Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study

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Summary

Background The emergence of highly active novel agents has led some to question the role of autologous haematopoietic stem-cell transplantation (HSCT) and subsequent consolidation therapy in newly diagnosed multiple myeloma. We therefore compared autologous HSCT with bortezomib–melphalan–prednisone (VMP) as intensification therapy, and bortezomib–lenalidomide–dexamethasone (VRD) consolidation therapy with no consolidation.

Methods In this randomised, open-label, phase 3 study we recruited previously untreated patients with multiple myeloma at 172 academic and community practice centres of the European Myeloma Network. Eligible patients were aged 18–65 years, had symptomatic multiple myeloma stage 1–3 according to the International Staging System (ISS), measurable disease (serum M protein >10 g/L or urine M protein >200 mg in 24 h or abnormal free light chain [FLC] ratio with involved FLC >100 mg/L, or proven plasmacytoma by biopsy), and WHO performance status grade 0–2 (grade 3 was allowed if secondary to myeloma). Patients were first randomly assigned (1:1) to receive either four 42-day cycles of bortezomib (1·3 mg/m² administered intravenously or subcutaneously on days 1, 4, 8, 11, 22, 25, 29, and 32) combined with melphalan (9 mg/m² administered orally on days 1–4) and prednisone (60 mg/m² administered orally on days 1–4) or autologous HSCT after high-dose melphalan (200 mg/m²), stratified by site and ISS disease stage. In centres with a double HSCT policy, the first randomisation (1:1:1) was to VMP or single or double HSCT. Afterwards, a second randomisation assigned patients to receive two 28-day cycles of consolidation therapy with bortezomib (1·3 mg/m² either intravenously or subcutaneously on days 1, 4, 8, and 11), lenalidomide (25 mg orally on days 1–21), and dexamethasone (20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12) or no consolidation; both groups received lenalidomide maintenance therapy (10 mg orally on days 1–21 of a 28-day cycle). The primary outcomes were progression-free survival from the first and second randomisations, analysed in the intention-to-treat population, which included all patients who underwent each randomisation. All patients who received at least one dose of study drugs were included in the safety analyses. This study is registered with the EU Clinical Trials Register (EudraCT 2009-017903-28) and ClinicalTrials.gov (NCT01208766), and has completed recruitment.

Findings Between Feb 25, 2011, and April 3, 2014, 1503 patients were enrolled. 1197 patients were eligible for the first randomisation, of whom 702 were assigned to autologous HSCT and 495 to VMP; 877 patients who were eligible for the first randomisation underwent the second randomisation to VRD consolidation (n=449) or no consolidation (n=428). The data cutoff date for the current analysis was Nov 26, 2018. At a median follow-up of 60·3 months (IQR 52·2–67·6), median progression-free survival was significantly improved with autologous HSCT compared with VMP (56·7 months [95% CI 49·3–64·5] *vs* 41·9 months [37·5–46·9]; hazard ratio [HR] 0·73, 0·62–0·85; p=0·0001). For the second randomisation, the number of events of progression or death at data cutoff was lower than that preplanned for the final analysis; therefore, the results from the second protocol-specified interim analysis, when 66% of events were reached, are reported (data cutoff Jan 18, 2018). At a median follow-up of 42·1 months (IQR 32·3–49·2),consolidation therapy with

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VRD significantly improved median progression-free survival compared with no consolidation (58·9 months [54·0–not estimable] *vs* 45·5 months [39·5–58·4]; HR 0·77, 0·63–0·95; p=0·014). The most common grade ≥3 adverse events in the autologous HSCT group compared to the VMP group included neutropenia (513 [79%] of 652 patients *vs* 137 [29%] of 472 patients), thrombocytopenia (541 [83%] *vs* 74 [16%]), gastrointestinal disorders (80 [12%] *vs* 25 [5%]), and infections (192 [30%] *vs* 18 [4%]). 239 (34%) of 702 patients in the autologous HSCT group and 135 (27%) of 495 in the VMP group had at least one serious adverse event. Infection was the most common serious adverse event in each of the treatment groups (206 [56%] of 368 and 70 [37%] of 189). 38 (12%) of 311 deaths from first randomisation were likely to be treatment related: 26 (68%) in the autologous HSCT group and 12 (32%) in the VMP group, most frequently due to infections (eight [21%]), cardiac events (six [16%]), and second primary malignancies (20 [53%]).

