End of Trial Report

Sponsor:	HOVON foundation
Trial:	HOVON 114 MM / EMN11
EudraCT:	2013-003265-34
Title of study:	Pomalidomide combined with Carfilzomib and Dexamethasone (PCd) for induction and consolidation followed by Pomalidomide combined with Dexamethason vs Pomalidomide maintenance for patients with Multiple Myeloma in progression after prior 1st line treatment with Lenalidomide and Bortezomib.
Report date:	18-DEC-2024

Signature	
Name:	P. Sonneveld
Function:	Principal Investigator
Date:	20-Dec-24
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Investigational sites & investigators

Country	City	Site Name	Last Name
Austria	Linz	AT-Linz-ORDENSKLINIKUM	Machherndl-Spandl
Austria	Vienna	AT-Vienna-WILHELMINEN	Zojer
Belgium	Antwerpen	BE-Antwerpen-ZNA-CADIX	Wu
Belgium	Haine-Saint-Paul	BE-Haine-Saint-Paul-JOLIMONT	Delrieu
Belgium	Turnhout	BE-Turnhout-AZSTELISABETH	Vrelust
Czech	Brno	CZ-Brno-UHBRNO	Pour
Czech	Hradec Kralove	CZ-Hradec Kralove-FNHK	Maisnar
Czech	Olomouc	CZ-Olomouc-FNOL	Minarík
Czech	Ostrava-Poruba	CZ-Ostrava-Poruba-FNO	Hajek
Czech	Plzen	CZ-Plzen-FNPLZEN	Jungová
Greece	Athens	GR-Athens-ALEXANDRA	Dimopoulos
Italy	Bologna	IT-Bologna-MALPHIGI	Cavo
Italy	Milano	IT-Milano-ISTITUTOTUMORI	Corradini
Italy	Roma	IT-Roma-SAPIENZA	Martelli
Italy	Torino	IT-Torino-MOLINETTEG	Larocca
Italy	Udine	IT-Udine-POLICLINCOUDINE	Patriarca
Netherlands	Amsterdam	NL-Amsterdam-AMC	Kersten
Netherlands	Amsterdam	NL-Amsterdam-VUMC	Zweegman
Netherlands	Breda	NL-Breda-AMPHIA	Klift, van der
Netherlands	Delft	NL-Delft-RDGG	Soechit
Netherlands	Den Haag	NL-Den Haag-HAGA	Ypma
Netherlands	Dordrecht	NL-Dordrecht-ASZ	Levin
Netherlands	Enschede	NL-Enschede-MST	Rooijen, van
Netherlands	Maastricht	NL-Maastricht-MUMC	Bos
Netherlands	Nieuwegein	NL-Nieuwegein-ANTONIUS	Weerdt, de
Netherlands	Nijmegen	NL-Nijmegen-RADBOUDUMC	Croockewit
Netherlands	Rotterdam	NL-Rotterdam-EMCDANIEL	Sonneveld
Netherlands	Rotterdam	NL-Rotterdam-MAASSTADZIEKENHUIS	Sandberg
Netherlands	Tilburg	NL-Tilburg-ETZ	Droogendijk
Netherlands	Utrecht	NL-Utrecht-UMCUTRECHT	Minnema
Netherlands	Zwolle	NL-Zwolle-ISALA	Kneppers
Turkey	Ankara	TR-Ankara-CEBECIHASTANESI	Beksac

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Publications

Pieter Sonneveld, Sonja Zweegman, Michele Cavo, Kazem Nasserinejad, Annemiek Broijl, Rosella Troia, Ludek Pour, Sandra Croockewit, Paolo Corradini, Francesca Patriarca, Kalung Wu, Jolanda Droogendijk, Gerard Bos, Roman Hajek, Maria Teresa Petrucci, Paula Ypma, Nicholas Zojer, Monique C. Minnema, Mario Boccadoro; *Carfilzomib, Pomalidomide, and Dexamethasone As Second-line Therapy for Lenalidomide-refractory Multiple Myeloma;* Hemasphere. 2022; 6(10): e786

Studied period

21-AUG-2015 till 25-AUG-2024

Phase of development

Phase 2

Objectives

Primary objectives

- Evaluate the efficacy defined as PFS of pomalidomide maintenance plus dexamethasone versus pomalidomide maintenance in patients who responded (≥ PR) to the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation.
- Evaluate efficacy of the combination of pomalidomide (POM), carfilzomib (CAR) and low dose dexamethasone (LD-DEX) for induction and consolidation in subjects with relapsed or refractory multiple myeloma (MM) after prior first-line treatment in the EMN02/HO95 trial who are refractory to Lenalidomide and/or Bortezomib. This objective will be investigated in patients who have or have not received a prior autologous transplant.

