We report the final results of the prospective phase 2 EMN12/HOVON-129 study for patients with newly diagnosed primary plasma cell leukaemia. Patients were assigned to one of two different treatment regimens based on age (younger patients, aged 18–65 years; older patients, 66 years or older). 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 seen in patients newly diagnosed with multiple myeloma, especially those with high-risk cytogenetic abnormalities, with negligible neurological toxicity.[17,18] Younger patients received four cycles of KRd induction, followed by the tandem of autologous HSCT and reduced-intensity allogeneic HSCT, or alternatively double autologous HSCT. Induction and transplantation were followed by KRd consolidation and maintenance treatment consisting of both carfilzomib and lenalidomide. Older patients received eight cycles of KRd induction, followed by carfilzomib-lenalidomide maintenance.

Methods

Study design and participants

This non-randomised phase 2, prospective, multicentre study enrolled patients with previously untreated, symptomatic primary plasma cell leukaemia (defined as $>2\times10^9$ circulating monoclonal plasma cells per L or plasmacytosis >20% of the differential white cell count) at 19 academic centres and hospitals (appendix p 12) in seven European countries (Belgium, Czech Republic, Denmark, Italy, Norway, The Netherlands, and the UK). Patients aged 18–65 years (younger patients) and 66 years or older (older patients) were treated in age-specific cohorts and were analysed separately. The protocol can be found in the appendix (pp 14–120).

Patients (aged ≥18 years) were eligible for participation if they had measurable disease (defined by the presence of serum M-protein ≥5 g/L, or urine M-protein ≥200 mg/24 h, or abnormal free-light chain [FLC] ratio with involved FLC ≥100 mg/L), and if they had WHO performance status 0–3 (WHO-3 only allowed when caused by primary plasma cell leukaemia and not by comorbid conditions).

Key exclusion criteria were CNS involvement by primary plasma cell leukaemia; active malignancy other than primary plasma cell leukaemia requiring treatment; active, uncontrolled infections; severe neurological or psychiatric disease; severe cardiac dysfunction (New York Heart Association [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; substantial hepatic dysfunction (serum bilirubin or aminotransferases ≥3·0 times upper limit of normal, unless related to primary plasma cell leukaemia); estimated glomerular filtration rate (GFR) of less than 15 mL/min; and previous treatment, except focal radiation to control local tumour progression or corticosteroids (maximum 7 days for symptom control or stabilisation).

Younger patients for whom an adequate number of stem cells (count of $\geq2\times10^6$ $CD34^+$ cells per kg [or according to national guidelines]) were collected were eligible to undergo autologous HSCT, in case of WHO performance 0–2, bilirubin and aminotransferases less than 3 times the upper limit of normal, absence of severe pulmonary, neurological, cardiac, or psychiatric disease, as well as absence of progressive disease. Eligibility criteria for allogeneic HSCT included the availability of an HLA-identical sibling or unrelated donor, and WHO-performance 0–2. Key exclusion criteria were response of less than partial response, progressive disease, or CNS involvement, as well as presence of active or uncontrolled infections, severe neurological or psychiatric disease, severe cardiac (NYHA classification II-IV) or pulmonary dysfunction, substantial hepatic dysfunction (serum bilirubin or aminotransferases ≥3·0 times upper limit of normal), and GFR of less than 30 mL/min.

Sex (male and female) and race were reported on case report forms by trial investigators during patient registration. Data on gender were not collected. All patients gave written informed consent before inclusion. The protocol (appendix) and consent documents were approved by independent ethics or institutional review boards at each site and the study was undertaken according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines on Good Clinical Practice.

Procedures

Younger patients received four 28-day cycles of KRd (carfilzomib on days 1, 2, 8, 9, 15, and 16 [starting dose, 20 mg/m² intravenously on days 1 and 2 of cycle 1; target dose, 36 mg/m² intravenously thereafter]; lenalidomide 25 mg orally on days 1–21; and dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22, and 23). Patients then underwent stem cell mobilisation with cyclophosphamide and granulocyte colony-stimulating factor, and standard autologous HSCT with melphalan at 200 mg/m² (intravenous route). This was followed by two courses of KRd consolidation treatment and reduced-intensity conditioning allogeneic HSCT for patients with an HLA-identical sibling or a suitable unrelated donor. 2 months after the allogeneic HSCT, carfilzomib maintenance was initiated. 8 months after allogeneic HSCT, 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 allogeneic HSCT, or if patient did not want to undergo allogeneic HSCT, a second course of HDM was administered between 2 and 3 months after the first course if the patient achieved at least partial response. This was followed by four cycles of KRd consolidation,

Correspondence to:
Prof N W C J van de Donk, Amsterdam UMC, Department of Hematology, Vrije Universiteit Amsterdam, 1081 HV, Amsterdam, Netherlands
n.vandedonk@amsterdamumc.nl

See Online for appendix

and subsequently carfilzomib-lenalidomide maintenance until progression or undue toxicity.

Details of induction treatment, stem-cell mobilisation, transplantation, consolidation, and maintenance are presented in the appendix (pp 2–3). Prespecified dose reductions or interruptions were permitted in the case of treatment-related adverse events, as detailed in the study protocol (appendix).

Older patients received eight cycles of KRd induction (carfilzomib on days 1, 2, 8, 9, 15, and 16 [starting dose,

