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Treatment of primary plasma cell leukaemia with carfilzomib and lenalidomide-based therapy (EMN12/HOVON-129): final analysis of a non-randomised, multicentre, phase 2 study

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

van de Donk NWCJ, M.M. (2023). Treatment of primary plasma cell leukaemia with carfilzomib and lenalidomide-based therapy (EMN12/HOVON-129): final analysis of a non-randomised, multicentre, phase 2 study. THE LANCET ONCOLOGY, 24(10), 1119-1133 [10.1016/s1470-2045(23)00405-9].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/956256> since: 2024-02-08

*Published:*

DOI: [http://doi.org/10.1016/s1470-2045\(23\)00405-9](http://doi.org/10.1016/s1470-2045(23)00405-9)

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# **Treatment of primary plasma cell leukemia with carfilzomib and lenalidomide-based therapy: results of the final analysis of the prospective phase 2 EMN12/HOVON-129 study**

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Text word count:

Abstract word count:

Number of figures:

Number of tables:

Number of supplementary figures:

Number of supplementary tables:

Number of references:

## Abstract

### Background

Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell disorder with a very poor prognosis. The aim of the EMN12/ HOVON-129 study was to improve the outcome of pPCL by incorporating carfilzomib and lenalidomide in induction, consolidation, and maintenance therapy.

**Methods.** The EMN12/HOVON-129 study is a prospective, non-randomized, phase 2, multicenter study, for previously untreated pPCL patients aged 18 years or older. Inclusion criteria were newly diagnosed pPCL (defined as  $>2 \times 10^9/L$  circulating monoclonal plasma cells or plasmacytosis  $>20\%$  of the differential white cell count) and WHO performance status 0-3. Main exclusion criteria were severe cardiac or pulmonary dysfunction; and creatinine clearance of  $<15$  ml/min. There were no restrictions based on blood counts.

Patients aged 18-65 years were treated with four cycles of carfilzomib-lenalidomide-dexamethasone (KRd). KRd induction was followed by tandem autologous stem cell transplantation (auto-SCT), 4 cycles of KRd consolidation, and then maintenance with carfilzomib and lenalidomide until progression. Patients who were eligible for allo-SCT, could also receive one auto-SCT, followed by 2 KRd consolidation cycles, reduced-intensity conditioning allo-SCT, and carfilzomib/lenalidomide maintenance. Elderly patients aged 66 years or older received 8 cycles of KRd induction followed by maintenance therapy with carfilzomib and lenalidomide until progression. The primary endpoint was PFS.

**Findings.** Between October 2015 and August 2021, 61 patients were enrolled and received KRd induction treatment (36 patients aged 18-65 years, and 25 aged  $\geq 66$  years). Patients had a high tumor burden with high rate of high-risk features (elevated LDH and high-risk cytogenetic abnormalities; more frequent in younger patients). With a median follow-up of 43.5 months (IQR 27.7-67.8), the median PFS was 15.5 months for younger patients. For elderly patients median follow-up was 32.0 months (IQR 24.7-34.6), and median PFS was 13.8 months. Best response on protocol was  $\geq$ PR in 86%,  $\geq$ VGPR in 83% and  $\geq$ CR in 50% for younger patients, and  $\geq$ PR in 80%,  $\geq$ VGPR in 68% and  $\geq$ CR in 36% for elderly patients.

Toxicity was most frequently observed directly after treatment initiation with infections (6% and 32% for younger and elderly patients, respectively) and respiratory events (6% and 16%) being the most common grade  $\geq 3$  adverse events during the first four KRd cycles.

**Interpretation.** Carfilzomib and lenalidomide-based therapy provides efficient and rapid disease control. This translated into an improved PFS and, at least in the setting of elderly patients, also in OS, compared to previously published data. However, results remain inferior in pPCL, compared to MM, highlighting the design of new studies incorporating novel immunotherapies.

**Funding.** BMS and AMGEN

**Statement of prior presentation:** Data were presented as an oral presentation at the 61rd annual meeting of the American Society of Hematology, Orlando, December 2019; as a poster presentation at the 64<sup>th</sup> annual meeting of the American Society of Hematology, New Orleans, December 2022; and as oral presentation during the 4<sup>th</sup> European Myeloma Network meeting, Amsterdam, Netherlands

## **Research in context**

### **Evidence before this study**

We searched PubMed for published clinical trials from database inception until May 1, 2023 using the search terms “primary plasma cell leukemia” OR “plasma cell leukemia”. The search was restricted to clinical trials with no language restrictions. We found two phase 2 studies for patients with newly diagnosed pPCL, which is a rare and aggressive plasma cell dyscrasia. The regimen of lenalidomide and dexamethasone was investigated in the first prospective phase 2 trial, which enrolled 23 patients with newly diagnosed pPCL. This study showed anti-tumour activity of lenalidomide and dexamethasone in both younger and elderly patients, with superior results in those undergoing autologous stem cell transplantation. The second phase 2 study for patients with newly diagnosed pPCL between 18 and 70 years of age assessed the efficacy of an induction regimen that combines bortezomib with standard chemotherapy and dexamethasone, followed by high-dose melphalan (HDM) and autologous stem cell transplantation (auto-SCT) and then either allogeneic stem cell transplantation or bortezomib/lenalidomide maintenance. This study, which enrolled 40 patients, showed high a response rate and improved PFS, compared to what was observed in retrospective series. The combination of a proteasome inhibitor and immunomodulatory drug has improved survival in newly diagnosed MM patients, with the triplet of carfilzomib-lenalidomide-dexamethasone (KRd) also showing promising results in patients with high-risk cytogenetic abnormalities. Information on this combination in pPCL is lacking.

### **Added value of this study**

To the best of our knowledge, this study is the first phase 2 trial to report the activity and safety of carfilzomib and lenalidomide-based treatment for patients with newly diagnosed pPCL aged 18 years and older (n=61). After induction, younger patients (18-65 years) also received HDM/auto-SCT, followed by reduced-intensity conditioning allogeneic stem cell transplantation or a second HDM/auto-SCT and then maintenance with carfilzomib and lenalidomide. Our results show that this combination is effective and feasible in a significant proportion of patients with pPCL with the best response rate after induction reported up till now. These data confirm the superiority of a IMiD/PI-based combination regimen, compared

to PI plus chemotherapy. This translated into an improved PFS and, at least in the setting of elderly patients, also in OS, compared to previously published data. Toxicity related to carfilzomib and lenalidomide was more common in the cohort of elderly patients, but adverse events were generally manageable.

### **Implications of all the available evidence**

Our results combined with existing evidence support the use of carfilzomib-lenalidomide-dexamethasone to rapidly reduce tumor load in patients with pPCL in order to prevent disease- and treatment-related complications. However, despite moderate progress, the prognosis of pPCL remains unsatisfactory. New trials are warranted to investigate novel drugs such as CD38 antibodies and T-cell immunotherapies (CAR T-cell therapy and bispecific antibodies).