Secondary objectives

- Evaluate the response rate (after 8 cycles of PCd) before the start of maintenance.
- Evaluate the safety and tolerability of the combination of pomalidomide, carfilzomib and low dose dexamethasone in subjects with relapsed or refractory multiple myeloma.

Exploratory

- Evaluation of biomarkers, including baseline markers predictive of response to pomalidomide combined with carfilzomib and dexamethasone.
- Evaluate the quality of life

Evaluate the gene expression profiles and SNPs in relation to the treatment outcomes and side-effects

Methodology

The primary endpoint for this trial is PFS from randomization.
There are no data yet on PFS after 8 cycles of carfilzomib + pomalidomide + dexamethasone re-induction plus consolidation chemotherapy. However, in the phase I/II pomalidomide-dexamethasone trial, median PFS was 6.3 months. In a trial with patients refractory to bortezomib and lenalidomide the response to pomalidomide plus dexamethasone was 25 %

and median OS 17 months. In a comparable group of patients treated with carfilzomib/dexamethasone median PFS after randomization was 8 months

Median PFS for lenalidomide maintenance in the IFM trial after HDM/AutoSCT was 42 months. Based on these data it is expected that the relapse rate in EMN02 will be 100/yr starting 2013 increasing to 150 yr starting 2014

For the current sample size calculation the following assumptions have been made:

- uniform accrual for 24 months;
- additional follow up of 24 months after the last patient has been randomized;
- two-sided significance level $\alpha = 0.05$;
- power $1 - \beta = 0.80$;
- median PFS in the pomalidomide maintenance arm = 9 months;
- median PFS in the pomalidomide maintenance plus dexamethasone arm = 15 months, which corresponds to a HR = 0.60

This results in a total number of patients to be randomized of 146 (= 73 per arm), and the final analysis will be performed when 126 events have been reported.

If we assume that 66% (based on the 34% discontinuation rate in the VISTA trial) of the patients will be randomized, then 146/0.66 = 222 patients have to be registered (= 9-10 per month).

This maximum number of 222 patients enable to estimate the response rate after 8 cycles Pom-Car-Dex with a standard error of about 3% in the whole group, and in the subgroups of transplanted (within EMN02/HO95 trial) and non-transplanted patients, the standard error will be about 5%.

Number of patients

Planned: 222

Enrolled: 112

Analyzed: 111

Enrolled but not analyzed, including reason:

Not eligible 1

Not evaluable for primary endpoint 25 went Off Protocol before randomization

Diagnosis and main criteria for inclusion

Report disease under study: Multiple Myeloma

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Diagnosis

Patients with symptomatic Multiple Myeloma who have a first progression on or after treatment in the EMN02/HO95 trial or who are refractory to lenalidomide and/or bortezomib.

Inclusion criteria from protocol

• Included in EMN02/HO95 trial. Induction therapy followed by autologous stem cell transplant (AutoSCT) and consolidation/ maintenance will be considered as one regimen.

• The subject must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures.

• Age ≥ 18 years at the time of signing the informed consent form.

• Able to adhere to the study visit schedule and other protocol requirements.

• Documented diagnosis of multiple myeloma and 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).

• Documented progression or refractory multiple myeloma as per the IMWG uniform response criteria (Durie, 2006) during or after the EMN02/HO95 trial. Normal renal function with a Creatinine Clearance > 45mL/min according to the Modification of Diet in Renal Disease (MDRD) equation for estimation of Glomerular Filtration Rate (GFR)

• WHO performance status score of 0, 1 or 2.

• Patients must be willing and capable to use adequate contraception during the therapy (all men, all pre-menopausal women).

• Patients must be able to adhere to the requirements of the Pregnancy Prevention Risk Management Plan.

• Patients must be eligible for autologous stem cell transplantation when not previously given in first line treatment.

• All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment.

• All subjects must agree not to share medication.

Exclusion criteria from protocol

• Patient received more than 1 regimen (EMN02/HO95), except local radiotherapy.

• Absolute neutrophil count (ANC) <1.0 x 10^9/L, unless related to MM.

• Platelet count < 75 x 10^9/L, unless related to MM.

• Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L).

• Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted).

• Significant hepatic dysfunction (Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN) or serum total bilirubin > 3.0 x ULN)

• Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:

- Basal or squamous cell carcinoma of the skin.
- Carcinoma in situ of the cervix or breast.
- Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).

• Previous therapy with pomalidomide or carfilzomib.

