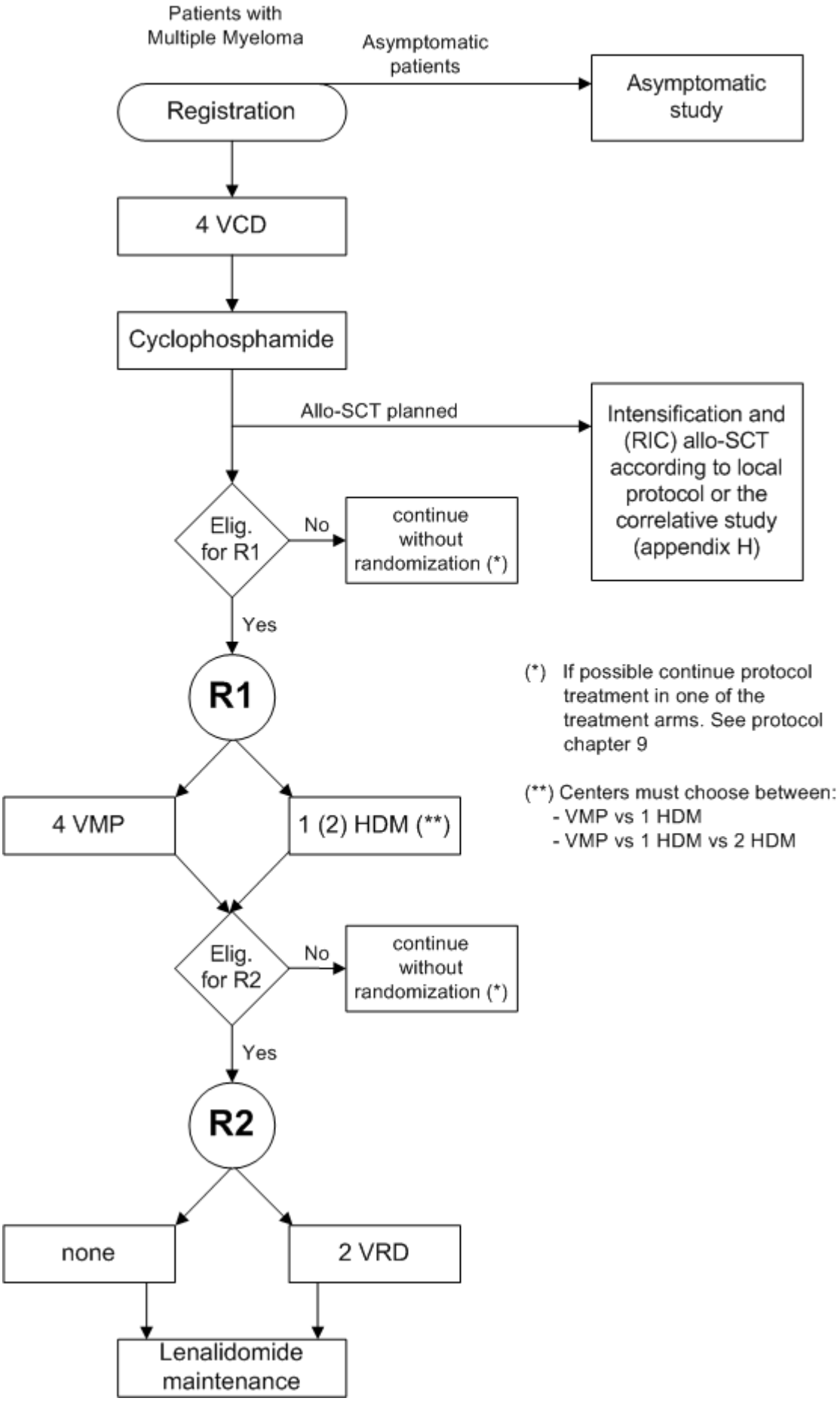
1. Overview

Summary
HOVON 95 MM = 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

Status
closed

Members
Participating groups: HOVON, GIMEMA, NMSG, DSMSG, CEMSG, CMG



Type of study
Prospective randomized Phase III study

Echelon level
Level D

Echelon level specification
For HDM treatment please make collaboration agreements with level A or B site.