## Introduction

Primary plasma cell leukemia (pPCL) is the most aggressive plasma cell malignancy with a very poor prognosis and high rate of early mortality due to disease-related and therapy-related complications, accounting for approximately 1-2% of patients with multiple myeloma (MM)<sup>1-9</sup>. Compared to MM, pPCL has a distinct clinical presentation with higher tumor burden, increased rate of renal failure and hypercalcemia, lower hemoglobin and platelet levels but with a lower incidence of bone lesions<sup>5,7,8,10-13</sup>. In addition, the prevalence of poor-risk characteristics, including high-risk cytogenetic abnormalities, elevated LDH and beta2-microglobulin, and extramedullary plasmacytomas is higher in pPCL, compared with newly diagnosed multiple myeloma<sup>3,5-8,11,13,14</sup>.

With conventional chemotherapy the median overall survival (OS) of pPCL patients was only 4-6 months<sup>2,6,15</sup>. Retrospective single-center and multicenter studies, as well as 2 prospective clinical trials have demonstrated that median OS has modestly improved to approximately 12-18 months with the incorporation of novel agents (lenalidomide and bortezomib) in first-line therapy<sup>3,5,13,16-22</sup>. High-dose melphalan followed by autologous stem cell transplantation (auto-SCT), or allogeneic stem cell transplantation (allo-SCT) may also improve prognosis in younger patients<sup>13,17,23,24</sup>. Furthermore, in two retrospective analyses, a trend towards improved OS was observed in patients, who received tandem auto-SCT, compared with those who received a single auto-SCT<sup>17,24</sup>. However, survival in pPCL remains unsatisfactory.

We here report the final results from the prospective phase 2 EMN12/HOVON-129 study for patients with newly diagnosed pPCL. Patients were assigned to one of two different treatment regimens based on age (younger patients, aged 18-65 years; elderly patients, 66 years and older). In this study all patients received induction treatment with the fast-acting carfilzomib-lenalidomide-dexamethasone (KRd) triplet regimen to rapidly control clinical manifestations and to prevent early death, because of irreversible disease complications, based on high efficacy in newly diagnosed MM patients, especially those with high-risk cytogenetic abnormalities, with negligible neurological toxicity<sup>25-28</sup>. Elderly patients received 8 KRd induction cycles, followed by carfilzomib/lenalidomide maintenance. Younger patients received 4 KRd induction cycles, followed by the tandem of auto-SCT and reduced-intensity



allo-SCT, or alternatively double auto-SCT. Remission-induction and transplant were followed by KRd consolidation and maintenance treatment consisting of both carfilzomib and lenalidomide.

## **Patients and methods**

### ***Study design and patients***

This non-randomized phase 2, prospective, multicenter, intergroup study enrolled patients with previously untreated, symptomatic pPCL at 19 academic centers and hospitals in 7 European countries (The Netherlands, Denmark, Norway, Belgium, Czech Republic, Italy, and United Kingdom). Patients between 18-65 years of age (younger patients) and  $\geq 66$  years (elderly patients) were treated in two different age-specific cohorts and were analyzed separately.

Newly diagnosed pPCL patients aged 18 years or older were eligible for participation if they had measurable disease (defined by the presence of serum M-protein  $\geq 5$  g/L, or urine M-protein  $\geq 500$  mg/24 hours, or abnormal free-light chain (FLC) ratio with involved FLC  $\geq 100$  mg/L), and if they had WHO-performance status 0-3 (WHO-3 only allowed when caused by pPCL and not by comorbid conditions).

Key exclusion criteria were central nervous system involvement by pPCL with disease refractory to intrathecal therapy; active malignancy other than pPCL requiring treatment; active, uncontrolled infections; severe neurological or psychiatric disease; severe cardiac dysfunction (NYHA classification II-IV) or myocardial infarction within 6 months, unstable angina pectoris, and cardiac arrhythmias, which are not controlled by conventional treatment (including medications and cardiac devices); severe pulmonary dysfunction; significant hepatic dysfunction (serum bilirubin or transaminases  $\geq 3.0$  times upper limit of normal, unless related to pPCL); eGFR  $< 15$  ml/min; previous treatment, except focal radiation to control local tumor progression, corticosteroids (maximum 7 days for symptom control or stabilization), or intrathecal therapy in case of CNS involvement.

Younger patients for whom an adequate number of stem cells ( $\geq 2 \times 10^6$  CD34<sup>+</sup> cells/kg [or according to national guidelines]) were collected were eligible to undergo auto-SCT, in case of WHO performance 0-2, bilirubin and transaminases  $< 3$  times the upper limit of normal, absence of severe pulmonary, neurologic, cardiac, or psychiatric disease, as well as absence of progressive disease. Eligibility criteria for allo-SCT included the availability of an HLA-identical sibling or unrelated donor (at least 9/10 allele-matched donor) and WHO-performance 0-2. Key exclusion criteria were response of less than PR, progressive disease,

CNS involvement, as well as presence of active/uncontrolled infections, severe neurological and psychiatric disease, severe cardiac (NYHA classification II-IV) or pulmonary dysfunction, or significant hepatic dysfunction (serum bilirubin or transaminases  $\geq 3.0$  times upper limit of normal), and GFR  $< 30$  ml/min.

All patients gave written informed consent before inclusion. The study was approved by independent ethics or institutional review boards at each site, and was undertaken according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines on Good Clinical Practice. This trial was registered at [www.trialregister.nl](http://www.trialregister.nl) (until June 2022) and <https://trialssearch.who.int/> as NTR5350.

## ***Procedures***

### ***Treatment plan for younger patients***

Patients received 4 cycles of KRd (carfilzomib on days 1, 2, 8, 9, 15, and 16 [starting dose, 20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1; target dose, 36 mg/m<sup>2</sup> thereafter]; lenalidomide 25 mg on days 1-21; and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23). Patients then underwent cyclophosphamide/G-CSF mobilized PBSC collection and standard auto-SCT with melphalan at 200 mg/m<sup>2</sup>. This was followed by 2 courses of KRd consolidation treatment and reduced-intensity conditioning (RIC) allo-SCT for patients with an HLA-identical sibling or a suitable unrelated donor (at least 9/10 allele-matched donor). Two months after the allo-SCT carfilzomib maintenance was initiated. Eight months after allo-SCT low-dose lenalidomide was added to carfilzomib. Maintenance was given until progression or undue toxicity. In case no donor could be identified, in case of ineligibility for allo-SCT, or if patient did not want to undergo allo-SCT, a second course of high dose melphalan was administered between 2 and 3 months after the first course if the patient achieved at least PR. This was followed by 4 cycles of KRd consolidation, and subsequent carfilzomib-lenalidomide maintenance. See the supplemental methods for details on induction treatment, stem cell mobilization, transplantation, consolidation, and maintenance.