• Hypersensitivity to thalidomide, lenalidomide, bortezomib or dexamethasone (this includes ≥ Grade 3 rash during prior thalidomide or lenalidomide or bortezomib therapy).

• Peripheral neuropathy ≥ Grade 2.

• Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment.

• LVEF ≤ 40%.

• QTc > 450 msec.

• History of torsade de pointes.

• History of ventricular tachycardia, ventricular fibrillation.

• Uncontrolled atrial fibrillation/flatter.

• Congestive heart failure (NY Heart Association Class III or IV).

• Myocardial infarction within 12 months prior to starting study treatment

• Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris.

• History of pulmonary hypertension.

• Uncontrolled infection.

• Subjects who received any of the following within the last 14 days of initiation of study treatment:

- Major surgery (kyphoplasty is not considered major surgery).
- Use of any anti-myeloma drug therapy.

• Use of any investigational agents (with the exception of lenalidomide) within 28 days or five half-lives (whichever is longer) of treatment.

• Incidence of gastrointestinal disease that may significantly alter the absorption of pomalidomide.

• Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.

• Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the informed consent form.

• Pregnant or breastfeeding females.

• Known human immunodeficiency virus (HIV) positivity, active infectious hepatitis A, B or C or chronic hepatitis B or C.

• Pre-existing pulmonary, cardiac or renal impairment that prevents hydration measures.

• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Investigational Medicinal Product(s), dose and mode of administration

Induction treatment

Intervention: Drug: 4 cycles Pomalidomide, Carfilzomib, Dexamethasone (PCd)

Pomalidomide:	4 mg	p.o.	days 1-21
Carfilzomib:	20/36 mg/m²	i.v.	days 1,2,8,9,15,16
Dexamethasone:	20 mg	p.o.	days 1,2,8,9,15,16

<High-dose Melphalan and auto SCT>

Consolidation treatment

Intervention: Drug:	4 cycles Pomalidomide, Carfilzomib, Dexamethasone (PCd)		
Pomalidomide:	4 mg	p.o.	days 1-21
Carfilzomib:	36 mg/m²	i.v.	days 1,2,8,9,15,16
Dexamethasone:	20 mg	p.o.	days 1,2,8,9,15,16