Type of monitoring for this study
Site evaluation visits

Target number of patients
1500

Current number of patients
0

Date of activation
21-Jan-2011

Approved by
NL_METC (2010-122): 04NOV10
NL_CA (NL31466.078.10): 06APR10
NL_CKS (2010-4798): 02SEP10

BE_METC (3629):08SEP10
BE_CA: 27JUL10

Change history / amendement
Amendmend 3
NL_METC: 30NOV12
NL_CA: 10JUL12

Amendmend 4
NL_METC: 16APR13
NL_CA: 28MAR13

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

2. Patient eligibility criteria

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

Randomization 1
- WHO performance 0-2;
- Bilirubin and transaminases < 2.5 times the upper limit of normal values;
- A suitable stem cell graft containing at least 4 x 10^6 CD34+ cells/kg (or according to national guidelines).

Randomization 2
- Bilirubin and transaminases < 2.5 times the upper limit of normal values;
- ANC >= 0.5 x 10^9/l and platelets > 20 x 10^9/l;
- Patient is able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan.

Exclusion criteria
- Known intolerance of Boron;
- Systemic AL amyloidosis;
- Primary Plasmacell Leukemia;
- Non-secretory MM;
- Previous chemotherapy or radiotherapy except local radiotherapy in case of local myeloma progression or corticosteroids maximum 5 days for symptom control;
- Severe cardiac dysfunction (NYHA classification II-IV, see appendix E);
- Significant hepatic dysfunction (serum bilirubin >= 30 mmol/l or transaminases >= 2.5 times normal level), unless related to myeloma;
- Patients with GFR <15 ml/min,
- Patients known to be HIV-positive;
- Patients with active, uncontrolled infections;
- Patients with neuropathy, CTC grade 2 or higher;
- Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;
- Patients who are not willing or capable to use adequate contraception during the therapy (all men, all pre-menopausal women);
- Lactating women.

Randomization 1
- Severe pulmonary, neurologic, or psychiatric disease;
- CTCAE grade 3-4 polyneuropathy during Bortezomib treatment;
- Allogeneic Stem Cell Transplantation (Allo SCT) planned;
- Progressive disease.

Randomization 2
- Progressive disease;
- Neuropathy, except CTCAE grade 1;
- CTCAE grade 3-4 polyneuropathy during Bortezomib treatment.

3. Registration (& randomization) of patients

Registration
- Institution name
- Name of responsible investigator
- Date of birth
- Date of informed consent
- Date of sample shipment (optional)
- Date of diagnosis of multiple myeloma
- Serum B2-microglobulin
- Serum albumin
- Eligibility criteria

Registered patients (Last update: 15APR14)

AT-Linz-A.ö.k Elisabethinen-Hem | 4
AT-Salzburg-SALK-3rdMed Onco | 2
AT-Vienna-Wilhelminen-HemOnc | 15