### Treatment plan for elderly patients

Patients received 8 cycles of KRd induction (carfilzomib on days 1, 2, 8, 9, 15, and 16 [starting dose, 20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1; target dose, 36 mg/m<sup>2</sup> thereafter]; lenalidomide 25 mg on days 1-21; dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23) and subsequently carfilzomib plus lenalidomide maintenance until progression or undue toxicity. During maintenance carfilzomib was administered at a dose 27 mg/m<sup>2</sup> on days 1, 2, 15, and 16 for the first 12 28-day cycles, and then 56 mg/m<sup>2</sup> on days 1 and 15. Lenalidomide was started at cycle 1 at a dose of 10 mg on days 1-21 of a 28-day cycle.

### *Investigations*

At inclusion, laboratory tests (blood cell count, creatinine, calcium, LDH, beta-2 microglobulin, albumin, hepatic enzymes, monoclonal proteins using serum and urine immunofixation combined with protein electrophoresis, and free-light chain assessment) were done locally. Bone marrow aspiration (for morphology and cytogenetic analysis by FISH on purified tumor cells), and biopsy were also performed at inclusion. A skeletal survey was done for all patients by low-dose whole-body CT or conventional radiography for assessment of osteolytic disease.

Laboratory efficacy data, including serum and urine monoclonal proteins, serum FLCs, white blood cell differential to assess circulating plasma cells, and bone marrow aspirate to confirm complete response, were collected at defined time points (after induction, after stem cell collection, after each transplantation, after consolidation, at intervals of 2 months during maintenance and follow-up until progression, and thereafter every 6 months). Response and disease progression were defined per the specific response criteria for pPCL as defined by the IMWG<sup>7</sup>. Minimal residual disease (MRD) was assessed by next-generation flow cytometry (sensitivity 1x10<sup>-5</sup>) using bone marrow aspirates obtained at the time of suspected complete or stringent complete response. The International Staging System disease stage was derived from the combination of serum β<sub>2</sub>-microglobulin and albumin concentrations, with higher stages indicating more advanced disease. Cytogenetic abnormalities and LDH level were also considered for definition of revised ISS stage<sup>29</sup>. Safety was monitored continuously throughout the study until 30 days after the last study treatment. Safety assessments included evaluation of adverse events at screening, after

signing informed consent, and at each study visit (except during planned hospitalizations for auto-SCT or allo-SCT); events were graded based on the US National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Other safety data collected included clinical laboratory testing, electrocardiography, physical examinations, and vital signs. An independent data and safety monitoring board (DSMB) periodically reviewed the safety data.

### ***Outcomes***

The primary endpoint for the study was progression-free survival (PFS; defined as the time from registration until progression or death due to any cause, whichever comes first). Secondary endpoints were OS (defined as time from registration until death from any cause), response, safety and toxicity. The endpoints were separately studied in younger and elderly patients

### ***Statistical analysis***

Median PFS was the primary endpoint of this study, and used for sample size calculation. Based on historical treatment data, the median PFS for younger patients was 9 months. A true median PFS with the treatment in this trial of a least 18.3 months was considered sufficiently promising for further investigation in clinical trials. Assuming uniform accrual for 4 years and an additional follow-up of 1 year after the last patient has been registered, then in order to have 80% power to detect this improvement, with 2-sided significance level  $\alpha = 0.05$ , a total of 36 patients needed to be registered. For elderly patients, median progression-free survival is approximately 6.5 months (based on historical treatment of non-transplant eligible patients. For an improvement of PFS to median 15.3 months, we would require 25 registered patients (assuming uniform accrual 4 years, additional follow up of 1 year, 2-sided significance level  $\alpha = 0.05$  and power  $1 - \beta = 0.80$ ).

Survival curves for PFS and OS were computed using the Kaplan-Meier method, and a 95% CI was constructed. Median PFS, including 95% CI, was also determined as this is the primary endpoint. For the younger patients, the null hypothesis would be rejected when the lower limit of the 95% CI of the estimated median PFS was larger than 9 months, while for the elderly patients it should be larger than 6.5 months.

Response rates were described as percentages with 95% CI. Treatment toxicity was analyzed primarily by tabulation of the incidence of adverse events CTCAE grade 2 or more. Data from all subjects who received any study drug would be included in the safety analyses. Adverse events were summarized by worst CTCAE grade.

All analyses were according to the intention to treat (ITT) principle, irrespective the actual treatment received. All analyses were performed using Stata, version 16.1 (StataCorp, College Station, TX) and R and R language (R Foundation for Statistical Computing, Vienna, Austria - Version 4.2.1 or higher).

## Results

### *Patient characteristics*

From October 2015 till August 2021, we enrolled 61 patients with pPCL: 36 aged 18-65 years and 25 aged  $\geq 66$  years. The patient characteristics are shown in Table 1. In the cohort with younger patients, the median age was 60 years (interquartile range (IQR) 52-63), and 20 patients (56%) were male. Patients had a high tumor burden with a median plasma cell percentage in BM biopsy of 80% (IQR 70-90). The frequency of unfavorable cytogenetic abnormalities was high with del(17p) in 15 (47%) of 32 evaluable patients, t(4;14) in 3 (9%) of 33, t(14;16) in 6 (19%) of 31, del(1p) in 10 (36%) of 28, and chromosome 1q abnormalities in 19 (61%) of 31. The proportion of patients with del(17p), t(4;14) and/or t(14;16) was 19 (59%) of 32 patients. A combination of 2 or more high-risk cytogenetic abnormalities (del(17p), t(4;14), t(14;16), or gain/ampl(1q); double-hit) was observed in 12 (34%) out of 35 evaluable patients. In 21 (58%) patients LDH was elevated. Four (11%) patients had International Staging System (ISS) stage I disease, 9 (25%) had stage II, and the majority (23 (64%)) had stage III disease. Among 34 evaluable patients, only 1 (3%) patient had revised ISS stage I, while 16 (47%) had R-ISS stage II and 17 (50%) R-ISS stage III. Extramedullary plasmacytomas were present in 6 patients (17%).

In the elderly patients cohort, the median age was 71 years (IQR 69-74) and 12 patients (48%) were male (Table 1). Patients presented with a high tumor burden (median plasma cell percentage in BM biopsy: 80% (IQR 73-90)). The t(11;14) was the most common cytogenetic abnormality (12 of 22 evaluable patients (55%)), and 6 of 22 (27%) evaluable patients carried del(17p), t(4;14) and/or t(14;16). Double-hit disease was observed in 3 of 22 evaluable patients (14%). Elevated LDH was present in 13 patients (52%) and 3 patients (12%) had extramedullary plasmacytomas. A substantial proportion of patients had a poor WHO performance status at the time of enrollment (WHO performance status  $\geq 2$ : 10 of 25 patients (40%)). Most patients presented with advanced stages of disease (ISS stage 3: 17 patients (74%); R-ISS stage 3: 10 patients (45%)).

