients with at least a PR, together with a 95% CI.
A preliminary efficacy analysis on response after induction treatment is planned when the data regarding induction treatment and response of the first 50 registered and eligible patients are available and have been evaluated. No conclusions will be drawn based on this analysis.

14.2.2 Toxicity analysis

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

14.2.3 Additional analyses

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

14.2.4 Statistical analysis plan (SAP)

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

14.3 Interim analysis

One interim analysis is planned, primarily to describe adverse events observed during induction therapy. This will be done when data of the first 20 registered patients regarding cycles 1-4 are available. The accrual will not be discontinued while waiting for these data. Results of the interim analysis will be presented confidentially to an independent data and safety monitoring board (DSMB). Only if the DSBM recommends that the study should be stopped or modified, the results will be made public to the principal investigators for further decisions. The DSMB is free in its public recommendations to the study coordinators and the confidential recommendations to the study statistician. For the interim analysis a detailed report will be generated and presented to the DSMB. It will include the number of entered patients and at that time evaluable patients, treatment given, and

incidence of SAE's and other adverse events and infections by grade. Adverse events will be described by summary table broken by site, CTCAE grade and relation to trial treatment. The study will be closely and sequentially monitored before the interim analysis. Monitoring will be based on the reported SAE's, which are not subjected to data delay. In addition, a separate report on the incidence of SAE's and other adverse events and infections, as described before, will be sent to the DSMB once a year. Again, the DSMB is free in her public recommendations to the study coordinators and the confidential recommendations to the study statistician.

14.4 Statistical analysis of the quality of life assessement

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

15 Registration and Randomization

15.1 Regulatory Documentation

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

15.2 Registration and Randomization

15.2.1 Registration

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

- Trial Online Process (TOP, https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

- By faxing the completed registration/randomization CRF +31.10.7041028 Monday through Friday, from 09:00 to 17:00 CET
- By phone +31.10.7041560 Monday through Friday, from 09:00 to 17:00 CET

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Sex
- Age at date of registration
- Date written informed consent
- Specific items patient gives consent for (see ICF)
- Eligibility criteria

Specific items:

- 'Risk Management Program' discussed with patient

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number (a sequence number by order of enrolment in the trial). Patient study number will be given immediately by TOP or phone and confirmed by fax or email.

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

15.2.2 Randomization

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

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

- Actual dose of ixazomib given during last induction cycle

Patients will be randomized, stratified by center and response ((s)CR vs VGPR vs PR) with a minimization procedure, ensuring balance within each stratum and overall balance.
The patient study number and the result of randomization will be communicated by the HOVON Data Center by email to the pharmacy of VU University Medical Center. Ixazomib citrate or placebo will be sent for the randomized patient to the pharmacy of the site. The result of the randomization will not be conferred to caregivers, patients, or their representatives until the end of the trial.

15.3 Unblinding procedure

The protocol treatment will be preferably unblinded after completion of the trial. While the safety of patients should always take priority, maintenance of blinding is crucial to the integrity of a double-blind trial. Before this planned unblinding, the blind for a specific patient should only be broken when information about the patient's protocol treatment is considered necessary to manage Serious Adverse Events (emergency unblinding). Unblinding procedures should preferably be initiated only after consultation of the principal investigator/coordinating investigator or his/her representative. To initiate an emergency unblinding the pharmacist on call for the VU University Medical Center should be contacted (see contact details chapter 4). The pharmacist on call will inform HOVON Data Center by e-mail about the emergency unblinding.
In addition non-emergency unblinding may be required in patients who are off protocol treatment in order to determine subsequent treatment regimens following progression. Unblinding procedures should only be initiated after consultation of the principal investigator/coordinating investigator or his/her representative.

16 Data collection and quality assurance

16.1 Case Report Forms

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

- Inclusion and exclusion criteria;
- Baseline status of patient including medical history and stage of disease;
- Timing and dosage of protocol treatment;
- Baseline concomitant diseases and adverse events;

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

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

16.2 Data quality assurance

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

16.3 Monitoring

This trial is part of the HOVON Site Evaluation Visit program. Site evaluation visits will be performed for HOVON trials to review the quality of the site and not specifically the quality of a certain trial. It will enable HOVON to collect quality data and facilitate improvement of the participating sites. Data cleaning or monitoring of the performance of specific trials is not the goal of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan.
The HOVON site evaluation visit plan applies to sites in the Netherlands only. Monitoring of the quality of trial conduct in participating sites from other countries will be organized by the coordinating investigator or co-sponsor. The frequency and content of the site visits in other countries will be at least equal to the specifications of the site evaluation visit plan, and are described in a monitoring plan provided by HOVON.
Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects

that during site visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

16.4 Audits and inspections

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

17 Ethics

17.1 Accredited ethics committee

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

17.2 Ethical conduct of the study

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

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. The investigator should take into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.

There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

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

17.4 Benefits and risks assessment.

The benefit will be that patients will be treated with a proteasome inhibitor/IMiD/corticosteroid based induction regimen, that has been shown to result in the highest response rates when compared non-head to head to European standard proteasome inhibitor/alkylating agent/corticosteroid or IMiD/alkylating agent/corticosteroid based regimens. Moreover, the oral proteasome inhibitor ixazomib citrate has been shown to induce considerably less neuropathy. The burden will be that following induction therapy, maintenance therapy will be given until progression. Although a benefit with respect to prolongation of PFS is expected, the extent is currently unknown. Patients may suffer from side effects, although these are generally mild with ixazomib citrate. Moreover, 50% of patients receive a placebo. There are no additional procedures required as compared to standard care. Patients will only be requested to participate in Quality of Life studies.

17.5 Trial insurance

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

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

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

18.1.2 Filing of essential documents

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

18.1.3 Record retention

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

18.1.4 Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures.

Storage of biological samples on site is subject to the site's guidelines; samples may be labeled with the patients identifying information (e.g. name, hospital record number).
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research, should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

18.2 Amendments

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

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

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

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

18.3 Annual progress report

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

18.4 End of study report

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

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

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

18.5 Publication policy

Final publication of trial results

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

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

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

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

Authorship

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

as author, or otherwise will be included in the acknowledgement. A different strategy may be followed based on the specific criteria of the journal to which the manuscript has been submitted.

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

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

Interim and partial publications

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

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

Abstracts and presentations

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

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

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

Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
Ca	Calcium
CA	Competent Authority
CBC	Complete Blood Count
CR	Complete Remission
CRAB	Calcium elevation, Renal insufficiency, Anemia and Bone abnormalities
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug Drug Interaction
DFS	Disease Free Survival
DSMB	Data Safety and Monitoring Board
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
FISH	Fluorescence In Situ Hybridisation
FLC	Free Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	GastroI Intestinal
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HRC	Hematocytology Review Committee
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFE	Immunofixation Electrophoresis
IFM	Intergroup Français de Myelome
IMP	Investigational Medicinal Product
ISS	International Staging System

ITT	Intention To Treat
IU	International Units
LDH	Lactate Dehydrogenase
METC	Medical Ethical Review Committee
MM	Multiple Myeloma
NCI	National Cancer Institute
NMSG	Nordic Myeloma Study Group
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PO	Per Os
PR	Partial Response
QoL	Quality of Life
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SPEP	Serum Protein Electro-Phoresis
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TMA	Tissue Micro Array
ULN	Upper Limit of Normal
UPEP	Urine Protein Electro-Phoresis
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

19 References

Reference List

1. Palumbo A, Hajek R, Delforge M et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N.Engl.J.Med. 2012;366:1759-1769.