Interpretation This study supports the use of autologous HSCT as intensification therapy and the use of consolidation therapy in patients with newly diagnosed multiple myeloma, even in the era of novel agents. The role of high-dose chemotherapy needs to be reassessed in future studies, in particular in patients with undetectable minimal residual disease after four-drug induction regimens including a monoclonal antiboby combined with an immunomodulatory agent and a proteasome inhibitor plus dexamethasone.

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Introduction

Over the past two decades, the treatment of multiple myeloma has been transformed by the emergence of new classes of drugs, including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies.[1] Incorporation of these drugs into treatment regimens for patients with newly diagnosed multiple myeloma[2,3] has increased the rates and depth of response[4–6] up to values previously reported with conventional chemotherapy plus autologous haematopoietic stem-cell transplantation (HSCT),[7] nearly tripling overall survival.[5,8–11] Given these remarkable improvements in clinical outcomes in the past decade, the established role of upfront autologous HSCT as the gold standard intensification treatment for patients who can tolerate chemotherapy at myeloablative doses has been questioned.[12–14] Additionally, the benefits associated with consolidation therapy based on novel drugs after the intensification phase warrant further investigation, with not all studies supporting the role of consolidation therapy after transplantation.[15]

To address these issues, we performed a multicentre, randomised, open-label, phase 3 study to compare the safety and efficacy of standard-dose intensification therapy consisting of bortezomib combined with melphalan and prednisone (VMP)[4] with that of high-dose melphalan plus autologous HSCT in newly diagnosed patients with multiple myeloma aged up to 65 years. The study also aimed to compare bortezomib–lenalidomide–dexamethasone (VRD) consolidation therapy with no consolidation in patients initially randomly assigned to receive either VMP or autologous HSCT. We also compared single HSCT with double HSCT.[16,17]

Methods

Study design and patients

This randomised, open-label, phase 3 trial (EMN02/HO95) was done in 172 academic and community practice centres in the European Myeloma Network (EMN; listed in the appendix pp 15–17). A web-based system was used to register patients in a database at the EMN data centre in Turin, Italy.

Eligible patients were aged 18–65 years, had a confirmed diagnosis of symptomatic multiple myeloma stage 1–3 according to the International Staging System (ISS), measurable disease as defined by the presence of serum M protein >10 g/L or urine M protein >200 mg in 24 h or abnormal free light chain (FLC) ratio with involved FLC >100 mg/L, or proven plasmacytoma by biopsy, and a WHO performance status grade 0–2 (grade 3 was allowed if secondary to myeloma). No estimated life expectancy of eligible patients was specified in the study protocol. Key exclusion criteria were previous treatment, except local radiotherapy, in case of local myeloma progression or corticosteroids maximum 5 days for symptom control; a calculated creatinine clearance of less than 15 mL/min; inadequate cardiac and hepatic function (as defined in the study protocol [appendix p 20]);and peripheral neuropathy of grade 2 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Patients from whom an adequate number of stem cells (≥4×10^6 CD34+ cells/kg of bodyweight; lower numbers of cells were allowed by national guidelines) were collected and those with less than grade 3 peripheral neuropathy were eligible to undergo the first randomisation to autologous HSCT or VMP. The full eligibility criteria are in the protocol (appendix p 18). All patients provided written informed consent. The study was approved by the independent ethics committee or institutional review board at each participating site and was done in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki.

Research in context

Evidence before this study

We searched PubMed for clinical trial reports published in English from database inception to Dec 31, 2010, using the search terms "multiple myeloma", "transplantation", "consolidation therapy", and "novel agents". This search did not identify any randomised studies comparing upfront autologous haematopoietic stem-cell transplantation (HSCT) with novel agent-based intensification therapy followed by autologous HSCT at first relapse, or any randomised studies comparing consolidation therapy with novel agents versus no consolidation therapy. On Nov 11, 2019, a repeated systematic review using the same search terms and language restrictions identified five phase 3 randomised studies that had been published in the intervening period. In two of them upfront double HSCT following induction therapy with lenalidomide and dexamethasone resulted in significantly improved progression-free survival and overall survival compared with lenalidomide and dexamethasone combined with an alkylating agent. In a subsequent study, patients who were randomly assigned to receive bortezomib–lenalidomide–dexamethasone (VRD) as induction therapy before and consolidation after upfront single HSCT had significantly improved progression-free survival (but not overall survival) than patients who were randomly assigned to VRD therapy alone. In another study, consolidation therapy with single-agent bortezomib in bortezomib-naive patients who had undergone conventional induction chemotherapy and subsequent single or double HSCT (either single or double) significantly improved the rate of at least very good partial response and progression-free survival (but not overall survival) compared to no consolidation therapy. More recently, a trial comparing single autologous HSCT with or without VRD consolidation therapy and double HSCT with no consolidation (all groups received subsequent lenalidomide maintenance) reported no difference in progression-free survival and overall survival.