### *Efficacy*

The cutoff date for this analysis was March 2, 2023. Of the 36 younger patients who started induction treatment, 33 (92%) received the planned 4 cycles of induction treatment (Figure 1). Median dose intensities were 99% (IQR 92-100) for carfilzomib, 95% (IQR 60-100) for lenalidomide, and 100% (IQR 88-100) for dexamethasone. Response after induction was  $\geq$ PR in 83% (n=30),  $\geq$ VGPR in 75% (n=27), and  $\geq$ CR in 14% (n=5) (Table 2). During or directly after induction therapy, 4 (11%) patients experienced disease progression, and 3 (8%) other patients went off protocol (2 withdrew consent and 1 because of suboptimal response). Two of the 29 patients who were considered for auto-SCT were not fit enough, and continued with KRd treatment (total of 8 courses), followed by maintenance treatment. The other 27 patients successfully harvested peripheral blood stem cells, with 4 patients needing two different stem cell mobilization attempts. The median number of collected stem cells was  $4.9 \times 10^6/\text{kg}$  (IQR 4.2-8.1).

After stem cell collection, 3 patients developed disease progression, while 24 underwent HDM/auto-SCT. The overall response rate after HDM/auto-SCT was 96% with  $\geq$ CR in 8 of the 24 patients (33%) and  $\geq$ VGPR in 23 (96%). One patient (4%) developed disease progression. Another patient achieved a VGPR after HDM, but relapsed soon thereafter.

Of the 24 patients who underwent auto-SCT, 2 went off protocol because of progression and 6 were considered for allo-SCT, and therefore received directly after auto-SCT two additional KRd consolidation cycles. Five of these 6 patients underwent reduced-intensity allo-SCT with stem cells from HLA-matched related donor (n=1), HLA-matched unrelated donor (n=2), or haploidentical related donor (n=2), while 1 patient was deemed ineligible for allo-SCT after KRd consolidation. Acute GVHD developed in 1 patient (grade 2), and chronic GVHD developed in another patient (severe). Response after allo-SCT was  $\geq$ VGPR in 100% (n=5) and  $\geq$ CR in 80% (n=4).

Sixteen patients did not receive allo-SCT, because of absence of a suitable donor, patient's condition (including presence of renal impairment) or patient's choice. Per protocol, 12 of these 16 patients received a second HDM/auto-SCT followed by 4 cycles of KRd consolidation, and 4 patients declined a second HDM/auto-SCT and continued directly with KRd consolidation. The overall response after second auto-SCT was 100% with  $\geq$ CR in 3 (25%) and  $\geq$ VGPR in 12 (100%).



Eighteen patients received maintenance, one (6%) patient only lenalidomide, one (6%) only carfilzomib, and 16 (89%) carfilzomib-lenalidomide. This included 3 patients after allo-SCT, 2 patients who were not eligible for auto-SCT and received maintenance after 8 KRd cycles, and 13 patients after 4 cycles of KRd consolidation following one (n=2) or double auto-SCT (n=11). Median duration of carfilzomib maintenance treatment was 22.1 months (95% CI 12.6-39.8), and the median duration of lenalidomide maintenance was 31.5 months (95% CI 17.5—not reached). The median duration of maintenance treatment until discontinuation of both drugs was 26.6 months (95% CI 14.9—not reached). Ten (56%) patients were in VGPR, 1 (6%) in CR, and 7 in sCR (39%) before initiation of maintenance. At the data cut-off, 7 of the 18 patients, who started with maintenance treatment, were still receiving maintenance, while 10 patients developed progressive disease and 1 stopped maintenance because of a toxicity (pulmonary sepsis). Five of the 10 VGPR patients had improvement in response during maintenance treatment (CR in 1 and sCR in 4).

The best response achieved during the entire program was  $\geq$ PR in 86% (n=31),  $\geq$ VGPR in 83% (n=30), and  $\geq$ CR in 50% (n=18). Among the 20 patients evaluated for MRD, 16 (80%) were negative for MRD.

Of the 25 elderly patients, 19 received the first 4 cycles of KRd induction (Figure 2). Early death occurred in 2 patients, 10 and 15 days after start of treatment (cause of death: unknown and *S. aureus*-related pneumonia, respectively). During or directly after the first 4 cycles of KRd, 4 additional patients went off protocol because of excessive toxicity (n=2) and withdrawal of consent (n=2). The median dose intensities were 76% (IQR 72-82) for carfilzomib, 66% (IQR 43-71) for lenalidomide, and 50% (IQR 47-62) for dexamethasone. The overall response rate after the first 4 KRd induction cycles was 80% (n=20) with  $\geq$ VGPR in 68% (n=17) and  $\geq$ CR in 24% (n=6) (Table 3). Nineteen of the 25 patients continued with KRd cycles 5-8. A total of 8 KRd induction cycles was received by 17 out of 19 patients, while 1 patient developed progression and 1 patient, who had achieved sCR, died 6 months after start of induction treatment because of influenza-related pneumonia. Depth of response improved with these 4 additional induction cycles ( $\geq$ PR: 95% (18 out of 19 patients);  $\geq$ VGPR: 89% (n=17);  $\geq$ CR 42% (n=8)). Sixteen out of 17 patients started maintenance treatment; 1 patient did not yet start with maintenance therapy after completing induction treatment (3

(19%) only carfilzomib maintenance and 13 (81%) carfilzomib-lenalidomide). Lenalidomide maintenance treatment was given for a median duration of 12.9 months (95% CI 5.1–NE) and carfilzomib for 10.4 months (95% CI 5.6–32.4). The median duration of maintenance treatment until discontinuation of both drugs was 10.3 months (95% CI 5.6–42.6). One out of 10 patients who initiated maintenance treatment with <CR, had an improvement in depth of response (VGPR to sCR). At the data cut-off, 2 of the 16 patients were still receiving maintenance, while 12 patients developed disease progression and 2 stopped because of adverse events.

Best response on protocol was  $\geq$ PR in 80%,  $\geq$ VGPR in 68% and  $\geq$ CR in 36%. Five out of 8 patients (63%) with  $\geq$ CR who could be evaluated for MRD, achieved MRD negativity ( $10^{-5}$ ).

### *Survival*

For younger patients the median follow-up was 43.5 months (IQR 27.7–67.8). The median PFS was 15.5 months (95% CI 9.4–38.4; Figure 3), which was sufficient to reject our null hypothesis (median PFS=9 months). Twenty patients had died (relapse-related mortality in 15/20 (75%) patients and non-relapse mortality in 5/20 patients (25%; 2 on protocol and 3 off-protocol)). Reasons for non-relapse mortality on protocol were a cardiac disorder after auto-SCT, and 1 human metapneumovirus respiratory infection 4 months after allo-SCT. Reasons for non-relapse mortality off-protocol were 3 infections (1 pneumonia, 1 neutropenic sepsis, and 1 SARS-Cov2 infection). Median OS was 28.4 months (95% CI 15.1–NE; Figure 3).