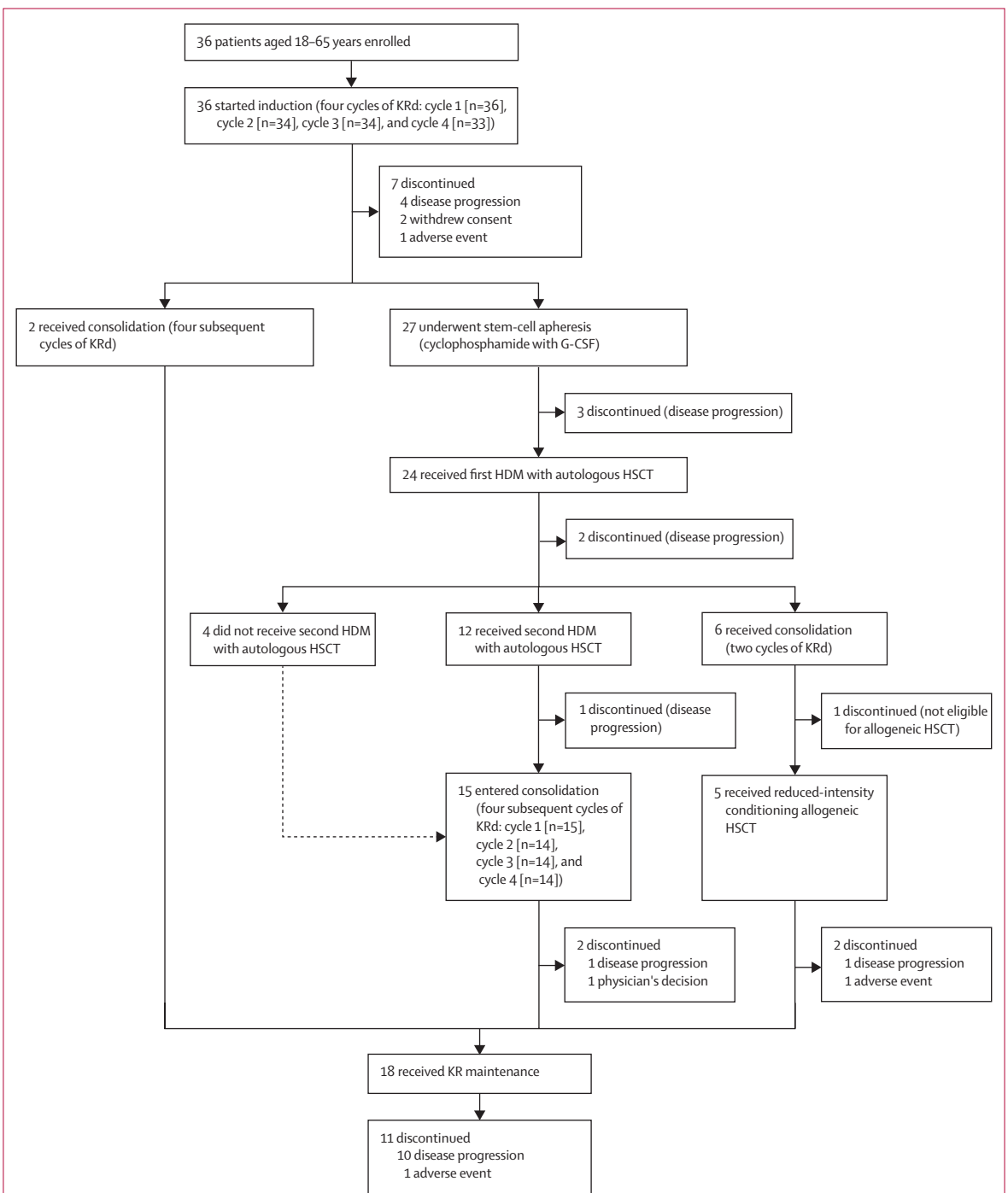

Figure 1: **Trial profile for patients aged 18–65 years**
KRd=carfilzomib, lenalidomide, and dexamethasone. KR=carfilzomib and lenalidomide. HDM=high-dose melphalan. HSCT=haematopoietic stem-cell transplantation. G-CSF=granulocyte colony-stimulating factor.

20 mg/m² intravenously on days 1 and 2 of cycle 1; target dose, 36 mg/m² intravenously thereafter]; lenalidomide 25 mg orally on days 1–21; dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22, and 23) and subsequently carfilzomib-lenalidomide maintenance until progression or undue toxicity. During maintenance, carfilzomib was administered at a dose of 27 mg/m² intravenously on days 1, 2, 15, and 16 for the first 12 28-day cycles, and then 56 mg/m² intravenously on days 1 and 15 in all subsequent cycles. Lenalidomide was started at cycle 1 at a dose of 10 mg orally on days 1–21 of a 28-day cycle.

Before and after carfilzomib treatment intravenous hydration (250–500 ml) was required during first cycle. All patients received rasburicase intravenously during first cycle to correct uric acid concentrations to normal concentrations before receiving carfilzomib doses. Patients also received antibacterial prophylaxis (cotrimoxazole or levofloxacin), antiviral prophylaxis (acyclovir or valacyclovir to prevent herpes simplex virus or varicella zoster virus infections), and antithrombotic prophylaxis. Treatment with bisphosphonates for 2 years was recommended after correction of factors predisposing to renal deterioration. All men and women of childbearing potential used contraception during the study.

Patients were withdrawn from protocol treatment in case of death, non-compliance of patient, patient not eligible in hindsight, excessive toxicity, disease progression, or pregnancy (female patient). Patients could also leave the study at any time for any reason. Patients who were withdrawn from treatment for reasons other than death, continued to be followed up.

At inclusion, laboratory tests (blood cell count, creatinine, calcium, LDH, β-2 microglobulin, albumin, hepatic enzymes, monoclonal proteins using serum and urine immunofixation combined with protein electrophoresis, and FLC assessment) were done locally. Bone marrow aspiration (for morphology and cytogenetic analysis by fluorescence in-situ hybridisation [FISH] on purified tumour cells), and biopsy were also performed. The cutoff level for the presence of a specific cytogenetic abnormality was set at 10% for chromosomal imbalances and 15% for translocations. Assessment of osteolytic disease was done for all patients at inclusion by low-dose whole-body CT scan or conventional radiography.