Added value of this study

This multicentre, randomised, open-label, phase 3 study (EMN02/HO95)—which is, to the best of our knowledge, the largest of its kind—was designed to prospectively address two widely debated issues in the field of multiple myeloma: the role of upfront autologous HSCT as intensification therapy in the era of highly active novel agents, and the role of consolidation therapy following the intensification phase. Newly diagnosed patients with multiple myeloma who were eligible for high-dose chemotherapy were randomly assigned to receive either autologous HSCT or bortezomib–melphalan–prednisone (VMP) as intensification therapy, and thereafter were assigned to receive either consolidation therapy with bortezomib–lenalidomide–dexamethasone (VRD) or no consolidation. We found that autologous HSCT was associated with a significant improvement in progression-free survival compared with VMP across all prognostic subgroups of patients. Additionally, VRD consolidation therapy significantly improved progression-free survival compared with no consolidation. No overall survival benefit was seen with autologous HSCT compared with VMP at a median follow-up of 60·3 months (IQR 52·2–67·6). However, the follow-up for this study remains short, and a difference might emerge with a longer duration of observation, as seen with other studies.

Implications of all the available evidence

Autologous HSCT seems to be more effective than VMP intensification, and consolidation therapy following the intensification phase seems to be more effective than observation in terms of progression-free survival. Results from this study further support and extend the existing body of evidence suggesting that upfront autologous HSCT continues to have an important role in the management of patients with newly diagnosed with multiple myeloma who are fit for high-dose chemotherapy, even in the era of active novel agents.

Randomisation and masking

The schedule for randomisation (1:1) to intensification therapy with either VMP or autologous HSCT was computer generated by the study coordinating team (independent of the study authors) using a permuted block design with a block size of 12, and was stratified by site and ISS disease stage (stage 1, 2, or 3). In centres with a double HSCT policy, the first randomisation (1:1:1) was to VMP or single or double HSCT, generated in the same manner and block size. Within 2 months from autologous HSCT or the last dose of VMP, patients who were eligible for the second randomisation were assigned to consolidation therapy with VRD or no consolidation, followed by lenalidomide maintenance until progression in both groups, with the randomisation sequence generated in the same manner but without stratification. There was no masking to treatment allocation for either randomisation.

Procedures

Before first randomisation, patients were treated with three or four 3-week cycles of induction therapy with bortezomib, cyclophosphamide, and dexamethasone (VCD) at the dosing schedule reported in the appendix (p 2), and underwent subsequent peripheral blood stem-cell mobilisation with cyclophosphamide (2 g/m² [recommended dose]) and granulocyte colony-stimulating factor (10 µg/kg subcutaneously from day 5 to the day of last apheresis). The study protocol was amended in November, 2012, to allow patients to receive up to four cycles of VCD and to switch from intravenous to subcutaneous administration of bortezomib.

Intensification therapy with VMP was administered for up to four 6-week cycles and consisted of bortezomib (1·3 mg/m² administered intravenously [before protocol amendment] or subcutaneously [after protocol amendment], on days 1, 4, 8, 11, 22, 25, 29, and 32) combined

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See Online for appendix

with melphalan (9 mg/m² administered orally on days 1–4) and prednisone (60 mg/m² administered orally on days 1–4). For patients undergoing HSCT, high-dose melphalan was given at the standard dose of 200 mg/m² intravenously in patients with a creatinine clearance of greater than 40 mL/min and at the reduced dose of 100 mg/m² in patients with creatinine clearance 15–40 mL/min. Two sequential courses of high-dose melphalan administered 2–3 months apart were planned in patients randomly assigned to receive double HSCT.