For the 24 patients who underwent first HDM/auto-SCT, median PFS and OS were 26.2 (95% CI 9.4–54.7) and not estimable (95% CI 17.0–NE) from date of first auto-SCT, respectively (Figure 3). In a landmark analysis from the date of the second transplant, PFS was comparable between patients who received a second auto-SCT or allo-SCT (median PFS was 31.2 months (95% CI 12.8–NE) for patients who received a second auto-SCT, and 49.2 months (95% CI 3.6--NE) for those who underwent allo-SCT; the PFS at 2 years was 58% for the second auto-SCT group and 60% for the allo-SCT patients; Supplemental Figure 1). OS from the date of second transplant was also comparable in both groups (median OS not estimable (95% CI 20.0–NE) for the patients who underwent second auto-SCT, and not estimable (5.5--NE) for the allo-SCT patients; the 2-year OS was 82% for the second auto-SCT patients and 53% for the allo-SCT patients).

In the cohort of elderly patients the median follow-up was 32.0 months (IQR 24.7-34.6). The median PFS was 13.8 months (95% CI 9.2-35.5; Figure 4), which was sufficient to reject the null hypothesis (median PFS=6.5 months). At the data cut-off, 18 patients had died. Relapse-related mortality occurred in 9/18 (50%) patients and non-relapse mortality in 9/18 (50%; 3 on protocol, 6 off protocol). Reasons for non-relapse mortality on protocol were two infections (pneumonia and sepsis) and one unknown cause of death. Reasons for non-relapse mortality off protocol were 1 SPM (duodenal adenocarcinoma), 1 infection, 1 exacerbation COPD, 1 disseminated intravascular coagulation, and 2 with unknown cause of death. Median OS was 24.8 months (95% CI 14.0-NE). Median OS was 24.8 months (95% CI 14.0-NE; Figure 4).

### *Safety*

Cumulative hematological and non-hematological toxicity grade  $\geq 3$  during induction was reported in 3 out of 36 (8%) and 16 out of 36 (44%) younger patients, respectively (Table 4). Non-hematological toxicity grade  $\geq 3$  included cardiac (6%), gastrointestinal (6%), respiratory (6%), vascular (6%), renal (6%), and infectious (6%) AEs (Table 4). During consolidation treatment the cumulative hematological and non-hematological toxicity was lower, compared to that observed during induction therapy (Table 4). Adverse events during maintenance are also shown in Table 4.

Two patients discontinued because of AEs (one patient after allo-SCT because of multiple infections, and one because of myocardial infarction during hospitalization because of pulmonary sepsis and choledocholithiasis requiring ERCP with biliary stenting and sphincterotomy). One patient developed myelodysplastic syndrome during pomalidomide-cyclophosphamide-dexamethasone treatment as second line treatment (2.5 years after start of protocol treatment).

Twenty-six out of 36 (72%) patients experienced a total of 64 serious adverse events (SAEs), mainly because of hospitalization (86%). Approximately one third (30%) of all SAEs occurred during the first KRd induction cycle and 44% occurred during induction treatment.

In the cohort with elderly pPCL patients, the rate of cumulative hematological and non-hematological toxicity grade  $\geq 3$  during the first 4 KRd induction cycles was 16% (4 out of 25

patients) and 64% (16 out of 25 patients), respectively (Table 5). Non-hematological toxicity grade  $\geq 3$  included cardiac (4%), gastrointestinal (8%), respiratory (16%), vascular (8%), renal (4%), and infectious (32%) AEs (Table 5). During KRd induction cycles 5-8 the cumulative hematological and non-hematological toxicity was lower, compared to that observed during the first 4 induction cycles (5% and 21%, respectively; Table 5). Adverse events during maintenance are shown in Table 5.

Study discontinuation due to adverse events occurred in 2 patients (one patient because of progressive neurological decline during maintenance, and one patient because of small intestine adenocarcinoma that developed during maintenance therapy, 30 months after initiation of treatment).

Nineteen out of 25 (76%) patients experienced a total of 54 serious adverse events (SAEs), mainly because of hospitalization (78%). Approximately one third (35%) of all SAEs occurred during the first KRd induction cycle and 61% occurred during the first 4 cycles of induction treatment.

## Discussion

We report the final results from the EMN12/HOVON-129 study for pPCL patients, in which we examined whether a carfilzomib and lenalidomide-based treatment in conjunction with transplantation for younger patients improves survival. Effective induction treatment in pPCL is highly important to achieve rapid disease control, to avoid early mortality, and to increase the proportion of patients receiving a first auto-SCT<sup>30</sup>. In this study, which is the third and up till now largest clinical trial for patients with this rare and difficult-to-treat disease, we observed a high rate of deep responses with carfilzomib and lenalidomide-based treatment in both younger and elderly patients with pPCL.

In our cohort of younger patients, KRd induction therapy induced substantial tumor reduction, with deepening of response over time following transplantation and during extended treatment with carfilzomib and lenalidomide in consolidation and maintenance. A high proportion of patients also obtained undetectable MRD (sensitivity of  $10^{-5}$ ). Although the median PFS of 15.5 months exceeded the study hypothesis (median PFS 9 months), PFS remains substantially inferior to what can be achieved with similar treatment strategies in newly diagnosed transplant-eligible MM patients including those with high-risk cytogenetic abnormalities<sup>25,31,32</sup>.

The high activity of KRd induction allowed two-thirds of patients to undergo a first course of HDM/auto-SCT. Importantly, these patients experienced pronounced improvement in PFS (median PFS 26.2 months from date of first auto-SCT). This compares favorably to the retrospective analyses reported by EBMT<sup>13,24</sup> and CIBMTR<sup>17,23</sup> (median PFS from auto-SCT: approximately 14 months), which may be related to frequent application of a second transplant and effective carfilzomib and lenalidomide-based consolidation and maintenance to sustain remission. Because of small numbers of patients, it is difficult to draw conclusions about the efficacy of allo-SCT versus second auto-SCT. However, survival after allo-SCT seems to be comparable with that observed after a second auto-SCT. This is in accordance with other reports showing limited efficacy of allo-SCT in controlling residual disease in pPCL, combined with high non-relapse mortality<sup>17,20,23</sup>.