AU-Brisbane-Pr Alexandra-Hema | 5
AU-Canbe-Canberra Hospita-Hema | 4
AU-Melbourn-Alfred Health-Hema | 5
AU-Sydney-Nepean Hospital-Hema | 3
BE-Antwerpen-Middelheim-Hema | 2
BE-Antwerpen-Stuivenberg-Hema | 13
BE-Haine-Saint--Jolimont-ServH | 2
BE-Liege-Citadelle-ServHem | 5
BE-Tournai-Chwapi-HemOnc | 1
BE-Turnho-AZ St Elisabeth-Hema | 6
CH-Aarau-Kantonsspital-Onk | 3
CH-Basel-UH-Hema | 3
CH-Bellinzona-IOSI-Hema | 3
CH-Bern-Inselspital-Onc | 5
CH-Chur-KS Graubünden-IntMed | 2
CH-Geneve (-Cantonal Univ-Hema | 1
CH-Liestal-KS Baselland-Onco | 3
CH-Luzern-Kantonsspital-Hema | 8
CH-St. Gall-Kantonsspital-Hema | 11
CH-Thun-STSAG-Onco | 1
CH-Zürich-Uv spital-Hema | 2
CZ-Brno-UH-HemaOnco | 21
CZ-Hradec -Hradec Kralove-hema | 23
CZ-Olomouc-Olomouc-Int | 13
CZ-Ostrava-Poruba-Ostrava-Hema | 13
CZ-Plzen-Plzen-Hema | 6
CZ-Prague 2-Praze-Hema | 4
DK-Aalborg-Sygehus-Hema | 9
DK-Aarhus C-Aarhus UH-Hema | 17
DK-Copenhagen-Rigshosp-Hema | 11
DK-Herlev-Herlev-Hema | 8
DK-Odense-Odense Hospital-Hema | 3
DK-Roskilde-Sygenhus-Hema | 6
GR-Athens-Alexandra-IntMed | 37
IS-Reykjavik-Landspitali-Hema | 2
IT-Alessa-Antonio e Biagio-Ema | 8
IT-Ancona-Umberto I-Ema | 18
IT-Ascoli Piceno-Mazzoni-Ema | 1
IT-Avellino-San G Moscati-Ema | 10
IT-Bari-Policlinico-Onco | 10
IT-Bergamo-Riuniti-Ema | 24
IT-Bologna-Malphigi-Ema Onco | 44
IT-Bolzano-AS Bolzano-Ema | 7
IT-Brescia-Civili-Ema | 21
IT-Brindisi-P O A Perino-Ema | 2
IT-Cagliari-P O Binagli-Ema | 8
IT-Candiolo-IRCC-Ema | 6
IT-Catania-Ferrarotto-Ema | 32
IT-Civitanova -AZUR Zona 8-Med | 1
IT-Cosenza CS-Annunziata-Ema | 10
IT-Cuneo-Croce e Carle-Ema | 19
IT-Foggia-Riuniti-Ema | 4
IT-Gallara-Antonio Abate-Oncoe | 1
IT-Genova-Martino-ClinEma | 7
IT-Genova-Martino-EmaI | 14
IT-Genova-Martino-UOEmaII | 8
IT-Latina-UH Polo Pontino-Ema | 3
IT-Lecco-Manzoni-Onco | 3
IT-Meldola-ISR-Onco | 7
IT-Messina-PU s Martino-Ema | 7
IT-Mestre-Osp dell'Angelo-Ema | 16
IT-Milano-IRCCS / Ema | 23
IT-Milano-Niguarda-Ema | 11
IT-Modena-Policlinico-Ema | 8

IT-Napoli-Cardarelli-EmaMidOss | 3
IT-Napoli-Federico-Ema | 4
IT-Nuoro-San Francesco-Ema | 11
IT-Padova-UDS-Ema | 17
IT-Palermo-Paolo Giaccone-Ema | 5
IT-Pavia-Maugeri-Ema | 5
IT-Perugia-St Maria-Ema | 18
IT-Pesaro-San Salvatore-Ema | 1
IT-Pescara-S Spirito-Ema | 14
IT-Ravenna-St Maria-Ema | 9
IT-Reggio Cala-Bianchi Morelli- | 19
IT-Reggio Em-S Maria Nuova-Ema | 22
IT-Rimini-Infermi-OncoEma | 6
IT-Rionero in Vultur-IRCCS-Ema | 7
IT-Roma-Regina Elina-Ema | 6
IT-Roma-S Eugenio-Ema | 12
IT-Roma-S Giovanni-Ema | 5
IT-Roma-San Camillo-Ema | 10
IT-Roma-Sant'Andrea-Ema | 2
IT-Roma-Sapienza-Ema | 49
IT-Roma-UC-Ema | 4
IT-Rozzano,Milan-Humanitas-Ema | 9
IT-Siena-Sclavo-Ema | 3
IT-Terni-S Maria-Onco | 17
IT-Torin-Molinette Bramant-Ema | 16
IT-Torino-Mauriziano | 67
IT-Tricase (Lecce)-Panico-Ema | 4
IT-Trieste-Maggiore-Ema | 8
IT-Udine-PU-Ema | 29
LU-Luxembourg-CHL-Hema | 1
NL-Alkmaar-MCAlkmaar-Hema | 7
NL-Amersfoort-Meander-IntGen | 6
NL-Amstelveen-Amstelland-InwGen | 1
NL-Amsterdam-AMC-Hema | 7
NL-Amsterdam-Lucas-InwGen | 5
NL-Amsterdam-OLVG-Hema | 8
NL-Amsterdam-VUMC-Hema | 15
NL-Apeldoorn-Gelre-IntGen | 2
NL-Arnhem-Rijnstate-InwGen | 7
NL-Bergen op Zoom-Lievensberg-I | 1
NL-Beverwijk-RKZ-IntGen | 1
NL-Breda-Amphia, Langend-IntGe | 13
NL-Capelle a/-IJsselland-IntGe | 5
NL-Delft-RdeGraaf-IntGen | 5
NL-Den Bosc-Jeroen Bosch-IntGe | 4
NL-Den Haag-Leyenburg-Hema | 18
NL-Deventer-Deventer ZH-InwGen | 7
NL-Dordr-Schweitzer Dord-IntGe | 15
NL-Drachten-Smellinghe-IntGen | 1
NL-Ede-Gelderse Vallei-IntGen | 6
NL-Eindhoven-Maxima MC-Hema | 4
NL-Enschede-MS Twente-IntGen | 8
NL-Geldrop-Anna-IntGen | 1
NL-Goes-De Ruyter-InwGen | 9
NL-Gorinchem-Beatrix-InwGen | 2
NL-Gouda-Groene Hart-IntGen | 4
NL-Groningen-UMCG-Hema | 6
NL-Haarlem-Kennemer-IntGen | 1
NL-Heerlen-Atrium-IntGen | 6
NL-Helmond-Elkerliek-IntGen | 3
NL-Hilversum-Tergooi-IntGen | 4
NL-Hoofddorp-Spaarne-IntMed | 6
NL-Hoorn-Westfriesgasthuis-IntG | 9
NL-Leiden-LUMC-Hema | 12