Laboratory measurements of 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). Although the study protocol specified that at these timepoints bone marrow aspirates should have been collected to confirm complete response and assess minimal residual disease, bone marrow aspiration was performed at a markedly lower frequency in the majority of patients. Response and disease progression were defined per the specific response criteria for primary plasma cell leukaemia as defined by the International Myeloma Working Group,[5] based on investigator judgement. Imaging (MRI or [PET-]CT whole body) was repeated for response evaluation in case of presence of soft tissue plasmacytomas at the time of study enrolment. Minimal residual disease status was assessed by next-generation flow cytometry (sensitivity 1×10^{-5}) using bone marrow aspirates obtained at the time of suspected complete response or stringent complete response.[29] Samples were stained using the EuroFlow liquid reference reagents and EuroFlow protocols and data were acquired on a FACSLyric flow cytometer (BD Biosciences, Erebodegem, Belgium) using EuroFlow instrument settings (EuroFlow, Rotterdam, The Netherlands).[29] The International Staging System (ISS) disease stage was derived from the combination of serum β2-microglobulin and albumin concentrations, with higher stages indicating more advanced disease. Cytogenetic abnormalities and LDH concentrations were also considered for definition of revised ISS stage.[19] 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

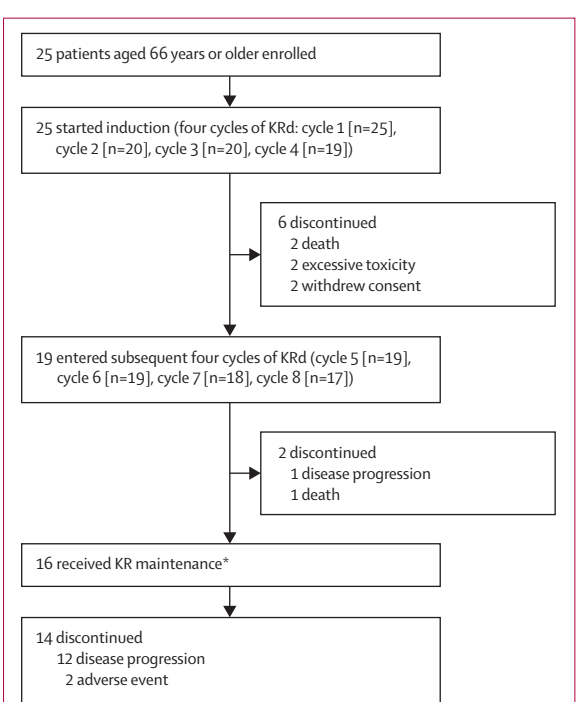

Figure 2: **Trial profile for patients aged 66 years or older**
KRd=carfilzomib, lenalidomide, and dexamethasone. KR=carfilzomib and lenalidomide. *One patient had not yet started maintenance as of the data cutoff date.

study visit (except during planned hospitalisations for autologous HSCT or allogeneic HSCT); events were graded based on the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), but only adverse events of CTCAE grade 2 or greater were collected in the database. Other safety data collected included clinical laboratory testing, electrocardiography, physical examinations, and vital signs. An independent data and safety monitoring board periodically reviewed the safety data.

	Younger patients (aged 18–65 years; n=36)	Older patients (aged ≥66 years; n=25)
Age, years	60 (52–63)	71 (69–74)
Race		
White	31 (86%)	24 (96%)
African	2 (6%)	0
Asian	2 (6%)	0
Other	1 (3%)	1 (4%)
Sex		
Male	20 (56%)	12 (48%)
Female	16 (44%)	13 (52%)
Time from diagnosis to screening, days	5 (3–9)	5 (2–8)
M-protein		
IgG	11 (31%)	14 (56%)
IgA	7 (19%)	0
IgM	0	1 (4%)
IgD	2 (6%)	2 (8%)
Light chain only	16 (44%)	8 (32%)
Extramedullary plasmacytomas ≥1*	6 (17%)	3 (12%)
Proportion of bone marrow plasma cells in smear, %	66 (40–83)	45 (31–73)
Proportion of bone marrow plasma cells in biopsy, %	80 (70–90)	80 (73–90)
Median peripheral blood plasma cells, $\times 10^9$ per L	4·1 (2·5–7·2)	3·8 (2·5–11·4)
Proportion of peripheral blood plasma cells, %	31 (24–52)	29 (23–50)
CRAB		
Calcium >2·75 mM	8 (22%)	3 (12%)
Creatinine >177 μM	8 (22%)	5 (20%)
Haemoglobin <6·2 mM	24 (67%)	15 (60%)
Bone disease	24 (67%)	17 (68%)
Corrected calcium, mM	2·5 (2·3–2·7)	2·5 (2·3–2·6)
Glomerular filtration rate, mL per min	54 (38–88)	56 (37–76)
Haemoglobin, mM	5·8 (5·1–6·5)	5·8 (5·3–6·7)
Platelet count, $\times 10^9$ per L	111 (48–180)	142 (65–203)
Albumin, g/L	36 (30–40)	35 (30–40)
β2 microglobulin, mg/L	7·8 (4·5–15·0)	7·3 (5·3–12·6)
WHO performance-status score		
0	6 (17%)	4 (16%)
1	18 (50%)	11 (44%)
2	8 (22%)	6 (24%)
3	4 (11%)	4 (16%)
ISS stage†		
1	4 (11%)	2 (9%)
2	9 (25%)	4 (17%)
3	23 (64%)	17 (74%)

(Table 1 continues on next page)

Outcomes

The primary endpoint for the study was progression-free survival (defined as the time from registration until progression or death due to any cause, whichever comes first; patients still alive were censored at the last response evaluation). Secondary endpoints were overall survival (defined as time from registration until death from any cause; patients still alive were censored at the date last known to be alive), response, safety, and toxicity. Other secondary objectives were to assess the prognostic value of baseline risk factors (including FISH abnormalities, β2-microglobulin, LDH, gene expression profile, and mutations as determined by sequencing), the prognostic value of minimal residual disease-negativity, and to establish the frequency of second primary malignancies. Because sequencing and gene expression assessments are ongoing, and patients are few, the prognostic value of baseline risk factors is not reported in the manuscript. In addition, as bone marrow collection for minimal residual disease evaluation was performed less frequently than was indicated in the protocol and at very different time points, landmark analyses to assess the prognostic value of minimal residual disease negativity were not performed. The endpoints were separately studied in younger and older patients.