2. Rajkumar SV. Second to none. Blood 2012;120:1537-1539.

3. Usmani SZ, Sexton R, Hoering A et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. Blood 2012;120:1597-1600.

4. Thomas A, Mailankody S, Korde N et al. Second malignancies after multiple myeloma: from 1960s to 2010s. Blood 2012;119:2731-2737.

5. Mateos MV, Oriol A, Martinez-Lopez J et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 2012

6. Kumar, S. A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM) 54th ASH Annual Meeting and Exposition 2012 Atlanta, Georgia.

7. Kumar S. Weekly MLN9708, an investigational oral proteasome inhibitor (PI), in relapsed/refractory multiple myeloma (MM): Results from a phase I study after full enrollment. J Clin Oncol, 2013; 31, abstract 8514.

8. Lonial, S. Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM) . ASCO Annual Meeting 2012 Chicago, Illinois.

9. San Miguel JF, Schlag R, Khuageva NK et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N.Engl.J.Med. 2008;359:906-917.

10. Morgan GJ, Gregory WM, Davies FE et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood 2012;119:7-15.

11. Brioli A, Kaiser MF, Pawlyn C et al. Biologically defined risk groups can be used to define the impact of thalidomide maintenance therapy in newly diagnosed multiple myeloma. Leuk.Lymphoma 2013

12. Gupta N. Clinical Pharmacokinetics of Intravenous and Oral MLN9708, An Investigational Proteasome Inhibitor: An Analysis of Data From Four Phase 1 Monotherapy Studies. Blood 116(21). 2013.

13. Gupta, N. Flat-Dosing Versus BSA-Based Dosing for MLN9708, An Investigational Proteasome Inhibitor: Population Pharmacokinetic (PK) Analysis of Pooled Data From 4 Phase-1 Studies. 53rd ASH Annual Meeting and Exposition.2011.San Diego, CA. 2013.

14. Chow, L. Q. MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results in Head and Neck Symposium. 2012.Phoenix, AZ . 2013.

15. Assouline, S. Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study . 17th EHA Annual Congress.2012.Amsterdam, the Netherlands. 2013.

16. Kumar, S. Oral weekly MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma (MM): A phase I/II study . ASCO Annual Meeting.2012.Chicago, Illinois . 2013.

17. Merlini, G. MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study . 54th ASH Annual Meeting and Exposition.2012.Atlanta, Georgia. 2013.

18. Richardson, P. G. MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts):Evaluation of weekly and twice-weekly dosing. 17th EHA Annual Congress.2012 Amsterdam, the Netherlands.

19. San Miguel, J. Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study. 17th EHA Annual Congress 2012 Amsterdam, the Netherlands.

20. Kumar S. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose Escalation Study . 53rd ASH Annual Meeting and Exposition 2011 San Diego, CA.

21. Kumar S. Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM). ASCO Annual Meeting 2012 Chicago, Illinois.

22. Ludwig H, Durie BG, McCarthy P et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood 2012;119:3003-3015.

23. Attal M, Lauwers-Cances V, Marit G et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N.Engl.J.Med. 2012;366:1782-1791.

24. McCarthy PL, Owzar K, Hofmeister CC et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N.Engl.J.Med. 2012;366:1770-1781.

25. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. British Journal of Haematology 2003;121:749-757.

26. Dimopoulos M, Terpos E, Comenzo RL et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia 2009;23:1545-1556.

27. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36:842-854.

28. Bartel TB, Haessler J, Brown TL et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076.

29. Zamagni E, Patriarca F, Nanni C et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 2011;118:5989-5995.

30. Terpos E, Mihou D, Szydlo R et al. The combination of intermediate doses of thalidomide with dexamethasone is an effective treatment for patients with refractory/relapsed multiple myeloma and normalizes abnormal bone remodeling, through the reduction of sRANKL/osteoprotegerin ratio. Leukemia 2005;19:1969-1976.

31. von M, I, Krebbel H, Hecht M et al. Bortezomib inhibits human osteoclastogenesis. Leukemia 2007;21:2025-2034.

32. Terpos E, Heath DJ, Rahemtulla A et al. Bortezomib reduces serum dickkopf-1 and receptor activator of nuclear factor-kappaB ligand concentrations and normalises indices of bone remodelling in patients with relapsed multiple myeloma. Br.J.Haematol. 2006;135:688-692.

A. Criteria for symptomatic MM and measurable disease

S.V. Rajkumar et al. (The Lancet Oncology, 2014: 15; e538-e548)

Criteria for symptomatic MM

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[1]

AND any one or more of the following myeloma defining events or biomarkers of malignancy, specifically:

Myeloma defining events
Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder:

- Hypercalcemia: serum calcium >0.25 mmol/l (>1 mg/dl) higher than ULN or >2.75 mmol/l (>11 mg/dl)
- Renal insufficiency: creatinine clearance[2] <40ml/min or serum creatinine >177 µmol/l (>2 mg/dl)
- Anemia: (hemoglobin >2 g/dl below normal limit of or hemoglobin <10 g/dl)

  (hemoglobin >1.24 mmol/l below normal limit of or hemoglobin <6.21 mmol/l)
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[3]

Biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage[1] ≥60%
- Involved: uninvolved serum free light chain ratio[4] ≥100
- >1 focal lesion[5] on MRI studies

Footnotes:
1. Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and the core biopsy, the highest value should be used.

2. Measured or estimated by validated equations.

3. If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

4. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham UK). The involved free light chain must be ≥100 mg/L.

5. At least 2 focal lesions must be 5 mm or more in size.

Criteria for measurable disease

Serum M-protein ≥ 10 g/L **or**

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

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

Proven plasmacytoma by biopsy *

* If plasmacytoma is the only measurable parameter, the patient is not allowed to be included in the study, because of difficult response evaluation.

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

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

C. Response criteria for Multiple Myeloma

Based on Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. (Blood, 2011: 117; 4691-4695)

IMWG uniform response criteria by response subcategory for multiple myeloma

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus ▪ Normal FLC ratio (0.26-1.65) and ▪ Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunophenotyping[c]
CR	▪ Negative IFE of serum and urine and ▪ Disappearance of any soft tissue plasmacytomas and ▪ < 5% plasma cells in bone marrow[b] ▪ In patients in whom the only measurable disease is by sFLC levels, CR is defined as a normal FLC ratio (0.26-1.65) in addition to the CR criteria listed above
VGPR	▪ Serum and urine M-protein detectable by IFE but not on electrophoresis or ▪ 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h ▪ In patients in whom the only measurable disease is by sFLC levels, VGPR is defined as a >90% decrease in the difference between involved and uninvolved sFLC levels
PR	▪ ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h ▪ In patients in whom the only measurable disease is by sFLC levels, PR is defined as a ≥ 50% decrease in the difference between involved and uninvolved sFLC levels ▪ If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% ▪ In addition to the above 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