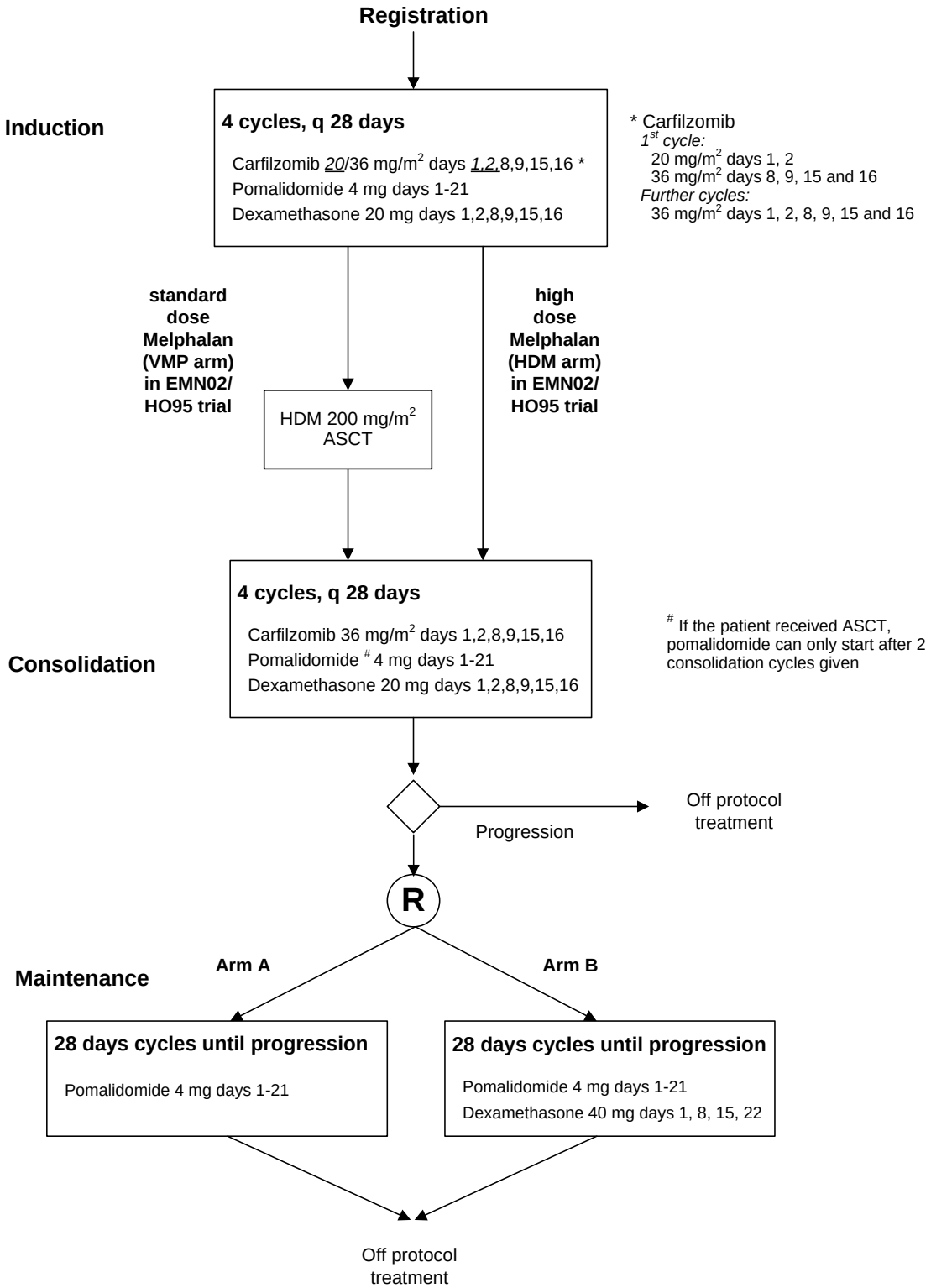
Arm A

Maintenance: Drug:	Pomalidomide		
Pomalidomide:	4 mg	p.o.	days 1-21

Arm B

Maintenance: Drug:	Pomalidomide		
Pomalidomide:	4 mg	p.o.	days 1-21
Dexamethasone:	40 mg	p.o.	days 1,8,15,22

Patients with MM in first relapse/progression after first line treatment in the EMN02/HO95 trial and who are refractory to Lenalidomide and/or Bortezomib.



Duration of treatment

Expected durations of therapies:

- Induction therapy 4 months
- Transplantation and recovery 2 – 4 months (if applicable)
- Consolidation therapy 4 months
- Maintenance therapy with pomalidomide or pomalidomide plus dexamethasone until disease progression.
- All patients will be followed until a maximum of 8 years after registration.

Comparator(s), dose and mode of administration

Please be referred to the diagram on the former page for dosing and mode of administration.

- Comparison of pomalidomide with pomalidomide plus dexamethasone

Criteria for evaluation - Efficacy

Primary endpoints:

- Progression free survival (PFS) from randomization, defined as time from randomization to progression or death from any cause which ever occur first. Patient still alive at the date of last contact will be censored.
- Response rate (sCR, CR, VGPR, PR) after induction and consolidation treatment

Secondary endpoints:

- Response rate after 8 cycles of PCD before start of maintenance
- Toxicity
- Improvement of response during/after maintenance
- Progression free survival calculated registration
- Overall survival calculated from time of registration or from start of maintenance treatment, until death from any cause. Patients still alive at the date of last contact will be censored.
- Quality of life as defined by the EORTC QLQ-C30 and QLQ-MY20.

Criteria for evaluation - Safety

One interim analysis is planned, primarily to describe adverse events observed during the carfilzomib + pomalidomide + dexamethasone re-induction chemotherapy. This will be done when data of the first 20 patients completing the 4 cycles of induction therapy are available. The accrual will not be discontinued while waiting for these data. Results of the interim analysis will be presented to the principal investigators and to an independent data and safety monitoring board (DSMB). 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.

Statistical methods

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

Efficacy analyses

The main endpoint efficacy analysis will be on PFS from randomization. The PFS will be formally compared between the two randomization arms based on hazard ratio (with 95% confidence interval) estimated applying a multivariate Cox regression analysis with adjustment for stratification factors.

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.

Other efficacy endpoints include response rates and overall survival rate. The response rates along with the 95% confidence intervals will be estimated. Cox regression, will be used to estimate and compare the hazard rates between the arms.

In case the accrual will be 24 months, randomization will take place 9 months after registration of a patient, and if 24 months of follow up after the last patient is required, then the final analysis may be performed after 24 + 9 + 24 = 57 months after start of the trial, if the complete data including 126 events are available.

Toxicity analyses

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.