Statistical analysis

Progression-free survival was the primary endpoint of this study and used for sample size calculation. Based on historical treatment data, the median progression-free survival for younger patients was estimated as 9 months. A true median progression-free survival with the treatment in this trial of at 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, a total of 36 patients was needed (2-sided significance level $\alpha=0\cdot05$ and power $1-\beta=0\cdot80$).[20] For older patients, median progression-free survival was approximately 6·5 months (based on historical treatment of non-transplant eligible patients). For an improvement of progression-free survival to median 15·3 months, a total of 25 patients was required (assuming uniform accrual of 4 years, additional follow up of 1 year, with similar power and significance level as for younger patients).[20] The required number of patients for both age groups was initially higher in our study. However, early after initiation of the trial, several new retrospective studies showed worse progression-free survival for patients with primary plasma cell leukaemia treated outside of clinical trials, compared with what was reported previously, and therefore the required number of patients for both age groups was decreased in the first amendment (Oct 7, 2019) to the numbers as described here.

Survival curves for progression-free survival and overall survival were computed using the Kaplan-Meier method. Median progression-free survival, 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 progression-free survival was larger than 9 months, whereas for the older patients it should be larger than 6·5 months.

Response rates were described as percentages with 95% CI. Treatment toxicity was analysed by the incidence of adverse events CTCAE grade 2 or greater. Data from all participants who received any study drug were included in the safety analyses.

Time-to-event and response endpoints were analysed in the intention-to-treat (ITT) population, irrespective of the actual treatment received.

Median duration of maintenance treatment was calculated using the Kaplan-Meier method.

As post-hoc analyses, we evaluated progression-free survival and overall survival from the date of first autologous HSCT in patients who received at least one autologous HSCT, as well as from the date of second transplant in patients who received double autologous HSCT or autologous–allogeneic tandem HSCT. Progression-free survival and overall survival were compared between patients who received autologous HSCT only and those who received autologous-allogeneic tandem HSCT; 2-year progression-free survival and overall survival were also compared between these groups in a post-hoc analysis. Post-hoc analyses were also performed to evaluate the association between response after the first four KRd induction cycles and subsequent progression-free survival and overall survival. All analyses were performed using Stata (version 16.1) and R (version 4.2.1 or higher).

For each of the two age groups, one interim analysis was performed, at the time that complete data of the first four cycles of KRd induction were available from the first 15 registered patients (older and younger patients separately). The aim of these interim analyses was primarily to describe adverse events and response observed during induction therapy with KRd. Results of the interim analyses were presented confidentially to an independent data and safety monitoring board, as well as to the principal investigators. The trial was registered at www.trialregister.nl (until June 2022) and https://trialsearch.who.int/ as NTR5350.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 23, 2015, till Aug 5, 2021, we enrolled 61 patients with primary plasma cell leukaemia (36 aged 18–65 years and 25 aged ≥66 years; figures 1 and 2). In the cohort with younger patients, the median age was 60 years (IQR 52–63), and 20 patients (56%) were male (table 1). In the older patients cohort, the median age was 71 years (IQR 69–74) and 12 patients (48%) were male (table 1). Patients presented with a high tumour burden, advanced disease stage (ISS and R-ISS), and high frequency of poor-risk features (eg, unfavourable cytogenetic abnormalities or elevated LDH).

	Younger patients (aged 18–65 years; n=36)	Older patients (aged ≥66 years; n=25)
(Continued from previous page)		
Cytogenetic abnormality‡		
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 high-risk cytogenetic abnormalities¶	12 (34%)	3 (14%)
LDH > ULN	21 (58%)	13 (52%)
Revised ISS stage‖		
I	1 (3%)	0
II	16 (47%)	12 (55%)
III	17 (50%)	10 (45%)

Data are n (%) or median (IQR). CRAB=hypercalcaemia, renal failure, anaemia, and bone disease. 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 or amplification 1q, 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; and two or more high-risk cytogenetic abnormalities, 35 and 22 patients. §The median percentage of del(17p)-positive cells in fluorescence in-situ hybridisation studies was 81% (IQR 10–98) for younger patients and 92% (86–100) for elderly patients. ¶Defined as presence of two 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).

Table 1: **Characteristics of patients at baseline**

The cutoff date for this analysis was March 2, 2023. In the cohort of younger patients, the median follow-up was 43·5 months (IQR 27·7–67·8), and 27 events of disease progression or death were reported. The median progression-free survival was 15·5 months (95% CI 9·4–38·4; figure 3), which was sufficient to reject our null hypothesis (median progression-free survival of 9 months). The best response achieved during the entire trial was partial response or better in 31 (86%), very good partial response or better in 30 (83%), and complete response or better in 18 (50%) patients (table 2). Among the 20 patients evaluated for minimal residual disease, 16 (80%) were negative for minimal residual disease (at a threshold of one tumour cell per 10^5 white cells).

20 patients (56%) have died (relapse-related mortality in 19 patients, and non-relapse mortality in one patient [withdrawn from protocol treatment; human meta-pneumovirus respiratory infection 4 months after allogeneic HSCT]). Median overall survival was