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

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

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

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

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

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

RELAPSE CRITERIA

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires one or more of the following: ▪ Increase of ≥ 25% from lowest response value in serum M-component (the absolute increase must be ≥ 0.5 g/dl)[b] and/or ▪ Increase of ≥ 25% from lowest response value in urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or ▪ In patients in whom the only measurable disease is by sFLC levels, increase of ≥ 25% from lowest response value in the differrence between involved and uninvolved sFLC levels (absolute increase must be >100 mg/L) ▪ If serum and urine M-protein are unmeasurable, and sFLCs are also unmeasurable, increase of ≥ 25% from lowest response value in bone marrow plasma cell percentage (absolute % must be ≥ 10%) ▪ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas ▪ Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcaemia (> 2.65 mmol/l) [11.5 mg/dl] 4. Decrease in hemoglobin of ≥ 1.25 mmol/l [2 g/dl] 5. Rise in serum creatinine by 177 µmol/l or more [2 mg/dl or more] 6. Hyperviscosity
Relapse from CR[a] (To be used only if the end point studied is DFS)[d]	Any one or more of the following: ▪ Reappearance of serum or urine M-protein by immunofixation or electrophoresis ▪ In patients in whom the only measurable disease is by sFLC levels, reappearance of abnormal sFLC levels (absolute increase must be >100 mg/L) ▪ Development of ≥ 5% plasma cells in the bone marrow[c] ▪ Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia 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
- Patients with measurable disease restricted to the SPEP will need to be followed by SPEP at each evaluation; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed by UPEP[a] at each evaluation
- 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. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

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

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

4 Unable to get out of bed

5 Death

E. Common Terminology Criteria for Adverse Events

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

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

F. Intake of ixazomib citrate and management of ixazomib citrate toxicity during an induction cycle and maintenance therapy

Ixazomib citrate will be given as a single, oral dose of 4.0 mg weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without study drug in a 28-day cycle. Patients should be instructed to swallow ixazomib citrate/placebo capsules whole with water and not to break, chew, or open the capsules. Ixazomib citrate should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. The capsule should be swallowed with a sip of water. A total of approximately 150 mL of water should be taken with the capsules. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

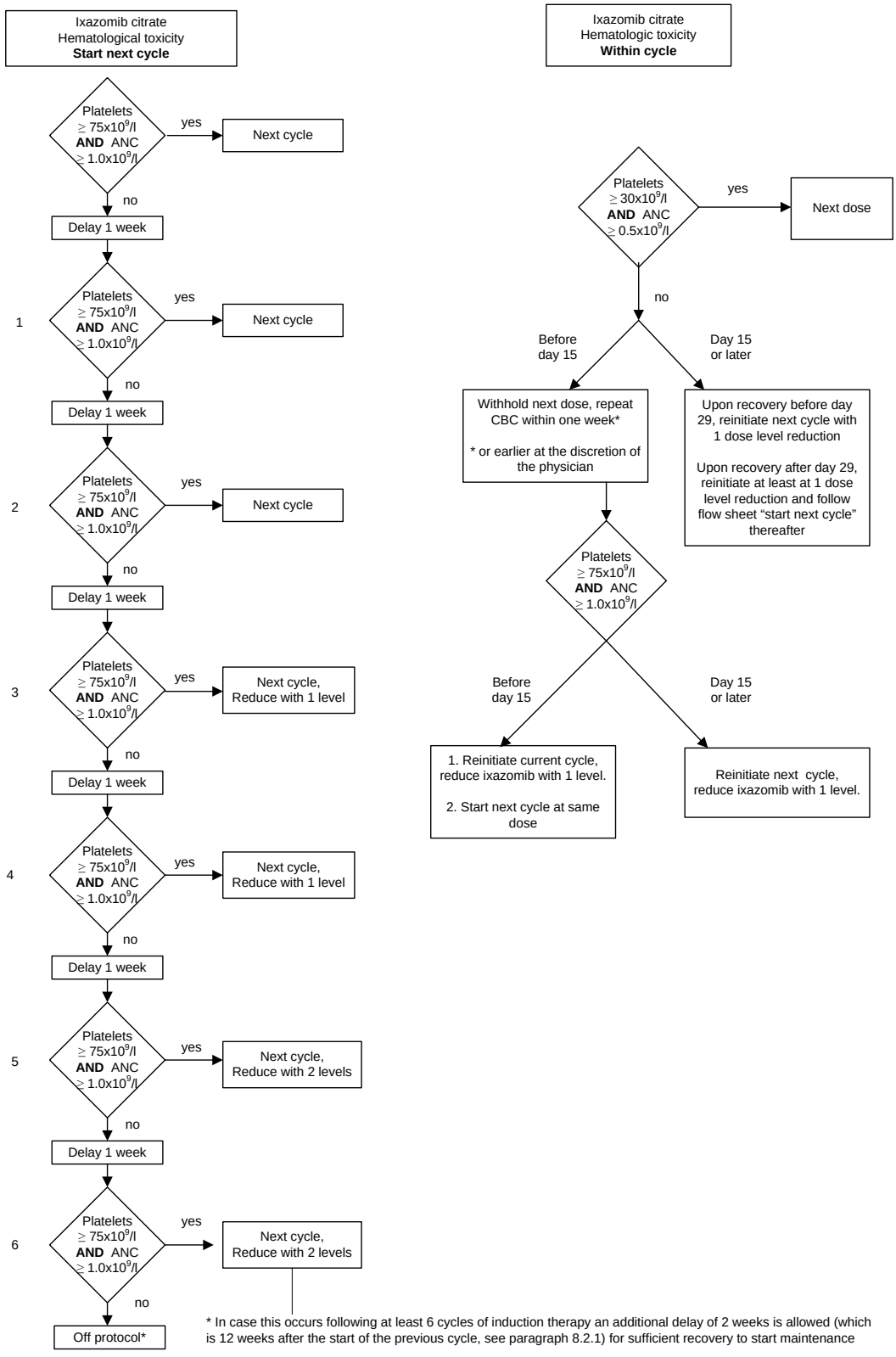
Dose levels

Dose Levels for ixazomib citrate during Induction and Maintenance Therapy

Dose Levels	Ixazomib citrate
Starting Dose	4 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -1	3 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -2	2,3 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -3	discontinue (off protocol treatment)

Dosage adjustments for hematologic toxicity.

See flow sheet and table at next pages.


Ixazomib citrate
Hematological toxicity
Start next cycle
Platelets ≥ 75x10^9/l AND ANC ≥ 1.0x10^9/l
yes
Next cycle
no
Delay 1 week
1
2
3
4
5
6
Next cycle, Reduce with 1 level
Next cycle, Reduce with 2 levels
Off protocol*
Ixazomib citrate
Hematologic toxicity
Within cycle
Platelets ≥ 30x10^9/l AND ANC ≥ 0.5x10^9/l
Next dose
Before day 15
Day 15 or later
Withhold next dose, repeat CBC within one week*
* or earlier at the discretion of the physician
Upon recovery before day 29, reinitiate next cycle with 1 dose level reduction
Upon recovery after day 29, reinitiate at least at 1 dose level reduction and follow flow sheet “start next cycle” thereafter
1. Reinitiate current cycle, reduce ixazomib with 1 level.
2. Start next cycle at same dose
Reinitiate next cycle, reduce ixazomib with 1 level.
* In case this occurs following at least 6 cycles of induction therapy an additional delay of 2 weeks is allowed (which is 12 weeks after the start of the previous cycle, see paragraph 8.2.1) for sufficient recovery to start maintenance