Patients assigned to consolidation therapy received two 28-day cycles of VRD, each consisting of bortezomib (1·3 mg/m² administered either intravenously or subcutaneously on days 1, 4, 8, and 11) combined with lenalidomide (25 mg administered orally on days 1–21) and dexamethasone (20 mg administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12), followed by lenalidomide maintenance therapy. Patients who were not eligible for consolidation could receive maintenance therapy. In the maintenance phase, lenalidomide was administered orally at a dose of 10 mg on days 1–21, in 28-day cycles, until progression or undue toxicity.

We enrolled patients with negative serum and urine immunofixation before starting maintenance therapy into a prespecified correlative substudy of minimal residual disease assessment by multiparametric eight-colour flow cytometry at a sensitivity level of 10^{-4} to 10^{-5}, as detailed in the appendix (p 3). Progression-free survival was assessed in patients with and without minimal residual disease.

Prespecified dose reductions and changes in the schedule of study drugs were permitted in the case of grade 4 haematological and grade 3–4 non-haematological treatment-related adverse events, as detailed in the study protocol (appendix pp 27–33).

Imaging techniques, including whole-body x-ray, low-dose CT, PET-CT, and MRI (according to local policy), were performed at study entry and every year thereafter, and when clinically required. Laboratory efficacy data, including serum and urine monoclonal proteins, serum FLCs, and bone marrow aspirate to confirm complete response, were assessed by the investigators at defined timepoints (after the third or fourth VCD cycle, after the second and fourth VMP cycle, 2 months after each course of high-dose melphalan, after the second VRD cycle, and every 2 cycles of lenalidomide; appendix p 38). Any complete response lacking confirmation from a bone marrow aspirate or biopsy sample was centrally downgraded to the very good partial response category. Safety assessments, including adverse event monitoring and reporting of pregnancies or suspected pregnancies, were done every 3 months while on treatment and until 30 days after the last dose of study drug. Adverse events were graded according to the CTCAE, version 4.0.

Reasons for withdrawing from the study included progressive disease, death, unacceptable toxicity, refusal to continue treatment, and withdrawal of consent for further follow-up data collection.

Outcomes

The primary outcomes were progression-free survival (defined as the time from randomisation to disease progression or death due to any cause) from the first and second randomisations. The secondary outcomes were: the proportion of patients achieving partial response or higher (including very good partial response and complete response), defined according to the International Uniform Response Criteria for Multiple Myeloma;[18] overall survival from the first and second randomisations (defined as time from randomisation to death from any cause); toxicity; and quality of life. The quality of life analysis is ongoing and the results will be reported elsewhere.

Exploratory analyses of the relationship between prognostic factors, including cytogenic abnormalities assessed by fluorescence in-situ hybridisation (FISH), ISS stage, and molecular profiles and response rates, progression-free survival, and overall survival, were prespecified. Here, we include the assessment of progression-free survival in prognostic subgroups, including patients with a standard-risk or a high-risk cytogenetic profile, as identified by the presence of one or more of the following on FISH analysis: translocation (4;14) in 10% or more enriched plasma cells; translocation (14;16) in 10% or more enriched plasma cells; or deletion (17p) in 20% or more enriched plasma cells. Analyses of progression-free survival also included additional and not prespecified prognostic variables, such as age, haemoglobin, platelet count, bone marrow plasma cells and lactate dehydrogenase.

Statistical analysis

The sample size was estimated based on the two primary study outcomes. Assuming a median progression-free survival from the first randomisation of 25 months in the VMP group and 32 months in the autologous HSCT group, based on previous studies, we estimated that 1202 patients would be required to undergo the first randomisation, and 507 events of disease progression or death would be needed to provide 80% power to detect a 22% reduced risk of disease progression or death (hazard ratio [HR] 0·78) in the autologous HSCT group compared with the VMP group, using Cox regression analysis, with an overall two-sided significance level of 0·05. We also estimated that 848 patients would be eligible for the second randomisation and 514 events would occur, giving 80% power to detect an HR for disease progression or death of 0·78 in the VRD consolidation versus no consolidation groups. Two prespecified interim analyses were performed after 33% and 66% of events had occurred; therefore, the p value for the final analysis was set at 0·045. Results of these interim analyses have been previously reported[19–22] and showed progression-free survival to be significantly longer in the autologous HSCT group than in the VMP group, and in the VRD consolidation therapy group than in the no consolidation group. An independent data monitoring committee reviewed the results of these interim analyses.