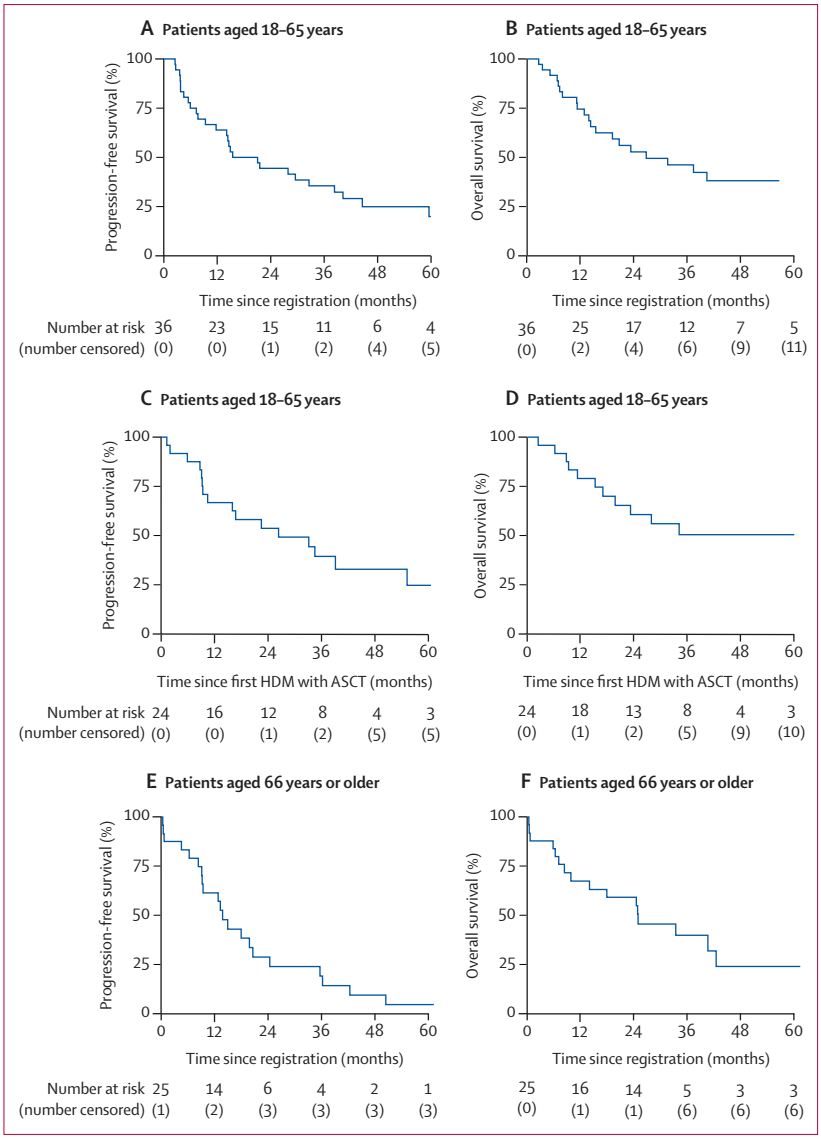

Figure 3: **Survival outcomes**
There were: (A) 27 events of disease progression or death, (B) 20 events of death, (C) 16 events of progression or death, (D) 11 events of death, (E) 21 events of progression or death, and (F) 18 events of death. ASCT=autologous stem-cell transplantation. HDM=high-dose melphalan.

28·4 months (95% CI 15·1—not evaluable [NE]; figure 3) with a low early mortality rate (8·3% at 6 months).

Of the 36 younger patients who started induction treatment, 33 (92%) received the planned four cycles of induction treatment and three (8%) patients withdrew from protocol treatment (one patient because of disease progression, one because of renal failure and suboptimal response, and one because of withdrawal of consent; figure 1). Median dose intensities were 99% (IQR 92–100) for carfilzomib, 95% (60–100) for lenalidomide, and 100% (88–100) for dexamethasone. Response after induction was partial response or better in 30 (83%), very good partial response or better in 27 (75%), and complete response or better in five (14%) of patients (table 2). Directly after induction therapy, three (8%) patients had disease progression, and one (3%) patient withdrew from protocol treatment because of withdrawal of consent.

Two of the 29 patients who were considered for autologous HSCT were not fit enough and continued with KRd treatment (total of eight courses), followed by maintenance treatment. The other 27 patients successfully harvested peripheral blood stem cells, with four patients needing two different stem-cell mobilisation attempts. The median number of collected stem cells was $4·9\times10^6$ cells per kg (IQR 4·2–8·1). Although numbers are small, for patients who completed four cycles of KRd induction and continued protocol treatment, there was no significant association between depth of response and progression-free survival or overall survival (appendix p 9).

After stem-cell collection, three of 27 patients developed disease progression, whereas 24 received HDM with autologous HSCT. The overall response rate after HDM with autologous HSCT was 96% with complete response or better in eight (33%) of the 24 patients and very good partial response or better in 23 (96%; table 2).

Of the 24 patients who underwent autologous HSCT, two withdrew from protocol treatment because of progression (one patient experienced disease progression directly after HDM with autologous HSCT, and another patient achieved very good partial response after transplantation, but relapsed soon thereafter). Six of the remaining 22 patients were considered for allogeneic HSCT, and therefore received directly after autologous HSCT two additional KRd consolidation cycles. Five of these six patients underwent reduced-intensity allogeneic HSCT with stem cells from an HLA-matched related donor (n=1), HLA-matched unrelated donor (n=2), or haploidentical related donor (n=2), whereas one patient was deemed ineligible for allogeneic HSCT after KRd consolidation. Acute graft-versus-host disease developed in one patient (grade 2), and chronic graft-versus-host disease developed in another patient (severe). Response after allogeneic HSCT was very good partial response or better in all five (100%) and complete response or better in four (80%) patients (table 2).

16 patients did not receive allogeneic HSCT, 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 with autologous HSCT followed by four cycles of KRd consolidation, and four patients declined a second HDM with autologous HSCT and continued directly with KRd consolidation. The overall response after second autologous HSCT was 100% with complete response or better in three (25%) and very good partial response or better in 12 (100%) patients (table 2).

18 patients received maintenance, one (6%) patient only lenalidomide, one (6%) only carfilzomib, and 16 (89%) carfilzomib-lenalidomide. This included three patients

	Patients aged 18–65 years					Patients aged 66 years or older		
	Response after induction (n=36)	Response after first autologous HSCT (n=24)	Response after second autologous HSCT (n=12)	Response after allogeneic HSCT (n=5)	Best response on protocol (n=36)	Response after induction cycles 1–4 (n=25)	Response after induction cycles 5–8 (n=19)	Best response on protocol (n=25)
Partial response or better	30 (83%)	23 (96%)	12 (100%)	5 (100%)	31 (86%)	20 (80%)	18 (95%)	20 (80%)
Very good partial response or better	27 (75%)	23 (96%)	12 (100%)	5 (100%)	30 (83%)	17 (68%)	17 (89%)	17 (68%)
Complete response or better	5 (14%)	8 (33%)	3 (25%)	4 (80%)	18 (50%)	6 (24%)	8 (42%)	9 (36%)
Stringent complete response	1 (3%)	3 (13%)	1 (8%)	2 (40%)	12 (33%)	3 (12%)	4 (21%)	5 (20%)
Complete response	4 (11%)	5 (21%)	2 (17%)	2 (40%)	6 (17%)	3 (12%)	4 (21%)	4 (16%)
Very good partial response	22 (61%)	15 (63%)	9 (75%)	1 (20%)	12 (33%)	11 (44%)	9 (47%)	8 (32%)
Partial response	3 (8%)	0	0	0	1 (3%)	3 (12%)	1 (5%)	3 (12%)
Stable disease	1 (3%)	0	0	0	1 (3%)	1 (4%)	0	1 (4%)
Progressive disease	3 (8%)	1 (4%)	0	0	2 (6%)	0	1 (5%)	0
Unevaluable	2 (6%)*	0	0	0	2 (6%)	5 (20%)†	0	5 (20%)

Data are n (%).HSCT=haematopoietic stem-cell transplantation. *Two 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. †Five patients were not evaluable for response because of early death in two patients (10 and 15 days after treatment initiation), excessive toxicity in two patients (protocol treatment was stopped 14 days and 19 days after its initiation), and withdrawal of consent in one patient (28 days after treatment initiation).