Dose adjustments for hematological toxicities

Criteria	Action
Within-Cycle Dose Modifications	
– If platelet count ≤ 30 × 109/L or ANC ≤ 0.50 × 109/L on a MLN9708 dosing day (other than Day 1)	– MLN9708 dose should be withheld. – Complete blood count (CBC) with differential should be repeated within one week or earlier at the discretion of the physician until the ANC ≥ $1.0x10^9$/L and/or platelet counts ≥ $75x10^9$/L. Upon recovery within the cycle, MLN9708 may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
– Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 9.1.2:ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	– Hold MLN9708 until resolution (ANC ≥ $1.0x10^9$/L and/or platelet counts ≥ $75x10^9$/L and/or nonhematologic toxicities ≤ Grade 1 or to the patient's baseline condition) – Upon recovery, reduce MLN9708 1 dose level. – The maximum delay before treatment should be discontinued will be 6 weeks.
Dose Modifications for Subsequent Treatment Cycles	
– All hematologic toxicities	– For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle,: – If dose was reduced within the cycle, start the next cycle at that same dose. – If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce MLN9708 by 1 dose level at the start of that cycle. – Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Dose modification instructions for ixazomib citrate for non-hematological toxicity during a cycle and during maintenance therapy

Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [14]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [14]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	Hold study drug until resolution to Grade ≤ 1 or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [14]
New or worsening Grade 4 peripheral neuropathy	Discontinue study drug	
Grade 2 Rash	Symptomatic recommendations as described below	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 2 Bullous Rash	Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit
Grade 3 Stevens-Johnson Syndrome	Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit
Grade 3 nonhematologic toxicity judged to be related to study drug	Hold study drug until resolution to Grade ≤ 1 or baseline	Symptomatic recommendations noted below
If not recovered to ≤ Grade 1 or baseline within 4 weeks	Reduce study drug 1 to next lower dose upon return to ≤ Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to ≤ Grade 1 or baseline within 4 weeks	Hold study drug until resolution to ≤Grade 1 or baseline Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to study drug	Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once Ixazomib citrate is reduced for any toxicity, the dose may not be re-escalated

Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib citrate treatment. Management guidelines regarding these events are outlined below. Further details of management of MLN9708 AEs are described in Section 6 of the MLN9708 IB. For hematological toxicity see flow sheet in appendix F.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment. Prophylactic antidiarrheals are not generally recommended.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with ixazomib citrate, primarily at the higher doses tested. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical steroids and/or antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Fluid Deficits

Dehydration should be avoided because ixazomib citrate may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with ixazomib citrate. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension have been reported with ixazomib citrate. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit

should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with ixazomib citrate. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, VELCADE. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

G. Intake of thalidomide and management of thalidomide related toxicity.

Thalidomide will be given as a single, oral dose of 100 mg daily for 28 days in a 28-day cycle. Thalidomide should be given before the night. If a dose of thalidomide is missed, the dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Dose Levels for Thalidomide during Induction Therapy

Dose Levels	Thalidomide
Starting Dose	100 mg every day
Dose Level -1	50 mg every day
Dose Level -2	no thalidomide

Dose Modification Instructions for Thalidomide for Polyneuropathy during a Cycle

Toxicity	**ActionThalidomide**
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/ 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 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

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

Toxicity	**ActionThalidomide**
Rash = Grade 1 or 2 (= limited localized rash)	Continue Thalidomide, 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 ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue Thalidomide
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (Constipation must resolve to ≤ Grade 2).
Thrombosis/embolism ≥ Grade 3	Hold dose for remainder of cycle. Initiate anticoagulation treatment Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.

Thalidomide is not reduced for for hematologic toxicity

H. Intake of dexamethasone and management of dexamethasone related toxicity

Dexamethasone will be given as a single, oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 of a 28-day cycle. Dexamethasone should be taken at approximately the same time each day. Dexamethasone should be taken at least 1 hour after ixazomib citrate and thalidomide. Each dose of dexamethasone should be taken with food or milk. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. If it is almost time for the next dose (within 6 hours), the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Dose Levels for Dexamethasone during Induction Therapy

Dose Level	Prednisone
Starting Dose	40 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -1	20 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -2	8 mg once weekly on days 1,8 and 15 every 28 days
Dose Level -3	discontinue

Dose Modification Instructions for Dexamethasone 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 ≥ Grade 3	Hold dose until symptoms are controlled. Add H2 blocker or proton pump inhibitors and decrease one dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Hold dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness (steroid myopathy) > Grade 2 Interfering with function	Decrease by one dose level. If weakness persist despite these measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist
Hyperglycaemia ≥ Grade 3	Treat with insulin or oral hypoglycaemic agents as needed. If uncontrolled despite these measures decrease dose by one dose level until levels are satisfactory
Acute pancreatitis	Discontinue dexamethasone and discontinue subject from the study.

Dexamethasone is not reduced for for hematologic toxicity

I. Correlative molecular studies - bone marrow and plasma cryopreservation

(See lab manual at HOVON website for practical guidance and protocols)

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. Bone marrow samples and peripheral blood cells and plasma will be collected at entry and in case bone marrow samples are taken to confirm either a complete remission or progressive disease/relapse. Peripheral blood will also be collected before the start of maintenance (after the last induction cycle) and at end of treatment (section 11.2.10).This material will be used for additional investigations in order to determine prognostic factors.This will include:

A. FISH analysis

Sending bone marrow for FISH analysis is mandatory in order to be included in the trial. FISH analysis will be performed on isolated plasmacells or by double-labelled identified myeloma cells slides according to EMN FISH recommandations (Ross et al., Haematologica 97, 1272-1277 (2012)) for chromosome del1p, gain 1q, t(4;14)(p16;q32), t(14;16)(q32;q23), t(11;14)(q13;q32), del13q/13-, del17p and hyperdiploidy (at least 2 of the chromosomes 5, 9, 11 and 15 should be analyzedConditions for FISH will be standardized by the HOVON Cytogenetic Working Party.

B. Gene expression and Genomic profiling

Whole genome transcriptional profiling will be used to establish the level of over 47,000 transcripts, representing 20,000 genes [Affymetrix U133 Plus 2.0 array]. Moreover, genomic profiling by genomic arrays or next generation sequencing approach will be performed. 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 (several papers Sonneveld lab; Broyl A Blood 2013, Kuiper R Leukemia 2012, Broyl A Blood 2010) .

Moreover, in view of the possible emergence of resistant clones during maintenance therapy, as suggested by the differential effect of thalidomide maintenance in molecular defined subgroups of MM patients, mutation analysis of the proteasome beta5 subunit and proteasome subunit expression analysis will be performed in order to unravel proteasome inhibitor resistance. In vitro prolonged exposure to proteasome inhibitors have been found to result in overexpression of the proteasome beta5 subunit followed by mutations indeed. In addition, the ratio of constitutive and immunoproteasome levels might predict the sensitivity to proteasome inhibitors as we showed in

leukemia. In view of this both at the start and during maintenance treatment mutation analysis of the proteasome beta5 subunit and proteasome subunit expression analysis will be performed at the VU University Medical Center (Niewerth D Blood, ASH 2012, abstract 1346, Franke NE Leukemia 2012, Oerlemans R Blood 2008).

C. SNP analysis

The involvement of specific genes in the drug metabolism and anti-tumor effect of ixazomib citrate 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.

The most likely explanation for the inter-individual variation in response and toxicity, being described for both thalidomide and ixazomib citrate, 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 on outcome 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. Moreover, a recent analysis from the group of Sonneveld showed variant polymorphism genotype to be related to the development of neuropathy (Broyl A Lancet Oncology 2010, Sonneveld P ASH educational 2010).