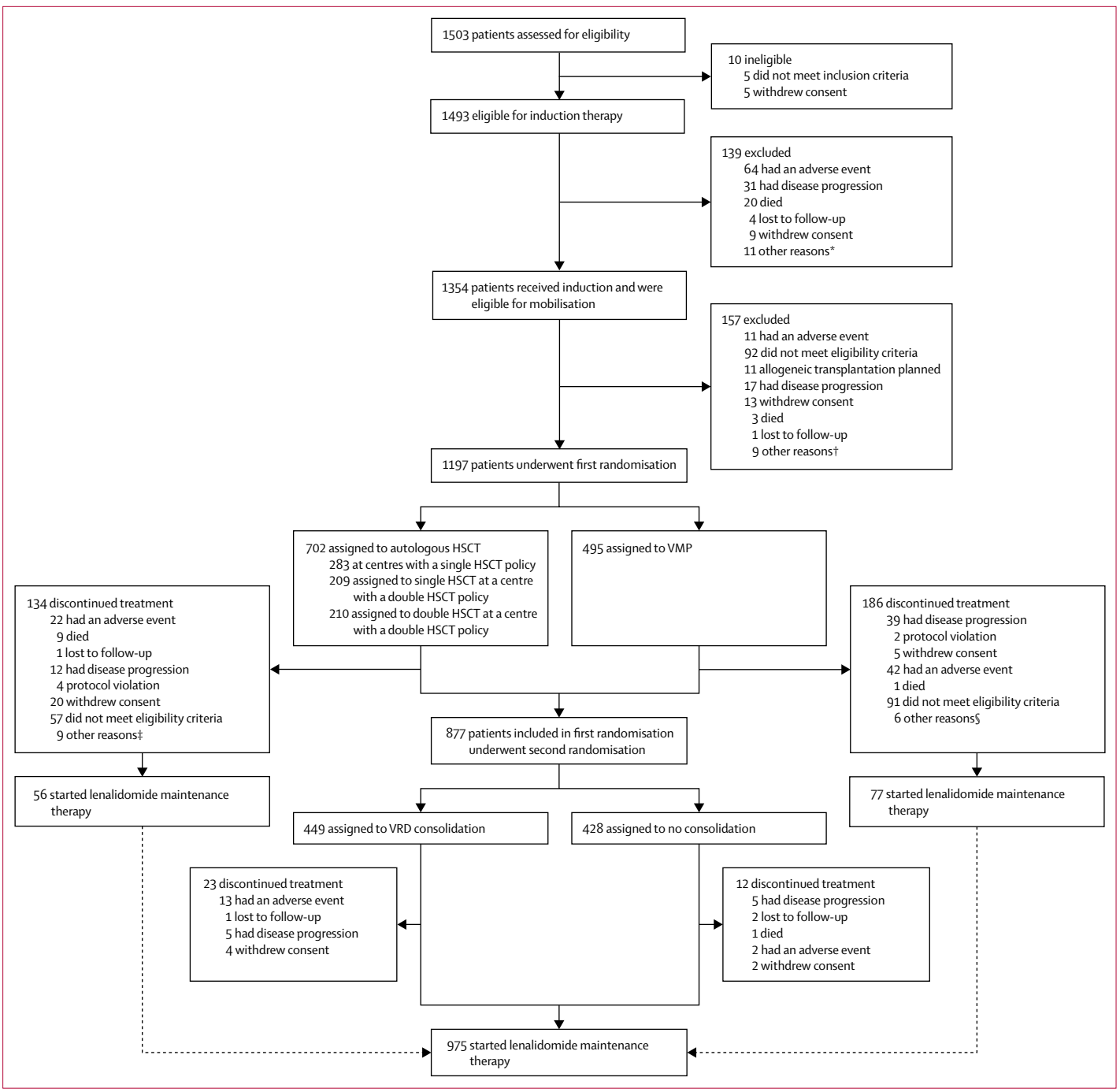

Figure 1: **Trial profile**

HSCT=haematopoietic stem-cell transplantation. VMP=bortezomib–melphalan–prednisone. VRD=bortezomib–lenalidomide–dexamethasone. *Concomitant light-chain amyloidosis (n=2), subsequent diagnosis of lymphoma (n=1), physician decision (n=4), concomitant malignancies (n=2), and non-compliance (n=2). †Physician decision (n=4), non-compliance (n=2), incomplete data (n=2), and concomitant malignancy (n=1). ‡Physician decision (n=6) and non-compliance (n=3). §Physician decision (n=3) and non-compliance (n=3).