Table 2: **Response rate in patients aged 18–65 years and patients aged 66 years or older**

after allogeneic HSCT, 2 patients who were not eligible for autologous HSCT and received maintenance after eight cycles of KRd, and 13 patients after four cycles of KRd consolidation following single (n=2) or double autologous HSCT (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), these values were derived with Kaplan-Meier analysis. Ten (56%) patients were in very good partial response, one (6%) in complete response, and seven in stringent complete response (39%) before initiation of maintenance. At the data cutoff, seven of the 18 patients, who started with maintenance treatment, were still receiving maintenance, whereas ten patients developed progressive disease and one stopped maintenance because of an infection (pulmonary sepsis). Five of the ten patients with very good partial response had improvement in response during maintenance treatment (complete response in one and stringent complete response in four).

For the 24 patients who underwent first HDM with autologous HSCT, median progression-free survival and overall survival were 26·2 months (95% CI 9·4–54·7) and not estimable (95% CI 17·0–NE) from date of first autologous HSCT, respectively (figure 3). In a post-hoc analysis from the date of the second transplant, progression-free survival was comparable between patients who received a second autologous HSCT or allogeneic HSCT (median progression-free survival was 31·2 months [95% CI 12·8–NE] for patients who received a second autologous HSCT, and 49·2 months [3·6–NE] for those who underwent allogeneic HSCT; the progression-free survival at 2 years was 58% [27–80] for the second autologous HSCT group and 60% [13–88] for the allogeneic HSCT patients; appendix p 10). Overall survival from the date of second transplant was also comparable in both groups (median overall survival not estimable (95% CI 20·0–NE) for the patients who underwent second autologous HSCT, and not estimable (5·5–NE) for allogeneic HSCT patients; the 2-year overall survival was 82% (45–95) for the second autologous HSCT patients and 53% (7–86) for allogeneic HSCT patients).

Fourteen (39%) of the 36 patients received second-line treatment. Pomalidomide-cyclophosphamide-dexamethasone was the most common second-line therapy (six [43%] of the 14 patients; appendix p 4).

In the cohort of older patients, the median follow-up was 32·0 months (IQR 24·7–34·6) and 21 events of disease progression or death have been reported. The median progression-free survival was 13·8 months (95% CI 9·2–35·5; figure 3), which was sufficient to reject the null hypothesis (median progression-free survival 6·5 months). Best response on protocol treatment was partial response or better in 20 (80%) of the participants, very good partial response or better in 17 (68%), and complete response or better in nine (36%; table 2). Five (63%) of eight patients with complete response or better who could be evaluated for minimal residual disease, achieved minimal residual disease negativity (10^{-5}).

At the data cutoff, 18 (72%) of 25 patients had died (relapse-related mortality occurred in 12 patients, non-relapse mortality in six patients [three on protocol treatment and three after withdrawal from protocol treatment]). Reasons for non-relapse mortality on protocol treatment were two infections and one unknown

cause of death. Reasons for non-relapse mortality after withdrawal from protocol treatment were second primary malignancy (n=1, duodenal adenocarcinoma), infection (n=1), and disseminated intravascular coagulation (n=1). Median overall survival was 24·8 months (95% CI 14·0–NE; figure 3). Early mortality was low at 16% at 6 months (95% CI 0–29).

Of the 25 older patients, 19 completed the first four cycles of KRd induction (figure 2). Early death occurred in two patients, 10 and 15 days after start of treatment (cause of death was: unknown in one participant and *Staphylococcus aureus*-related pneumonia in one, respectively). During or directly after the first four cycles of KRd, four additional patients were withdrawn from protocol treatment, two because of excessive toxicity and two withdrew consent. The median dose intensities were 76% (IQR 72–82) for carfilzomib, 66% (43–71) for lenalidomide, and 50% (47–62) for dexamethasone. Partial response or better after the first four KRd induction cycles was observed in 20 (80%), very good partial response or better in 17 (68%), and complete response or better in six (24%; table 2) participants. Although numbers are small, for patients who completed four cycles of KRd induction and continued KRd treatment, there was no significant association between depth of response and progression-free survival or overall survival (appendix p 11). 19 patients continued with subsequent four KRd cycles. A total of eight cycles of KRd induction was received by 17 of 19 patients, whereas one patient developed progression and one patient, who had achieved stringent complete response, died 6 months after start of induction treatment because of influenza-related pneumonia. Depth of response improved with these four additional induction cycles (of 19 patients 18 [95%] had partial response or better, 17 [89%] very good partial response or better, and eight [42%] complete response or better; table 2). 16 of 17 patients started maintenance treatment; one patient did not yet start with maintenance therapy after completing induction treatment at the time of data cutoff (three [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 (5·6–32·4). The median duration of maintenance treatment until discontinuation of both drugs was 10·3 months (5·6–42·6), these values were derived with Kaplan-Meier analysis. One of ten patients who initiated maintenance treatment with less than complete response, had an improvement in depth of response (very good partial response to stringent complete response). At the data cutoff, two of the 16 patients were still receiving maintenance, whereas 12 patients developed disease progression and two stopped because of adverse events. 13 (52%) of the 25 patients received second line treatment (appendix p 4).