D. MRD analysis

The importance of MRD in the outcome of MM has become clear in patients being treated with PIs and IMiDs. However, the prognostic value of MRD in patients receiving ixazomib citrate both in induction and maintenance is unknown. Moreover, the optimal duration of maintenance is unknown. In order to design randomized clinical maintenance trials based on MRD, the number of patients reaching MRD and the prognostic value of reaching MRD should be known. Therefore, MRD will be investigated by performing flow cytometric analsysis of patientswho reach a complete remission.

E. Proteasome protein expression levels of the constitutive proteasome units and there immunoproteasome counterparts en β5 subunit mutation analysis

In VUmc hematology research laboratory, it was recently found that differential expression levels of constitutive and immunoproteasomes in pediatric ALL and AML constitute an underlying mechanism of sensitivity to bortezomib and new generation proteasome inhibitors. A higher ratio of immune proteasome/constitutive proteasome correlated with a increased sensitivity to proteasome inhibitors. In view of the similarities in the biological background of acquired proteasome inhibitor resistance between multiple myeloma cellines and leukemic cellines, in this study we will investigate whether the proteasome protein expression levels correlate with response (Niewerth D Blood, ASH 2012, abstract 1346)

Moreover, in case of progression during maintenance therapy with ixazomib citrate, the presence of β5-subunit mutations will be investigated (Franke NE Leukemia 2012, Oerlemans R Blood 2008)

F. 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

Bone marrow samples and peripheral blood cells and plasma will be collected at entry and in case bone marrow samples are taken to confirm either a complete remission or progressive disease/relapse. Peripheral blood will also be collected before the start of maintenance treatment (after the last induction cycle) and at end of treatment. For further details on logistics and laboratory procedures see lab manual at HOVON 126 website (Lab manual HOVON-126).

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 and proteasome subunit analysis

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)

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 126 website (Lab manual HOVON-126)

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:	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:	myeloma.hematology@erasmusmc.nl

Ad C SNP analysis

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. Alternatively the plasma cell purification of Ficoll separated bone marrow by using a CD138 magnetic cell sorting selection followed by cryopreservation may be performed in the participating countries for later shipment.

In all participating centers blood samples will be taken 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.

J. Prognostic value of FDG-PET-CT at diagnosis and in follow-up

Assessment of the prognostic value of FluoroDeoxyGlucose - Positron Emission Tomography - Computer Tomography (FDG-PET-CT) at diagnosis and following induction therapy in patients treated in the HOVON126/NMSG21.13 protocol

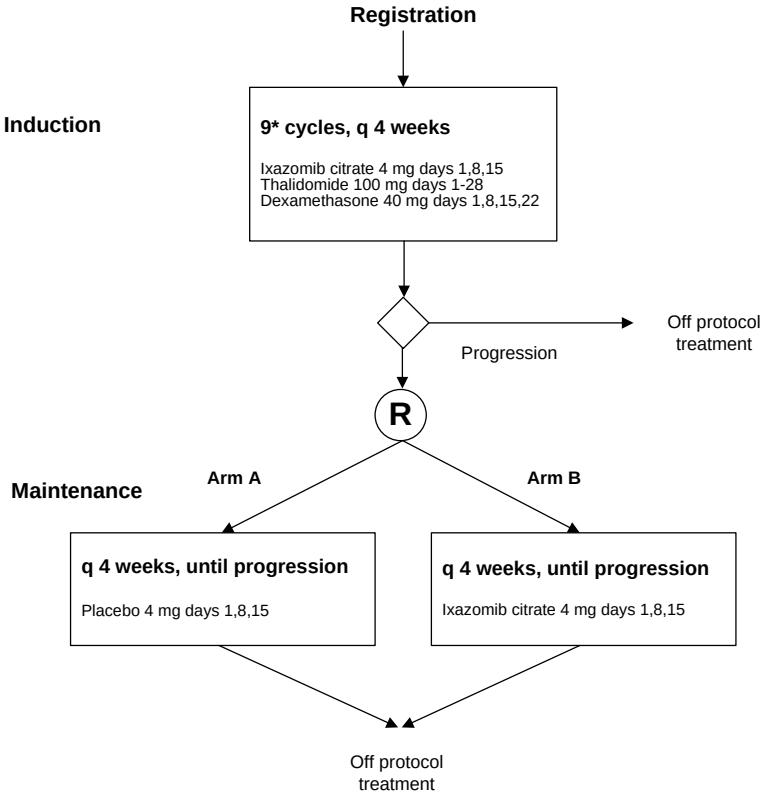
Short title:

Prognostic value of FDG-PET-CT at diagnosis and in follow-up

Principal Investigator	S. Zweegman
Executive coordinator	Y. Jauw
Writing committee	N. Abildgaard
	A. Broyl
	M. van Duin
	M. Hansson
	E. Haukas
	O.S. Hoekstra
	S.K. Klein
	M-D Levin
	M.C. Minnema
	P.H.G.M. Raijmakers
	P. Sonneveld
	A. Waage
	J.M. Zijlstra
Sponsor	HOVON
	VU Medical Center,
	P.O.Box 7057
	1007 MB Amsterdam
Statistician	B. van der Holt
Data management	HOVON Data Center and VUmc Imaging review center
Registration :	Erasmus MC, Cancer Institute
	Clinical Trial Center
	P.O. Box 2040
	3000 CA Rotterdam
	internal postal address Hs-423
	tel. +31.10. 7041560
	fax +31.10. 7041028
First version	August 27, 2014
Final version	Jan 31, 2015

1 Scheme of study

Previously untreated patients with MM
Age ≥ 66 years or patients ≤ 65 years and ineligible for high dose therapy and peripheral stem cell transplantation



FDG-PET-CT before start of induction therapy

FDG-PET-CT after completion of induction therapy, before start of maintenance therapy

FDG-PET-CT at the time CR is reached and MRD assessment in bone marrow by MFC is performed, see paragraph 10.1 for details

* Start of maintenance therapy is allowed after a minimum of 6 induction cycles as described in 8.2.1

2 Table of contents

Page

3 Synopsis

Study phase	Prospective systematic evaluation
Study objectives	Primary objectives: - To assess the prognostic value of FDG-PET at diagnosis in terms of progression free survival (PFS). - To determine the conversion rate, defined as complete normalization, of FDG-PET after induction therapy Secondary objectives: - To compare the response rate as determined by FDG-PET with classical biochemical response monitoring according to IMWG - To assess the prognostic value of FDG-PET-CT at diagnosis in terms of overall survival (OS) - To assess the prognostic value of post-induction remission status as determined with FDG-PET in terms of PFS and OS - To compare the prognostic value of post-induction remission status as determined with FDG-PET with the minimal residual disease (MRD) status - To correlate MM related bone disease as detected by FDG-PET-CT with distinct patterns of gene expression of malignant plasma cells and of the bone marrow microenvironment
Study design	Side study of HOVON126/NMSG21.13
Patient population	Patients included in HOVON126/NMSG21.13
Number of patients	60
Planned start and end of recuitment	Running time HOVON126/NMSG21.13 Start Q2 2015 End Q4 2016