How do our results compare with the other prospective phase 2 study for transplant-eligible newly diagnosed pPCL patients? In the IFM study, which used comparable eligibility criteria

as in our study, 39 patients were treated with bortezomib combined with chemotherapy (i.e. bortezomib-cyclophosphamide-dexamethasone alternating with bortezomib-adriamycin-dexamethasone) followed by HDM/auto-SCT, and then either allo-SCT or a second auto-SCT and subsequent bortezomib-lenalidomide maintenance<sup>20</sup>. An identical proportion of patients received a first course of HDM/auto-SCT (67% in both studies)<sup>20</sup>. Despite the limitations of cross-trial comparisons, our data suggests that KRd induction compares favorably to bortezomib/chemotherapy-based induction with a larger proportion of pPCL patients achieving  $\geq$ VGPR with KRd induction, compared to PI and chemotherapy in the IFM study (75% vs 36%). This confirms the superiority of a combination therapy regimen based on a proteasome inhibitor and IMiD over a proteasome inhibitor and chemotherapy as has been demonstrated in newly diagnosed MM<sup>26,33</sup>. Also best response achieved during the entire treatment was superior in our series, compared to the IFM study ( $\geq$ PR: 86% vs 69%,;  $\geq$ VGPR: 83% vs 59%;  $\geq$ CR: 50% vs 33%). Surprisingly, the higher quality response with KRd did not translate into an improved PFS or OS, compared to what was achieved in the IFM study (median PFS 15.1 months; median OS 36.3 months). This may be related to differences in patient populations with a higher proportion of patients with high-risk abnormalities (del(17p): 47% vs 28%) and more advanced disease (ISS stage III: 64 vs 43%) in our study, compared to the IFM study<sup>20</sup>. Alternatively, it may also be explained by the aggressive nature of the disease with high proliferative activity and genomic instability with rapid outgrowth of resistant clones during treatment strategies with triplet induction/consolidation regimens integrated with transplantation.

Our results are especially promising in the cohort of elderly patients with an increase in both rate and quality of response, compared to what has been reported before in transplant-ineligible patients<sup>6,21</sup>. In addition, the median PFS of 13.8 months represents an improvement over the historical expectation of 6.5 months<sup>6,9</sup>. Furthermore, the median OS in our study (24.8 months) doubled compared to what has been reported in recent retrospective studies and, particularly, in the only other prospective trial (with the doublet lenalidomide-dexamethasone) so far conducted in transplant-ineligible, elderly patients with pPCL (median OS 12 months)<sup>21</sup>.

Importantly, with the measures to mitigate risks of adverse events, such as per protocol hydration, infectious prophylaxis and TLS prophylaxis, the treatment strategy with carfilzomib and lenalidomide incorporated in induction, consolidation, and maintenance had a manageable toxicity profile in younger patients, comparable to what is observed in transplant-eligible newly diagnosed MM. Cardiac toxicities were in the expected range, and neurotoxicity was uncommon. Treatment-related toxicities were more common in the cohort with elderly patients, but adverse events were generally manageable. A substantial proportion of these patients had a poor performance status at enrollment into the study, which, together with high tumor burden, may have contributed to the toxicity observed in these patients. The majority of the adverse events could be managed by appropriate dose reductions and adequate supportive care. Overall we see a positive benefit/risk ratio in this difficult to treat patient population.

Compared to MM, our data remain unsatisfactory, and prevention of relapse remains a key challenge in the treatment of pPCL patients. It is important to avoid disease progression by offering patients continuous treatment with short treatment-free intervals, because a substantial proportion of our patients developed progression in periods without therapeutic pressure such as in the period of stem cell mobilization and during the recovery phase after transplantation, reflecting the proliferative capacity of this disease<sup>14</sup>. New clinical trials are needed to evaluate whether incorporation of new agents such as CD38-targeting antibodies or T-cell redirecting therapies (e.g. CAR T-cell therapy and bispecific antibodies) in the treatment strategy further improves depth of response and survival of newly diagnosed pPCL patients. Venetoclax, which is effective in t(11;14) MM is also a promising new drug for pPCL with t(11;14)<sup>34,35</sup>. The frequent occurrence of early relapse in pPCL patients despite deep responses indicates the rapid development of resistance or the outgrowth of clones with a resistant phenotype, and suggests that sequencing different regimens without cross-resistance may prevent outgrowth of resistant clones and improve survival.

The strengths of our study include the treatment of a uniform cohort of pPCL patients and long duration of follow-up. Because a substantial proportion of patients present with aggressive disease presentation with significant organ dysfunction, we used very liberal eligibility criteria (e.g. without restrictions for blood counts, a creatinine clearance of  $\geq 15$

ml/min, and WHO performance 0-3), while typically more stringent eligibility criteria are used in MM trials. This indicates that our data are a true real-world reflection of the management of these patients. A limitation of our study is that we could not report MRD-negativity at uniform time points, as these assessments were typically done at the time of achieving CR. Future studies should look at MRD and sustained MRD-negativity at fixed time-points, preferentially at the level of  $10^{-6}$ . Another limitation of our study is the use of different consolidation strategies in younger patients (allo-SCT or a second auto-SCT), with relatively low application of allo-SCT. This is likely related to recent studies showing lack of clear benefit of allo-SCT in pPCL<sup>17,20,23</sup>, and thus reflects contemporary practice. Because of differences in treatment strategy between the younger and elderly patients, and baseline characteristics (higher proportion of high-risk features in younger patients), we did not formally compare both age groups in this study.

In summary, results from this phase 2 study reported here demonstrate that incorporation of carfilzomib and lenalidomide in induction, consolidation and maintenance induces deep responses in both younger and elderly pPCL patients, with especially in elderly/transplant-ineligible patients improved survival. However, overall PFS and OS remain unsatisfactory. New trials should evaluate the incorporation of novel immunotherapies into the treatment of pPCL patients, whereby effective therapies rapidly alternate each other to prevent early progression. Trial enrollment may benefit from the inclusion of patients with a lower proportion of circulating plasma cells, which have the same poor prognosis as patients with >20% circulating plasma cells<sup>9,36</sup>, or by enrolling pPCL patients into trials designed for the treatment of ultra-high risk MM patients<sup>37-39</sup>.



**Conflicts of interest please add your conflicts if they exist**

N.W.C.J.v.d.D. has received research support from Janssen Pharmaceuticals, AMGEN, Celgene, Novartis, Cellectis and BMS, and serves in advisory boards for Janssen Pharmaceuticals, AMGEN, Celgene, BMS, Takeda, Roche, Novartis, Bayer, Adaptive, and Servier;

M.C.M. has a consultancy or advisory role for Gilead Sciences, BMS, Alnylam, Janssen Cilag, Takeda, and Servier; all paid to employer, hospitality from Celgene;

B.v.d.H.

F.S.

K.L.W.

A.B. receives honoraria from Celgene, Janssen, Amgen, Takeda and Sanofi;

W.W.H.R.

A.G.

G.P.

L.P.

V.H.J.v.d.V.

T.L.

M.O.

M.G.

L.G.

M.C.

T.S.

J.C.

S.Z. has received research funding from Celgene, Takeda, Janssen, and serves in advisory boards for Janssen, Takeda, BMS, Oncoceptides and Sanofi, all paid to institution;

R.H.

R.B.

A.J.V.

M.B.

F.G.