Efficacy was analysed in the intention-to-treat population, which includes all patients who underwent the first and second randomisations. Patients who did not undergo the first randomisation, including those with early disease progression while receiving induction therapy, were considered not assessable. The primary analysis of the second randomisation was restricted to patients also included in the first randomisation. Progression-free survival and overall survival were estimated by the Kaplan-Meier method from the

	Autologous HSCT group (n=702)	VMP intensification group (n=495)	VRD consolidation group (n=449)	No consolidation group (n=428)
Age, years	58·00 (52·25–62·00)	58·00 (51·00–62·00)	57·00 (52·00–62·00)	58·00 (52·00–62·00)
Sex				
Female	290 (41%)	216 (44%)	190 (42%)	185 (43%)
Male	412 (59%)	279 (56%)	259 (58%)	243 (57%)
β_2 microglobulin, mg/L	3·30 (2·34–4·80)	3·30 (2·40–5·04)	3·30 (2·40–5·00)	3·20 (2·31–4·79)
β_2 microglobulin ≤ 3·5 mg/L	388 (55%)	272 (55%)	252 (56%)	234 (55%)
β_2 microglobulin > 5·5 mg/L	136 (19%)	103 (21%)	95 (21%)	74 (17%)
Albumin, g/dL	3·80 (3·33–4·24)	3·80 (3·28–4·20)	3·80 (3·34–4·20)	3·82 (3·30–4·23)
Albumin ≤ 3·5 g/dL	236 (34%)	185 (37%)	159 (35%)	151 (35%)
ISS stage				
I	291 (41%)	205 (41%)	189 (42%)	181 (42%)
II	273 (39%)	187 (38%)	165 (37%)	172 (40%)
III	138 (20%)	103 (21%)	95 (21%)	75 (18%)
Standard-risk cytogenetics*	402/537 (75%)	264/354 (75%)	259/336 (77%)	244/321 (76%)
High-risk cytogenetics*†	135/537 (25%)	90/354 (25%)	77/336 (23%)	77/321 (24%)
del(17p)	64/589 (11%)	41/410 (10%)	39/371 (9%)	35/357 (10%)
t(4;14)	63/572 (11%)	48/394 (12%)	36/359 (10%)	39/346 (11%)
t(14;16)	20/548 (4%)	15/378 (4%)	11/355 (3%)	14/325 (4%)
Revised ISS stage				
I	156 (22%)	94 (19%)	108 (24%)	84 (20%)
II	391 (56%)	270 (55%)	234 (52%)	237 (55%)
III	58 (8%)	38 (8%)	39 (9%)	28 (7%)
Unknown	97 (14%)	93 (19%)	68 (15%)	79 (18%)
Haemoglobin, g/dL	11·10 (9·70–12·58)	11·00 (9·60–12·60)	11·10 (9·50–12·42)	11·00 (9·70–12·60)
Haemoglobin < 10·5 g/dL	264 (38%)	195 (39%)	178 (40%)	160 (37·6%)
Platelet count, $\times 10^3$/mL	225 (177–280)	232 (180–283)	231 (180–282)	231 (185–283)
Platelet count <150 $\times 10^3$/mL	92 (13%)	65 (13%)	53 (12%)	50 (12%)
Bone marrow plasma cells	50·00 (30·00–80·00)	50·00 (27·00–70·00)	50·00 (30·00–79·00)	50·00 (25·50–75·00)
Bone marrow plasma cells ≥60%*	297/662 (45%)	184/464 (40%)	187/415 (45%)	172/407 (42%)
Lactate dehydrogenase > upper limit*	99/659 (15%)	56/462 (12%)	59/418 (14%)	48/400 (12%)
Creatinine, mg/dL	0·90 (0·75–1·10)	0·92 (0·76–1·18)	0·90 (0·74–1·10)	0·88 (0·72–1·09)
Creatinine clearance, mL/min	88·00 (63·00–106·94)	81·50 (60·00–100·00)	86·00 (60·75–108·00)	86·00 (64·95–105·00)

Data are n (%), n/N (%), or median (IQR). HSCT=haematopoietic stem-cell transplantation. VMP=bortezomib–melphalan–prednisone. VRD=bortezomib–lenalidomide–dexamethasone. ISS=International Staging System. *Proportions calculated using the number of evaluable patients. †Defined by one or more of the following abnormalities: del(17p), t(4;14), or t(14;16).