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Principal Investigator	S.Zweegman	VU University Medical Center Amsterdam
Executive coordinator	Y. Jauw	VU University Medical Center Amsterdam
Study Coordinators	A. Broyl	Erasmus MC Cancer Institute Rotterdam
	P.G.H.M. Raijmakers	VU University Medical Center Amsterdam
	A. Waage	University Hospital Trondheim
Representative of Sponsor (HOVON)	J.J. Cornelissen, chairman	VU University Medical Center Amsterdam
Registration	Y.Jauw	y.jauw@vumc.nl VU University Medical Center Amsterdam
Monitoring		
- Clinical data	HOVON Data Center	Erasmus MC Cancer Institute – Clinical Trial Office
- Imaging	Imaging Center	VU University Medical Center Amsterdam
Writing Committee	N. Abildgaard	Odense University Hospital Odense
	A. Broyl	Erasmus MC Cancer Institute Rotterdam
	M. van Duin	Erasmus MC Cancer Institute Rotterdam
	M. Hansson	Skane University Hospital Lund
	E. Haukas	Stavanger University Hospital Stavanger
	O.S. Hoekstra	VU University Medical Center Amsterdam
	S.K. Klein	Meander Medical Center Amersfoort
	M-D. Levin	Albert Schweitzer Hospital, Dordrecht
	M.C. Minnema	Utrecht University Medical Center
	P.G.H.M. Raijmakers	VU University Medical Center Amsterdam
	P. Sonneveld	Erasmus MC Cancer Institute Rotterdam
	A. Waage	University Hospital Trondheim
	S. Zweegman	VU University Medical Center Amsterdam
	J.M. Zijlstra	VU University Medical Center Amsterdam
Statistician	B. van der Holt	Erasmus MC Cancer Institute – Clinical Trial Center Rotterdam
CRF collection of		
a. Clinical data	HOVON Data Center	Erasmus MC Cancer Institute – Clinical Trial Center Rotterdam
b. Imaging data	Imaging Center	VU University Medical Center Amsterdam

5 Introduction and rationale

5.1 Introduction

Bone disease, defined as osteolytic lesions and osteoporosis, is common in patients with symptomatic/stage III Multiple Myeloma (MM), with up to 90% of patients developing bone lesions and up to 60% of patients experiencing a pathologic fracture in the course of the disease.[1] The hallmark of myeloma bone disease is a disbalance between bone resorption and deposition of new bone through increased osteoclast activity and inhibition of osteoblasts by Dickkopf-1 and frizzle-related protein 2 produced by MM cells, respectively.[2] The clinical consequences of imbalanced bone destruction include bone pain, pathologic fractures, hypercalcemia and spinal cord compression syndromes, which can be devastating for patients and significantly impact overall quality of life. Moreover, the presence of lytic bone disease has been found to be of prognostic importance, reflected by the Salmon and Durie clinical staging system.[3] Patients without or with one lesion only, defined as stage I, showed an overall survival (OS) of approximately 7 years as compared to 2-3 years in patients with stage III, which can be diagnosed in case of more than 1 osteolytic lesions. More recently, the presence of only one osteolytic lesions on whole body X-ray (WBXR) was found to be an independent prognostic factor.[4] Although, the prognostic value of osteolytic lesions detected by CT is not supported by prospective data the International Myeloma Working Group (IMWG) recently decided that an osteolytic lesion of more than 5 mm definitely indicates the presence of MM bone disease. Therefore, in the guidelines of the International Myeloma Working Group (IMWG), apart from other criteria, the presence of one or more bone lesions either on WBXR or CT-scan indicates the presence of symptomatic MM, for which treatment is required.[5] Because of the devastating effects of bone disease and the fact that the sensitivity of conventional WBXR analysis is low, given that at least 30% of trabecular bone substance must be lost in order to give rise to visible lytic lesions in many centres a CT-scan of the whole body is now being performed in order to detect MM related bone disease. CT has been found to have a superior detection rate as compared to WBXR, although lesions in the skull, the ribs and extremities might be missed.[1 6]

5.2 Prognostic impact of bone disease detected by FDG-PET at diagnosis of MM

As indicated, in contrast to its high sensitivity for the detection of bone disease, whole body CT was not found to be of prognostic value for the clinical outcome. In contrast, recently, data on the prognostic value of baseline FDG-PET-CT were published by two groups.[7;8] The extent of the disease, defined as the number of FDG-positive lesions as well as the maximum Standard Uptake Value (SUV) at diagnosis was found to be correlated with inferior outcome. In the 'Total Therapy 3'-study, Bartel et al. found that the presence of more than three focal lesions, as well as the presence

of extramedullary disease (EMD) at baseline was correlated with poor outcome: 5-year OS was 73% versus 90% and 50% versus 87%, respectively. Recently, Zamagni et al. had similar findings by showing a correlation between the presence of extramedullary disease (EMD) or high SUV and outcome (EMD: 4-year OS 64% versus 90%; SUV >4,2: 76% versus 92%).{Zamagni, 2011}

5.3 Quality of response by using FDG-PET in relation to prognosis

The international myeloma working group has defined international uniform response criteria. New treatment options, leading to a high complete remission (CR) rate, recently led to the introduction of molecular CR determined by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) of rearranged B-cell receptor genes and immunophenotypic CR determined by multiparametric flowcytometry (MFC) as response criteria, both indicating a deeper level of response.[9-13] Although accomplishing molecular or immunophenotypic CR is a predictor of superior outcome, still such patients do develop relapses. Besides an insufficient sensitivity of techniques used to detect minimal residual disease (MRD), the presence of focal disease can explain why relapses occur even in MRD-negative patients. The studies investigating the prognostic value of FDG-PET scans support this hypothesis. Reaching FDG-PET negativity (PET-CR or complete metabolic response (CMR)) during the course of the treatment resulted in an improved outcome. The 30-month estimated EFS was 89% in PET-CR versus 63% for those with persistent FDG uptake in the study of Bartel.[7] These numbers were 92% and 71% for OS. Similarly, in the study of Zamagni et al.{Zamagni, 2011} PFS and OS were superior in case of PET-CR versus those without PET-CR; the 4-year estimates of PFS and OS were 47% and 79% respectively versus 32% and 66% in PET-positive patients.

5.4 Biological features of MM related bone disease; Do specific gene expression profiles of malignant plasma cells or the plasma cell negative bone marrow fraction predict MM bone disease?