P.S. has received honoraria from Amgen, BMS, Celgene, Janssen, Karyopharm, Takeda, and receives research funding from Amgen, Celgene, Janssen, Karyopharm, SkylineDx, Takeda; P.M. has received honoraria from and/or served on Scientific Boards for Abbvie, Alexion, Amgen, Astra-Zeneca, Astellas, Bei-Gene, Bristol-Myers Squibb/Celgene, Gilead, Glaxo-Smith-Kline, Grifols, Incyte, Janssen, Jazz, Novartis, Pfizer, Roche, Sanofi, and Takeda; All other authors declared no conflicts of interest.

### **Acknowledgements**

The authors thank the safety monitoring committee members: J.D. Cavenagh, London, UK; N. Kröger, Hamburg, Germany; H. van Tinteren, Amsterdam, The Netherlands.

This study was supported by AMGEN and Celgene (a Bristol-Myers Squibb company). We also thank the statistician Andrea Capra from the European Myeloma Network (Italy) for help with the statistical analysis.

### **Author contributions**

All authors contributed to the acquisition, analysis, or interpretation of data for this work. All authors critically reviewed the work for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had access to and verified the underlying data. NvdD, BvdH and PM contributed to conceptualisation, formal analysis, methodology, and writing of the original draft. BvdH contributed to software and visualisation. NvdD, MB, PS, and PM contributed to supervision. All authors contributed equally to data curation, investigation, resources, validation, and writing of the manuscript in terms of review and editing. All authors had access to all the data reported in the study and had final responsibility for the decision to submit this manuscript for publication.

**Table 1. Characteristics of Patients at Baseline.**

Characteristic	Younger patients (n=36)	Older patients (n=25)
Median age (IQR) — yr	60 (52-63)	71 (69-74)
Race— no. (%)		
Caucasian	31 (86)	24 (96)
African	2 (6)	0 (0)
Asian	2 (6)	0 (0)
Other	1 (3)	1 (4)
Sex — no. (%)		
Male	20 (56)	12 (48)
Female	16 (44)	13 (52)
Median time from diagnosis to screening (IQR) — days	5 (3-9)	5 (2-8)
M-protein		
IgG	11 (31)	14 (56)
IgA	7 (19)	0 (0)
IgM	0 (0)	1 (4)
IgD	2 (6)	2 (8)
BJ only	16 (44)	8 (32)
Extramedullary plasmacytomas $\geq 1$ — no. (%)†	6 (17)	3 (12)
Median bone marrow plasma cell % in smear (IQR)	66 (40-83)	45 (31-73)
Median bone marrow plasma cell % in biopsy (IQR)	80 (70-90)	80 (73-90)
Median PB plasma cells ( $\times 10^9/L$ ) (IQR)	4.1 (2.5-7.2)	3.8 (2.5-11.4)
Median proportion of PB plasma cells (IQR)	31 (24-52)	29 (23-50)
CRAB		
Calcium $>2.75$ mM — no. (%)	8 (22)	3 (12)
Creatinine $>177$ $\mu$ M — no. (%)	8 (22)	5 (20)
Hemoglobin $<6.2$ mM — no. (%)	24 (67)	15 (60)
Bone disease — no. (%)	24 (67)	17 (68)
Median corrected calcium (mM) (IQR)	2.5 (2.3-2.7)	2.5 (2.3-2.6)
Median GFR (ml/min) (IQR)	54 (38-88)	56 (37-76)
Median hemoglobin (mM) (IQR)	5.8 (5.1-6.5)	5.8 (5.3-6.7)
Median platelet count ( $\times 10^9/L$ ) (IQR)	111 (48-180)	142 (65-203)
Median albumin (g/L) (IQR)	36 (30-40)	35 (30-40)
Median $\beta 2$ microglobulin (mg/L) (IQR)	7.8 (4.5-15.0)	7.3 (5.3-12.6)
WHO performance-status score — no. (%)		
0	6 (17)	4 (16)
1	18 (50)	11 (44)
2	8 (22)	6 (24)
3	4 (11)	4 (16)
ISS stage — no. (%)‡		
I	4 (11)	2 (9)
II	9 (25)	4 (17)
III	23 (64)	17 (74)
Cytogenetic abnormality — no. (%)**		
del(17p)***	15 (47)	4 (18)
t(4;14)	3 (9)	1 (4)
t(14;16)	6 (19)	1 (4)
t(11;14)	8 (26)	12 (55)
del(1p)	10 (36)	6 (27)
Gain or amplification 1q	19 (61)	12 (52)
del(13q)	22 (71)	11 (52)
Hyperdiploidy	3 (13)	2 (17)
del(17p), t(4;14), or t(14;16)	19 (59)	6 (27)
Combination of 2 or more high-risk cytogenetic abnormalities $\downarrow$	12 (34)	3 (14)

LDH > ULN — no. (%)	21 (58)	13 (52)
Revised ISS stage — no. (%)§		
I	1 (3)	0 (0)
II	16 (47)	12 (55)
III	17 (50)	10 (45)

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ULN, upper limit of normal

† Patients with soft-tissue plasmacytomas not associated with the bone were included.

‡ Denominator is evaluable patients, n=36 for younger patients and n=23 for elderly patients.

.\*\* Denominator is evaluable patients: del(17p), 32 younger patients and 22 elderly patients; t(4;14), 33 and 24 patients; t(14;16), 31 and 23 patients; t(11;14), 31 and 22 patients; del(1p), 28 and 22 patients; gain/amp1q, 31 and 23 patients; del(13q), 31 and 21 patients; hyperdiploidy, 24 and 12 patients; del(17p), t(4;14), or t(14;16), 32 and 22 patients; 2 or more high-risk cytogenetic abnormalities, 35 and 22 patients.

\*\*\*The median percentage of del(17p)-positive cells in FISH studies was 81% for younger patients and 92% for elderly patients.

‡ Defined as presence of 2 or more of the following: t(4;14); t(14;16); del(17p), as well as gain or amplification of 1q.

§ Denominator is evaluable patients, n=34 for younger and n=22 for elderly patients.

**Figure 2. Response rate in patients aged 18-65 years**

	<b>Response after induction (n=36)</b>	<b>After first auto-SCT (n=24)</b>	<b>After second HDM (n=12)</b>	<b>After allo-SCT (n=5)</b>	<b>Best response on protocol (n=36)</b>
≥PR	30 (83)	23 (96)	12 (100)	5 (100)	31 (86)
≥VGPR	27 (75)	23 (96)	12 (100)	5 (100)	30 (83)
≥CR	5 (14)	8 (33)	3 (25)	4 (80)	18 (50)
sCR	1 (3)	3 (13)	1 (8)	2 (40)	12 (33)
CR	4 (11)	5 (21)	2 (17)	2 (40)	6 (17)
VGPR	22 (61)	15 (63)	9 (75)	1 (20)	12 (33)
PR	3 (8)	0 (0)	0	0	1 (3)
SD	1 (3)	0	0	0	1 (3)
PD	3 (8)	1 (4)	0	0	2 (6)
NE	2 (6)*	0	0	0	2 (6)

\*2 patients were not evaluable for response; one patient because of withdrawal of consent 14 days after treatment initiation and one patient went off-protocol 28 days after protocol initiation because of development of renal failure in the absence of disease progression.

