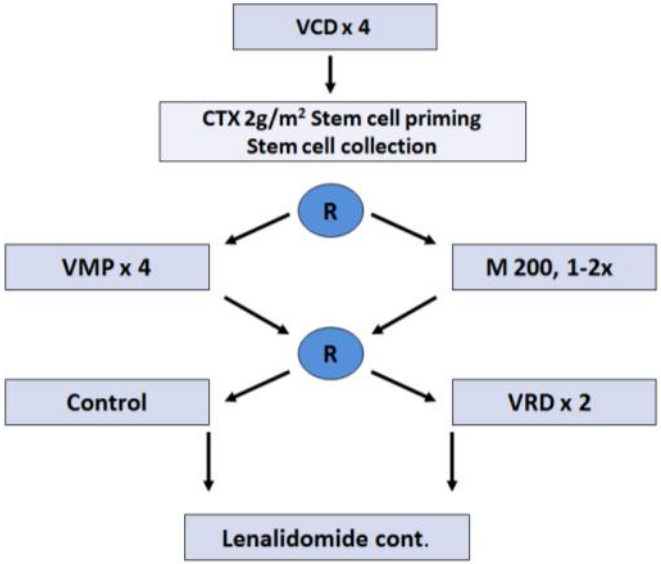

All patients will receive 4 cycles of VCD.

Patients will continue with Cyclophosphamide + G-CSF, independent from the response to VCD (except: patients with PD go off protocol).

Randomization 1: Patients will be randomized between High Dose Melphalan or Intensification therapy with VMP. Patients randomized to HDM will be treated with High Dose Melphalan followed by autologous stem cell reinfusion. Patients randomized to VMP treatment will receive 4 cycles of VMP.

Randomization 2: Patients randomized to consolidation treatment will get 2 cycles of Bortezomib, Lenalidomide, Dexamethasone (VRD).

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

Study design:

- Prospective, multicenter, intergroup, randomized phase III trial

Inclusion Criteria (selected):

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

Exclusion Criteria (selected):

- Known intolerance of Boron
- Systemic AL amyloidosis
- Primary Plasmacell Leukemia
- Non-secretory MM
- Previous chemotherapy or radiotherapy except local radiotherapy in case of local myeloma progression or corticosteroids maximum 5 days for symptom control
- Severe cardiac dysfunction (NYHA classification II-IV)
- Significant hepatic dysfunction, unless related to myeloma
- Patients with GFR <15 ml/min
- Patients with neuropathy CTC grade 2 or higher

AGMT Arbeitsgemeinschaft Medikamentöse Tumortherapie

HO95/EMN02

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

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Arbeitsgemeinschaft medikamentöse Tumortherapie (AGMT)
Univ. Prof. Dr. Richard Greil

Study procedures:

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

o.i. on indication

[1]Includes immuno-electropheresis, immuno-fixation, quantitative serum free light-chain analysis,

[2]at diagnosis and when needed to confirm CR. Must be analysed on morphology for CR and for immunophenotyping to confirm stringent CR (sCR)

[3]for male patients with active child wish

[4]for SNP analysis

[5]for Gene Expression Profiling

[6]at entry, and before and during Lenalidomide treatment according to the Pregnancy Prevention Risk Management Plan

[7]during maintenance: haematology and immunochemistry tested every two weeks in the first month, then every four weeks

[8]skeletal survey only every 12 months during maintenance/follow up

Study Objectives:

- Comparison of Bortezomib, Melphalan, Prednisone (VMP) versus High Dose Melphalan followed autologous stem cell transplantation (ASCT)
- Comparison of Bortezomib, Lenalidomide, Dexamethasone (VRD) as consolidation versus no consolidation
- Comparison of single versus tandem high dose Melphalan with ASCT

Centralized Laboratory Rotterdam

Bone marrow and peripheral blood samples will be collected and shipped to the central laboratory of Rotterdam before treatment start, at complete response and at relapse. Cytogenetic analysis, gene expression profiling, SNP analysis will be analyzed centrally.