Adverse events of grade 2 or worse, that occurred during the trial, except those related to transplantation (standard of care), are summarised in table 3 and 4. In the cohort

	Adverse events during induction (n=36)				Adverse events during consolidation (n=21)*				Adverse events on maintenance (n=18)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Any haematological adverse event	2 (6%)	2 (6%)	1 (3%)	0	1 (5%)	1 (5%)	0	0	0	4 (22%)	2 (11%)	0
Neutropenia	1 (3%)	0	0	0	0	1 (5%)	0	0	0	4 (22%)	0	0
Thrombocytopenia	1 (3%)	1 (3%)	1 (3%)	0	0	0	0	0	0	0	2 (11%)	0
Anaemia	3 (8%)	1 (3%)	0	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Any non-haematological toxicity	10 (28%)	11 (31%)	5 (14%)	0	5 (24%)	2 (10%)	2 (10%)	0	7 (39%)	5 (28%)	1 (6%)	0
Infections and infestations	6 (17%)	2 (6%)	0	0	4 (19%)	0	1 (5%)	0	5 (28%)	4 (22%)	0	0
Cardiac disorders	2 (6%)	2 (6%)	0	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	10 (28%)	2 (6%)	0	0	0	0	0	0	3 (17%)	1 (6%)	0	0
Gastrointestinal disorders	5 (14%)	2 (6%)	0	0	2 (10%)	0	0	0	4 (22%)	1 (6%)	0	0
Nervous system disorders	1 (3%)	0	0	0	2 (10%)	0	0	0	2 (11%)	0	0	0
Vascular disorders	4 (11%)	2 (6%)	0	0	1 (5%)	1 (5%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Metabolism and nutrition disorders	2 (6%)	1 (3%)	1 (3%)	0	0	1 (5%)	0	0	0	0	0	0
Renal and urinary disorders	0	0	2 (6%)	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Respiratory, thoracic, and mediastinal disorders	5 (14%)	2 (6%)	0	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Neoplasms benign, malignant, and unspecified	0	0	0	0	0	0	0	0	0	0	0	0
Psychiatric disorders	1 (3%)	0	2 (6%)	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	4 (11%)	1 (3%)	0	0	0	0	0	0	0	0	0	0
Hepatobiliary	0	0	0	0	0	0	0	0	0	0	0	0

Data are n (%). HDM=high-dose melphalan. ASCT=autologous stem cell transplantation. *Ten patients received carfilzomib–lenalidomide–dexamethasone consolidation after first HDM with ASCT, and 11 after second HDM with ASCT.

Table 3: **Adverse events in patients aged 18–65 years**

	Adverse events during induction cycles 1–4 (n=25)				Adverse events during induction cycles 5–8 (n=19)				Adverse events on maintenance (n=16)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Any haematological adverse event	1 (4%)	2 (8%)	2 (8%)	0	1 (5%)	1 (5%)	0	0	2 (13%)	0	0	0
Neutropenia	0	1 (4%)	1 (4%)	0	0	1 (5%)	0	0	0	0	0	0
Thrombocytopenia	0	1 (4%)	2 (8%)	0	0	1 (5%)	0	0	1 (6%)	0	0	0
Anaemia	1 (4%)	2 (8%)	0	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Any non-haematological toxicity	4 (16%)	11 (44%)	3 (12%)	2 (8%)	5 (26%)	3 (16%)	0	1 (5%)	4 (25%)	6 (38%)	1 (6%)	0
Infections and infestations	4 (16%)	6 (24%)	1 (4%)	1 (4%)	3 (16%)	3 (16%)	0	1 (5%)	2 (12%)	3 (19%)	0	0
Cardiac disorders	2 (8%)	0	1 (4%)	0	1 (5%)	0	0	0	0	0	0	0
General disorders and administration site conditions	2 (8%)	2 (8%)	0	1 (4%)	2 (11%)	0	0	0	4 (25%)	1 (6%)	0	0
Gastrointestinal disorders	1 (4%)	2 (8%)	0	0	0	0	0	0	2 (12%)	2 (12%)	1 (6%)	0
Nervous system disorders	0	0	0	0	2 (11%)	0	0	0	1 (6%)	0	0	0
Vascular disorders	1 (4%)	2 (8%)	0	0	1 (5%)	0	0	0	1 (6%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (4%)	0	0	0	0	0	0	0	1 (6%)	0	0	0
Metabolism and nutrition disorders	1 (4%)	2 (8%)	0	0	0	0	0	0	0	1 (6%)	0	0
Renal and urinary disorders	0	0	1 (4%)	0	0	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	2 (8%)	3 (12%)	1 (4%)	0	0	0	0	0	2 (12%)	1 (6%)	0	0
Neoplasms benign, malignant, and unspecified	0	0	0	0	0	0	0	0	0	1 (6%)	0	0
Psychiatric disorders	3 (12%)	0	0	0	1 (5%)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	3 (12%)	2 (8%)	0	0	0	0	0	0	3 (19%)	0	0	0
Hepatobiliary	0	1 (4%)	1 (4%)	0	0	0	0	0	0	0	0	0

Table 4: **Adverse events in patients aged 66 years or older**

with younger patients (n=36), cumulative haematological and non-haematological toxicity grade 3 or greater during induction was reported in three (8%) and 16 (44%) patients, respectively (table 3). Non-haematological toxicity grade 3 or greater during induction included cardiac (in two [6%] patients), gastrointestinal (in two [6%] patients), respiratory (in two [6%] patients), vascular (in two [6%] patients), renal (in two [6%] patients), and infectious (in two [6%] patients) adverse events. During consolidation treatment the grade 3 or greater cumulative haematological (in one [5%] of 21 patients) and non-haematological toxicity (in four [19%] patients) was lower compared with that observed during induction therapy (table 3). Adverse events during maintenance are also shown in table 3.

Two patients discontinued treatment because of adverse events (one patient after allogeneic HSCT because of multiple infections and one because of myocardial infarction during hospitalization because of pulmonary sepsis and choledocholithiasis requiring endoscopic retrograde cholangiopancreatography with biliary stenting and sphincterotomy). One patient developed myelodysplastic syndrome during pomalidomide–cyclophosphamide–dexamethasone treatment as second line treatment (2·5 years from discontinuing protocol treatment). 26 (72%) of 36 patients experienced a total of 64 treatment-related serious adverse events. Approximately a third (30%) of all serious adverse events occurred during the first KRd induction cycle and 44% occurred during induction treatment. The most common treatment-related serious adverse events were infections (appendix pp 5–6). No treatment-related mortality was observed. To manage adverse events during induction, the dose of carfilzomib was decreased (with at least 20%) in seven (19%) of the 36 patients, of lenalidomide in 18 (50%), and of dexamethasone in 13 (36%). During post-transplant consolidation, the dose of carfilzomib was decreased in three (14%) of the 21 patients, of lenalidomide in four (19%), and of dexamethasone in five (24%).