**Table 3. Response rate in patients aged 66 years or older**

	<b>Response induction cycles 1-4 (n=25)</b>	<b>Response induction cycles 5-8 (n=19)</b>	<b>Best response on protocol (n=25)</b>
≥PR	20 (80)	18 (95)	20 (80)
≥VGPR	17 (68)	17 (89)	17 (68)
≥CR	6 (24)	8 (42)	9 (36)
sCR	3 (12)	4 (21)	5 (20)
CR	3 (12)	4 (21)	4 (16)
VGPR	11 (44)	9 (47)	8 (32)
PR	3 (12)	1 (5)	3 (12)
SD	1 (4)	0	1 (4)
PD	0	1 (5)	0
NE	5 (20)*	0	5 (20)

\*5 patients were not evaluable for response because of early death in 2 patients (10 and 15 days after treatment initiation), excessive toxicity in 2 patient (protocol treatment was stopped 14 days and 19 days after its initiation), and 1 withdrawal of consent in 1 patient (28 days after treatment initiation).

Adverse event	AE during induction (n=36)			AE during consolidation (n=21)			AE on maintenance (n=18)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Any hematological AE, No. (%)	2 (6)	2 (6)	1 (3)	1 (5)	1 (5)	-	-	4 (22)	2 (11)
Neutropenia	1 (3)	-	-	-	1 (5)	-	-	4 (22)	-
Thrombocytopenia	1 (3)	1 (3)	1 (3)	-	-	-	-	-	2 (11)
Anemia	3 (8)	1 (3)	-	1 (5)	-	-	1 (6)	-	-
Any non-hematologic toxicity, No. (%)	10 (34)	11 (38)	5 (17)	5 (24)	2 (10)	2 (10)	7 (39)	5 (28)	1 (6)
Infections and infestations	6 (17)	2 (6)	-	4 (19)	-	1 (5)	5 (28)	4 (22)	-
Cardiac disorders	2 (6)	2 (6)	-	-	-	-	-	-	-
General disorders and administration site conditions	10 (28)	2 (6)	-	-	-	-	3 (17)	1 (6)	-
Gastrointestinal disorders	5 (14)	2 (6)	-	2 (10)	-	-	4 (22)	1 (6)	-
Nervous system disorders	1 (3)	-	-	2 (10)	-	-	2 (11)	-	-
Vascular disorders	4 (11)	2 (6)	-	1 (5)	1 (5)	-	-	-	-
Musculoskeletal and connective tissue disorders	-	-	-	1 (5)	-	-	1 (6)	-	-
Metabolism and nutrition disorders	2 (6)	1 (3)	1 (3)	-	1 (5)	-	-	-	-
Renal and urinary disorders	-	-	2 (6)	1 (5)	-	-	1 (6)	-	-
Respiratory, thoracic and mediastinal disorders	5 (14)	2 (6)	-	1 (5)	-	-	1 (6)	-	-
Psychiatric disorders	1 (3)	-	2 (6)	-	-	-	-	-	-
Skin and subcutaneous tissue disorder	4 (11)	1 (3)	-	-	-	-	-	-	-
Hepatobiliary	-	-	-	-	-	-	-	-	-

**Table. 4 Adverse events in patients aged 18-65 years**

Adverse event	AE during induction cycles 1-4 (n=25)			AE during induction cycles 5-8 (n=19)			AE on maintenance (n=16)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Any hematological AE, No. (%)	1 (4)	1 (4)	3 (12)	1 (5)	1 (5)	-	2 (13)	-	-
Neutropenia	-	1 (4)	1 (4)	-	1 (5)	-	-	-	-
Thrombocytopenia	-	1 (4)	2 (8)	-	1 (5)	-	1 (6)	-	-
Anemia	1 (4)	2 (8)	-	1 (5)	-	-	1 (6)	-	-
Any non-hematologic toxicity, No. (%)	4 (16)	11 (44)	5 (20)	5 (26)	3 (16)	1 (5)	4 (25)	5 (31)	2 (12)
Infections and infestations	4 (16)	6 (24)	2 (8)	3 (16)	3 (16)	1 (5)	2 (12)	3 (19)	1 (6)
Cardiac disorders	2 (8)	-	1 (4)	1 (5)	-	-	-	-	-
General disorders and administration site conditions	2 (8)	2 (8)	1 (4)	2 (11)	-	-	4 (25)	1 (6)	-
Gastrointestinal disorders	1 (4)	2 (8)	-	-	-	-	2 (12)	2 (12)	1 (6)
Nervous system disorders	-	-	-	2 (11)	-	-	1 (6)	-	-
Vascular disorders	1 (4)	2 (8)	-	1 (5)	-	-	1 (6)	-	-
Musculoskeletal and connective tissue disorders	1 (4)	-	-	-	-	-	1 (6)	-	-
Metabolism and nutrition disorders	1 (4)	2 (8)	-	-	-	-	-	1 (6)	-
Renal and urinary disorders	-	-	1 (4)	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	2 (8)	3 (12)	1 (4)	-	-	-	2 (12)	1 (6)	-
Psychiatric disorders	3 (12)	-	-	1 (5)	-	-	-	-	-
Skin and subcutaneous tissue disorder	3 (12)	2 (8)	-	-	-	-	3 (19)	-	-
Hepatobiliary	-	1 (4)	1 (4)	-	-	-	-	-	-

**Table 5. Adverse events in patients aged 66 years and older**



## Figure legends

### Figure 1. Trial profile

A) Trial profile for patients 18-65 years.

B) Trial profile for patients  $\geq 66$  years.

Abbreviations: KRd, carfilzomb, lenalidomide, and dexamethasone; KR, carfilzomib and lenalidomide; HDM, high-dose melphalan; ASCT, autologous stem cell transplantation; G-CSF, granulocyte colony-stimulating factor; RIC ALLO-SCT, reduced-intensity conditioning allogeneic stem cell transplantation

### Figure 2. PFS and OS from registration, and PFS and OS after HDM1

#### PFS and OS for patients aged 18-65 years

Kaplan-Meier survival curves of patients aged 18-65 years. (A) PFS from registration; (B) OS from registration; (C) PFS from HDM1; (D) OS from HDM1.

N indicates number of patients; p/d, number of progression/death; d, number of death

### Figure 3. PFS and OS from registration for patients aged $\geq 66$ years

Kaplan-Meier survival curves of patients aged  $\geq 66$  years. (A) PFS from registration; (B) OS from registration.

N indicates number of patients; p/d, number of progression/death; d, number of death

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