Additional analyses

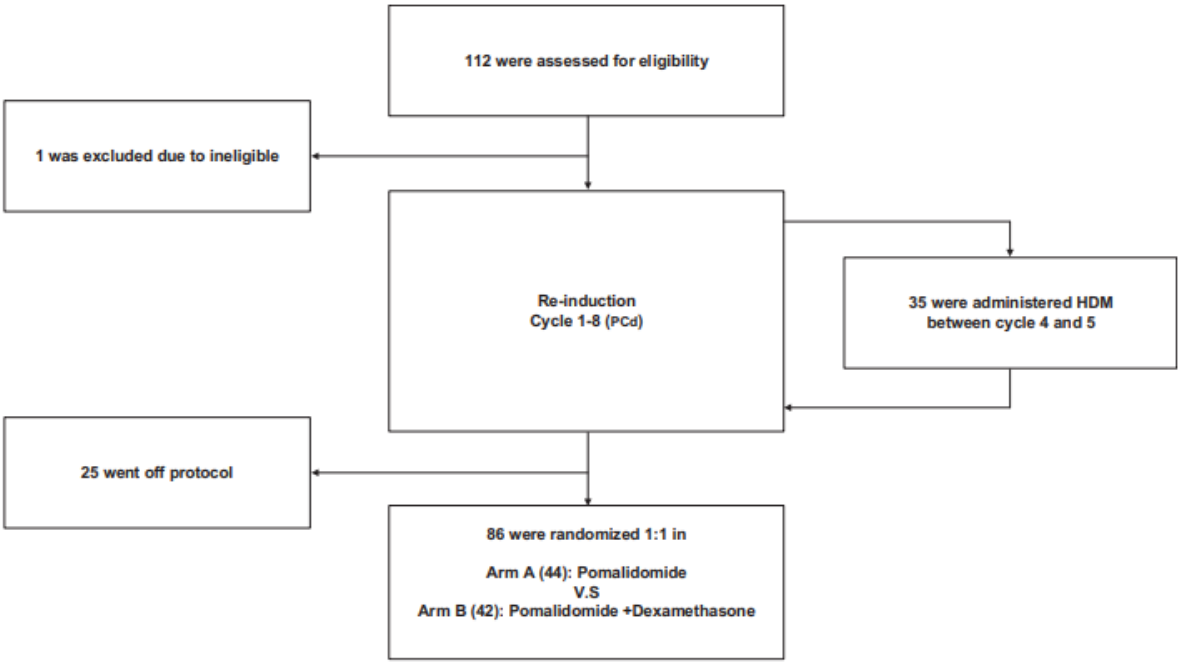
Additional analyses may involve the analysis of prognostic factors, e.g. ISS stage, FISH analysis, molecular analysis, with respect to PFS, response rate and OS. Logistic and Cox regression could be used for this purpose. To include all patients in (multivariate) analyses, a multiple imputation algorithm 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.

Quality of Life assessments

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 and consolidation chemotherapy and during the maintenance treatments. 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.

Summary of efficacy results

Randomization consort diagram:



Due to the completion of EMN02 and the observed decreasing accrual, this trial was closed for inclusion after 112 registered patients. One ineligible patient was excluded from all analyses. 86 patients (77%) completed 8 cycles of KPd. Forty-one of 43 patients randomized to the VMP arm in EMN02 were eligible for HDM/ASCT and 35 of these (85%) received their first HDM plus ASCT after 4 cycles of KPd using cryopreserved stem cells previously collected. The median time to discontinuation of pomalidomide w/o dexamethasone was 17 months.

Best response was 37% ≥ complete response, 75% ≥ very good partial response, 92% ≥ partial response, respectively. At a median follow-up of 40 months median PFS was 26 and 32 months for patients who received KPd plus HDM/ASCT and 17 months for patients on KPd (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.37-1.00, P = 0.051). PFS was better after longer duration of prior lenalidomide (HR 3.56, 95% CI 1.42-8.96, P = 0.035). PFS from randomization was 27 months with pomalidomide plus dexamethasone versus 18 months with pomalidomide monotherapy, respectively (HR 0.68, 95% CI 0.41-1.13, P = 0.14). Median overall survival (OS) was 67 months.

Summary of safety results

KPd-emerging grade 3 and 4 adverse events included hematologic (41%), cardiovascular (6%), respiratory (3%), infections (17%), and neuropathy (2%). KPd followed by continuous pomalidomide is an effective and safe triple drug regimen in second-line for patients previously exposed to bortezomib and/or refractory to lenalidomide.

Conclusions

This phase 2 trial demonstrates that KPd followed by continuous pomalidomide is an effective and safe triple drug regimen in second-line for patients who have been previously treated and are refractory to lenalidomide. A 92% overall response and 18–27 months PFS is clinically relevant in this population, especially when other novel treatments are not available. HDM followed by ASCT is feasible and effective in eligible patients in the context of this regimen.