In the cohort with older patients (n=25), the rate of cumulative haematological and non-haematological toxicity grade 3 or greater during the first four KRd induction cycles was 16% (n=4) and 64% (n=16), respectively (table 4). Non-haematological toxicity grade 3 or greater during the first 4 KRd cycles included cardiac (in one [4%] patient), gastrointestinal (in two [8%] patients), respiratory (in four [16%] patients), vascular (in two [8%] patients), renal (in one [4%] patient), and infectious (in eight [32%] patients) adverse events. During KRd induction cycles 5–8 the cumulative haematological and non-haematological toxicity grade 3 or greater was lower compared with that observed during the first four induction cycles (in one [5%] patient and in four [21%] of 19 patients, respectively; table 4). Adverse events during maintenance are shown in table 4.

Study discontinuation due to adverse events occurred in two patients (one patient because of progressive neurological decline during maintenance, and one patient because of duodenal adenocarcinoma that developed during maintenance therapy, 30 months after initiation of treatment). 19 (76%) of 25 patients

experienced a total of 54 serious adverse events. Approximately a third (35%) of all serious adverse events occurred during the first KRd induction cycle and 61% occurred during the first four cycles of induction treatment. The most common treatment-related serious adverse events were infections (appendix pp 7–8). To manage adverse events, the dose of carfilzomib was decreased (with at least 20%) in 12 (48%) of the 25 patients during induction treatment (cycles 1–8), of lenalidomide in 16 (64%), and of dexamethasone in 17 (68%). Three treatment-related deaths were reported: two infections and one unknown cause of death.

Discussion

We report the final results from the EMN12/HOVON-129 study, in which we treated patients with primary plasma cell leukaemia with a carfilzomib and lenalidomide-based treatment in conjunction with stem cell transplantation for younger patients. This study met its primary endpoints with improved progression-free survival, compared with historical cohorts. We also observed a high rate of deep responses with carfilzomib and lenalidomide-based treatment in both younger and older patients with primary plasma cell leukaemia.

In the cohort of younger patients, there was 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 minimal residual disease (sensitivity of 10^{-5}). Although the median progression-free survival of 15·5 months exceeded the study hypothesis (median progression-free survival of 9 months), progression-free survival remains substantially inferior to what can be achieved with similar treatment strategies in newly diagnosed transplant-eligible patients with multiple myeloma including those with high-risk cytogenetic abnormalites.[17,21]

In the Intergroupe Francophone du Myélome (IFM) study, which used comparable eligibility criteria, 39 patients were treated with bortezomib combined with chemotherapy (ie, bortezomib–cyclophosphamide–dexamethasone alternating with bortezomib–adriamycin–dexamethasone) followed by HDM with autologous HSCT, and then either allogeneic HSCT or a second autologous HSCT and subsequent bortezomib–lenalidomide maintenance.[13] An identical proportion of patients received a first course of HDM with autologous HSCT (67% in both studies).[13] Despite the limitations of cross-trial comparisons, our data suggests that KRd induction led to a larger proportion of patients with primary plasma cell leukaemia achieving very good partial response or better compared with the IFM study (75% *vs* 36%). This suggests the superiority of a combination therapy regimen based on a proteasome inhibitor and immunomodulatory drug over a proteasome inhibitor and chemotherapy in newly diagnosed primary plasma cell leukemia.[17,22] Also, best response achieved during the entire treatment was superior in our series compared with the IFM study (86% *vs* 69% with partial response or better, 83% *vs* 59% with very good partial response or better, and 50% *vs* 33% with complete response or better). Surprisingly, the higher quality response with KRd did not translate into an improved progression-free survival or overall survival, compared with what was achieved in the IFM study (median progression-free survival of 15·1 months and median overall survival of 36·3 months). This difference could be related to differences in patient populations with a higher proportion of patients with high-risk abnormalities (47% *vs* 28% for del[17p]) and more advanced disease (64% *vs* 43% for ISS stage 3) in our study, compared with the IFM study.[13]

The high activity of KRd induction allowed two-thirds of patients to undergo a first course of HDM with autologous HSCT. Of note, these patients had a pronounced improvement in progression-free survival (median progression-free survival of 26·2 months from date of first autologous HSCT). This compares favourably with the retrospective analyses reported by EBMT[9,16] and CIBMTR[11,15] studies (median progression-free survival from autologous HSCT of approximately 14 months), which might be related to the relatively frequent application of a second transplant (48·6% of patients) and effective carfilzomib and lenalidomide-based consolidation and maintenance to sustain remission in our study. Because of the small sample size, it is difficult to draw conclusions about the efficacy of allogeneic HSCT versus second autologous HSCT. However, allogeneic HSCT did not improve survival, compared with what was achieved with second autologous HSCT. This is in accordance with other reports showing little efficacy of allogeneic HSCT in controlling residual disease in primary plasma cell leukaemia, combined with high non-relapse mortality.[11,13,15] However, the efficacy of allogeneic HSCT might have been negatively affected by the use of polyclonal antithymocyte globulins as part of the conditioning regimen in three of five patients, because of the potential elimination of tumour-reactive T-cells by these antibodies.

Our results are especially promising in the cohort of older patients with an increase in both rate and quality of response, compared with what has been reported before in transplant-ineligible patients.[4,14] In addition, the median progression-free survival of 13·8 months represents an improvement over the historical expectation of 6·5 months.[4,7] Furthermore, the median overall survival in our study (24·8 months) doubled compared with what has been reported in retrospective studies and, particularly, in the only other prospective trial (with the doublet lenalidomide–dexamethasone) so far conducted in transplant-ineligible, older patients with primary plasma cell leukaemia (median overall survival of 12 months).[14]

Importantly, with the measures to mitigate risks of adverse events, such as per-protocol hydration, infectious