GEP of malignant plasma cells allow to define the molecular classification of MM, revealing 7 distinct molecular entities. Among these a gene profile associated with less bone disease (GEP LB) was associated with superior survival.[19] Further analysis showed a high expression of the IL-6 ligand receptor and low expression of Wnt signalling antagonists FRZB and DKK-1.[20] Bartel et al. found a similar inverse correlation between GEP-LB and the number of focal lesions at FDG-PET. Conversely, a high risk GEP was found in the group of patients with bone disease detected by FDG-PET, MRI and WBXR.[7] Recently, in the Dutch-Belgian/German HOVON-65/GMMG-HD4 trial hierarchical clustering identified 10 subgroups; 6 corresponded to clusters described in the University of Arkansas for Medical Science (UAMS) classification, CD-1 (n = 13, 4.1%), CD-2 (n = 34, 1.6%), MF

(n = 32, 1.0%), MS (n = 33, 1.3%), proliferation-associated genes (n = 15, 4.7%), and hyperdiploid (n = 77, 24.1%). Moreover, the UAMS low percentage of bone disease cluster was identified as a subcluster of the MF cluster (n = 15, 4.7%). One subgroup (n = 39, 12.2%) showed a myeloid signature. Three novel subgroups were defined, including a subgroup of 37 patients (11.6%) characterized by high expression of genes involved in the nuclear factor kappa light-chain-enhancer of activated B cells pathway, which include TNFAIP3 and CD40. Another subgroup of 22 patients (6.9%) was characterized by distinct overexpression of cancer testis antigens without overexpression of proliferation genes. The third novel cluster of 9 patients (2.8%) showed up-regulation of protein tyrosine phosphatases PRL-3 and PTPRZ1 as well as SOCS3. There is limited information on the GEP of the plasma cell negative bone marrow fraction. Several groups have reported that BM-derived mesenchymal stem cells from MM patients (MM-hMSCs) show a distinctive gene expression profile and an enhanced production of cytokines, including IL-6, DKK1, IL-1β, and SDF-1 as compared to normal donor-derived hMSCs (ND-hMSCs).[21;22] In addition, impaired osteogenic differentiation ability, compared to ND-hMSCs has been found.[23] However, these are cultured hMSCs. Firstly, this is laborious and secondly, by culturing, GEP might have been altered. Although GEP of the negative bone marrow fraction following CD138 isolation is hampered by being a heterogeneous cell population, we plan to perform GEP not only of malignant plasma cells but also from the remaining non-plasma cell containing bone marrow fraction, in order to investigate whether specific gene profiles are related to bone disease as defined by FDG-PET-CT.

5.5 Rationale of the study

What is the prognostic value of FDG-PET at diagnosis and after induction therapy?
Although there is clear evidence of the prognostic value of FDG-PET scans in the transplant eligible newly diagnosed MM patients, the prognostic value in the elderly non-transplant eligible patients at diagnosis and following induction therapy is currently unknown. The prognostic value might differ, especially the prognostic value after 9 cycles of induction therapy with Ixazomib/Thalidomide/Dexamethasone in view of the less intense treatment. In view of the importance of residual disease for prognosis, and for the negative impact of residual bone disease on the quality of life in specific, we aim to investigate this in patients being included in the HOVON126/NMSG21.13 trial. This might pave the way for future treatment strategies that are guided by the presence of residual (bone)disease and for the introduction of therapy directed to treatment of bone disease in specific.

Does MM bone disease as detected by FDG-PET CT reflect specific biologic processes involved in MM bone disease?

GEP of malignant plasma cells has recently been found to detect specific subgroups of MM patients, differing in clinical symptoms and prognosis. In addition, a GEP associated with less bone disease has recently been identified. However, to our knowledge there is no information on these molecular parameters in relation to FDG-PET in specific. This is of interest as in contrast to CT scan providing information on the presence and extent of osteolytic lesions, FDG-PET adds information on the metabolic activity of bone disease.

6 Study objectives

6.1 Primary objectives

- To assess the prognostic value of FDG-PET at diagnosis in terms of progression free survival (PFS).
- To determine the conversion rate, defined as complete normalization, of FDG-PET-CT after induction therapy.

6.2 Secondary objectives

- To compare the response rate as determined by FDG-PET with classical biochemical response monitoring according to IMWG and with minimal residual disease as defined by Multi Flow Cytometry (MFC) of bone marrow
- To assess the prognostic value of FDG-PET-CT at diagnosis in terms of overall survival (OS)
- To assess the prognostic value of post-induction remission status as determined with FDG-PET in terms of PFS and OS
- To compare the prognostic value of post-induction remission status as determined with FDG-PET with the minimal residual disease (MRD) status
- To correlate MM related bone disease as detected by FDG-PET-CT (number of focal lesions and SUV parameters with distinct patterns of gene expression of malignant plasma cells and of the bone marrow microenvironment

7 Study design

This study is a prospective systematic evaluation of imaging techniques in patients included in the HOVON126/NMSG21.13 study (a randomized phase II trial in elderly patients with previously untreated symptomatic Multiple Myeloma comparing ixazomib-thalidomide-low dose dexamethasone induction followed by maintenance therapy with ixazomib or placebo in newly diagnosed multiple

myeloma patients not eligible for autologous stem cell transplantation). Separate permission for participation in this imaging side study will be asked.

A FDG-PET-low-dose CT will be performed after inclusion in the HOVON-126 and before start of induction treatment. The FDG-PET-low-dose CT will be reviewed after completion of the study and will not be used for clinical decision making. Every FDG-PET-low-dose CT will be interpreted by a team of nuclear medicine physicians with extensive experience in the MM field. These readers will be unaware of the clinical symptoms and treatment.
In case of medical need for bone disease examination on protocol, imaging techniques according to local protocols (either skeletal X-ray, (FDG-PET)-CT scan or MRI) will be performed that will be interpreted by the local radiologist/nuclear physicians.

8 Study population

Patients must be included in the HOVON126/NMSG21.13 study.

9 Eligibility criteria

9.1 Inclusion criteria

- Inclusion in the HOVON126/NMSG21.13 study

9.1.1 Exclusion criteria

- Physical inability to access PET-CT and to remain motionless for the time of investigation
- Uncontrolled diabetes

10 Required clinical evaluations

The clinical evaluations will be performed as indicated in the HOVON126/NMSG21.13 protocol in order to determine the prognostic value of MM related bone disease as detected by FDG-PET-CT in terms of PFS and OS.

10.1 Required investigations apart from the HOVON126/NMSG21.13 protocol

- Assessment of MM related bone disease at entry by FDG-PET-CT
- The response of bone involvement will be evaluated with FDG-PET-CT

A. at entry and before randomization of maintenance therapy after completion of 9 cycles of induction treatment OR after a minimum of 6 cycles in case there is non-hematological toxicity NOT related to ixazomib citrate, requiring discontinuation of induction therapy
B. at the time CR is reached and MRD assessment in bone marrow by MFC is performed
C. in case a second MRD assessment will be performed and FDG-PET negativity (PET-CR or complete metabolic response (CMR)) has not been reached yet, an additionalFDG-PET-CT will be performed.
In case CR/sCR are reached before the end of induction therapy and FDG-PET negativity (CMR) has been reached already, no FDG-PET-CT will be performed before randomization of maintenance therapy in case there is no loss of CR/sCR.

11 Endpoints

11.1 Primary endpoint

- Result of FDG-PET-CT at entry and result of FDG-PET-CT after induction
- Progression free survival, defined as time from registration in the HOVON126/NMSG21.13 study to progression or death from any cause
- Conversion rate, defined as complete normalization (complete metabolic response), of FDG-PET

11.2 Secondary endpoints (all determined in the HOVON-126 trial)

- Remission status as determined by the IMWG criteria after completion of induction therapy
- Overall survival, measured from time of registration
- Minimal residual disease status as defined by Multi Flow Cytometry
- Gene expression profile of malignant plasma cells and non-plasma cell containing bone marrow

12 Data collection

Clinical data will be collected on Case Report Forms to document parameters necessary to evaluate the study endpoints.