NL-Maastricht-AZM-IntGen | 15
NL-Nieuwegein-Antonius Ng-IntGe | 8
NL-Nijmegen-Canisius-InwGen | 11
NL-Nijmegen-Radboud-Hema | 18
NL-Oss-Bernhoven-InwGen | 4
NL-Roermond-Laurentius-InwGen | 3
NL-Roosendaal-Franciscus-IntGe | 4
NL-Rotterdam-EMC Centrum-Hema | 14
NL-Rotterdam-Franciscus-IntGen | 5
NL-Rotterdam-Ikazia-InwGen | 3
NL-Rotterdam-Maasstad-IntGen | 9
NL-Schiedam-Vlietland-IntGen | 6
NL-Tilburg-Elisabeth-IntGen | 11
NL-Utrecht-UMCU-Hema | 9
NL-Venlo-VieCuri-InwGen | 3
NL-Vlissingen-De Ruyter-InwGen | 3
NL-Winterswijk-Beatrix-IntGen | 6
NL-Zaandam-ZaansMC-IntGen | 3
NL-Zwolle-Isala Sophia-IntGen | 11
NO-Alesund-Helse Sunnmore-Hema | 3
NO-Forde-Hosp-Hema | 3
NO-Oslo-Rikshosp-Hema | 6
NO-Rud-Baerum Hospital-IntMed | 5
NO-Stavanger-UH Rogaland-Hema | 3
NO-Tromsø-UH North-Hema | 4
NO-Trondheim-Olav-Hema | 5
PT-Lisboa-Inst Onco-Hema | 5
SE-Boras-Boras-Hema | 3
SE-Falun-Falu-IntMed | 1
SE-Goteborg-Sahlgrenska-Hema | 11
SE-Linköping-UH-Hema | 3
SE-Luleå-Sunderby-Intmed | 4
SE-Lund-Skane-Hema | 22
SE-Örebro-Örebro UH-Hema | 1
SE-Uddevalla-NU-IntMed | 4
SE-Umeå-UH North-Hema | 3
SE-Vaxjo-Vaxjo-IntMed | 1
TR-Adana-Baskent UH-Hema | 5
TR-Ankara-Cebeci-Hema | 41
TR-Ankara-Gazi UH-Hema | 12
TR-Kayseri-Erciyes-Hema | 2

Registration criteria
The following information will be requested:

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

4. Participating parties

Principal Investigator(s)
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