13 Statistical Consideration

The main objective of the study is to explore the prognostic value of focal lesions and SUVmax detected by FDG-PET-low dose CT at diagnosis with respect to progression free survival, as being described by two groups in a patient population undergoing autologous stem cell transplantation.[7;8]
A separate Cox regression model with PFS as outcome will be designed. In such a model, adjustments can be made for ISS, cytogenetic abnormalities [deletion 13, t(4;14), deletion 17p and amplification 1q], lactate dehydrogenase, biological bone markers, and GEP results.
The hazard ratio's (HR) and associated significance levels from the different multivariate models will be compared with each other to obtain an indication which technique is most promising in terms of predicting the PFS. In order to assess the prognostic value of FDG-PET-low dose CT at diagnosis, various cut-off values for the FDG-avid focal-lesions and for SUVmax on PET may be employed.
It is difficult to estimate the number of required patients to assess the prognostic value of a certain technique. Inclusion of 60 patients seems realistic, both in terms of participation rate and logistic restrictions. It is reasonable to assume that median PFS from registration in the HOVON-126 will be about 24 months. Furthermore, assume that half of the patients (n=30) have a "high" SUV of the lesion with the highest uptake, and expected 2-year PFS of 35% and half of the patients (n=30) have a "low" SUV of the lesion with the highest uptake and expected 2-year PFS of 65% (hazard ratio = 2.44). With uniform inclusion during 18 months (= expected accrual period of HOVON-126), additional follow up of 36 months after the last registered patient, and two-sided significance level $\alpha = 0.05$, we have 78% power to detect this difference. The analysis should be performed when in at least 43 patients in this side study an event for PFS has been reported (and 45 events for 80% power). Other cut-off points may result in different numbers of patients in subgroups, also with different PFS at 2 years and therefore other HRs. In fact, in the study of Bartel et al., more than 3 FDG-avid focal lesions was found in 34% of patients and to be significantly associated with a worse event-free survival; a HR of 2.98 was found. Similarly, in the study of Zamagni et al., more than 3 FDG-avid focal lesions, being observed in approximately 30% patients, was found to be significantly associated with a worse PFS; a HR of 1.80 was found. In addition, the 46% of patients with a SUV >4.2 were found to have a worse PFS; a HR of 2.19. However, it should be stressed that all these analyses are exploratory, so only hypothesis-generating, and results should be confirmed in other trials.

There is information of two prospective studies on the prognostic value of normalisation of FDG-PET-CT following induction therapy.[7;8] Again, this concerns younger patients eligible for autologous stem cell transplantation, being treated either according to the Total Therapy III programme or with thalidomide/dexamethasone induction therapy followed by double autologous stem cell transplantation. Complete normalization of FDG-PET-CT was associated with a significantly better

event-free survival in this patient group. In the study of Bartel et al., 71% of patients showed normalisation of the FDG-PET-CT, resulting in a superior 30-month event-free survival of 89% versus 63% in patients without normalization, which yields a HR for the EFS of ln(0.63)/ln(0.89) = 3.96. In the study of Zamagni et al. 37% of patients showed normalization following induction therapy. The 4-year estimated PFS was 69% in those patients with compete normalisation of FDG-PET-CT versus 44% in those without normalization, which yields a HR for the PFS of ln(0.44)/ln(0.69) = 2.21. With 30% patients without normalization, and 70% with normalization, in order to detect with 80% power and two-sided significance level $\alpha = 0.05$ a HR = 3.96, a total of 16 events should be observed. This is feasible, supposing that about half of the patients with a baseline PET will be evaluable for normalization of PET after induction.

This study also aims to obtain information on the normalization rate in this patient group in itself. As induction therapy is less intensive compared to the study of Bartel et al. and more intensive compared to the study of Zamagni et al., different normalisation rates may be expected.

14 References

1 Roodman GD. Skeletal imaging and management of bone disease. Hematology.Am.Soc.Hematol.Educ.Program. 2008313-319.

2 Hiruma Y, Honjo T, Jelinek DF et al. Increased signaling through p62 in the marrow microenvironment increases myeloma cell growth and osteoclast formation. Blood 2009;113:4894-4902.

3 Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842-854.

4 Cavo M, Galieni P, Zuffa E et al. Prognostic variables and clinical staging in multiple myeloma. Blood 1989;74:1774-1780.

5 Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473.

6 Regelink JC, Minnema MC, Terpos E et al. Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. Br.J Haematol. 2013;162:50-61.

7 Bartel TB, Haessler J, Brown TL et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076.

8 Zamagni E, Patriarca F, Nanni C et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 2011;118:5989-5995.

9 Lonial S, Gleason C. Down to the bitter end. Blood 2014;123:3061-3062.

10 Martinez-Lopez J, Lahuerta JJ, Pepin F et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood 2014;123:3073-3079.

11 Rawstron AC, Child JA, de Tute RM et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol 2013;31:2540-2547.

12 Paiva B, Gutierrez NC, Rosinol L et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood 2012;119:687-691.

13 Paiva B, Martinez-Lopez J, Vidriales MB et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. J.Clin.Oncol. 2011;29:1627-1633.

14 Raje N, Roodman GD. Advances in the biology and treatment of bone disease in multiple myeloma. Clin.Cancer Res. 2011;17:1278-1286.

15 Tian E, Zhan F, Walker R et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. N.Engl.J.Med. 2003;349:2483-2494.

16 Kaiser M, Mieth M, Liebisch P et al. Serum concentrations of DKK-1 correlate with the extent of bone disease in patients with multiple myeloma. Eur.J Haematol. 2008;80:490-494.

17 Terpos E, Christoulas D, Katodritou E et al. Elevated circulating sclerostin correlates with advanced disease features and abnormal bone remodeling in symptomatic myeloma: Reduction post-bortezomib monotherapy. Int.J.Cancer 2012;131:1466-1471.

18 Mohty M, Malard F, Mohty B et al. The effects of bortezomib on bone disease in patients with multiple myeloma. Cancer 2014;120:618-623.

19 Zhan F, Huang Y, Colla S et al. The molecular classification of multiple myeloma. Blood 2006;108:2020-2028.

20 Zhan F, Barlogie B, Mulligan G, Shaughnessy JD, Jr., Bryant B. High-risk myeloma: a gene expression based risk-stratification model for newly diagnosed multiple myeloma treated with high-dose therapy is predictive of outcome in relapsed disease treated with single-agent bortezomib or high-dose dexamethasone. Blood 2008;111:968-969.

21 Garayoa M, Garcia JL, Santamaria C et al. Mesenchymal stem cells from multiple myeloma patients display distinct genomic profile as compared with those from normal donors. Leukemia 2009;23:1515-1527.

22 Xu S, Cecilia SG, De VK et al. Upregulation of miR-135b is involved in the impaired osteogenic differentiation of mesenchymal stem cells derived from multiple myeloma patients. PLoS.One. 2013;8:e79752.

23 Xu S, Evans H, Buckle C et al. Impaired osteogenic differentiation of mesenchymal stem cells derived from multiple myeloma patients is associated with a blockade in the deactivation of the Notch signaling pathway. Leukemia 2012;26:2546-2549.

K. Positron Emission Tomography methods

Positron emission tomography

[18F]-FDG-PET measurements will be performed according to the EANM FDG PET guidelines 2.0 (Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2014 Dec 2. [Epub ahead of print]).

PET analysis:

A team of nuclear medicine physicians with extensive experience in the MM field will interpret the images on an image display and identify the abnormal lesions, using focally enhanced uptake vs. background and incompatible with physiology as the primary criterion for test positivity. Currently, there are 2 reference standards; the one used by Bartel et al. (F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076) and the one used by Zamagni et al. (Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 2011;118:5989-5995). Both reference standards will be used.