Table 1: **Demographic and baseline clinical characteristics in the intention-to-treat population**

respective dates of randomisation; treatment groups were compared using the log-rank test.[23] A multivariable Cox regression analysis, adjusted for the stratification factor, was used for primary comparisons between treatment groups and to estimate HRs and 95% CIs. Responses were compared between treatment groups using the χ^2 test.

Safety was assessed in all patients who received at least one dose of study drugs. Reported toxicities were tabulated as adverse events and second primary malignancies, and were compared between treatment groups using either a χ^2 or Fisher's exact test. Rates of second primary malignancies were calculated as the ratio of the number of second primary malignancies to the number of patient-years at risk and were compared between groups using a binomial exact test. All analyses were performed using R and Stata (version 15.0).

Data were monitored by an external contract organisation and verified for accuracy by a supporting research team at the EMN data centre.

This trial is registered with the EU Clinical Trials Register (EudraCT 2009-017903-28) and ClinicalTrials.gov (NCT01208766).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 25, 2011, and April 3, 2014, 1503 patients were enrolled, of whom 1493 started the induction phase and 1354 met the eligibility criteria for stem-cell mobilisation. 296 patients were excluded before the first randomisation (figure 1), 48 of whom had early disease progression.

1197 patients who had received three (n=635) or four (n=562) cycles of VCD induction therapy underwent the first randomisation and were assigned to autologous HSCT (n=702) or VMP (n=495). In the autologous HSCT group, 419 patients were assigned to single (n=209) or double (n=210) HSCT at sites with a double HSCT policy as standard practice. 877 patients who had been included in the first randomisation underwent the second randomisation: 449 patients were allocated to the VRD group and 428 to the no consolidation group. Baseline demographics and disease characteristics were well balanced among the treatment groups (table 1).

The median time from starting induction therapy to the first randomisation was 3·7 months (IQR 3·3–4·1). At the time of data cutoff (Nov 26, 2018) for the final analysis of progression-free survival from the first randomisation, the median overall duration of follow-up was 60·5 months (IQR 59·2–61·7) in the autologous HSCT group and 59·4 months (58·0–61·8) in the VMP group. 645 events of disease progression or death were reported, accounting for 346 (49%) of 702 patients in the autologous HSCT group and 299 (60%) of 495 in the VMP group. Median progression-free survival was 56·7 months (95% CI 49·3–64·5) for patients randomly assigned to autologous HSCT versus 41·9 months (37·5–46·9) for those assigned to VMP (HR 0·73, 95% CI 0·62–0·85, adjusted p=0·0001; figure 2A).

The superiority of autologous HSCT over VMP was retained across all subgroups of patients with favourable and unfavourable prognosis (appendix p 7). In particular, in patients with prespecified variables predicting for poorer prognosis, the HR for progression-free survival favouring autologous HSCT over VMP was 0·72 (95% CI 0·59–0·87) in patients with ISS disease stage 2 or 3, 0·48 (0·30–0·78) in patients with revised ISS stage 3, and 0·63 (0·46–0·88) in those with a high-risk cytogenetic profile (appendix p 7). On multivariable Cox regression analysis, independent factors that predicted extended progression-free survival included random allocation to the autologous HSCT group, achievement of best very good partial response or higher, absence of adverse cytogenetics, revised ISS stage 1, and normal platelet counts (appendix p 4). The 5-year overall survival from the first randomisation was 75·1% (95% CI 71·7–78·5) for patients in the autologous HSCT group and 71·6% (67·4–76·1) for those in the VMP group (HR 0·90, 0·71–1·13, adjusted p=0·35; figure 2B). Overall survival was significantly improved with autologous HSCT compared with VMP group in the subgroup of patients with a high-risk cytogenetic profile (HR 0·66, 0·45–0·99; p=0·042; appendix p 8) and, in particular, in the subgroup of patients carrying del(17p) (HR 0·48, 0·27–0·86; p=0·014; appendix p 9).

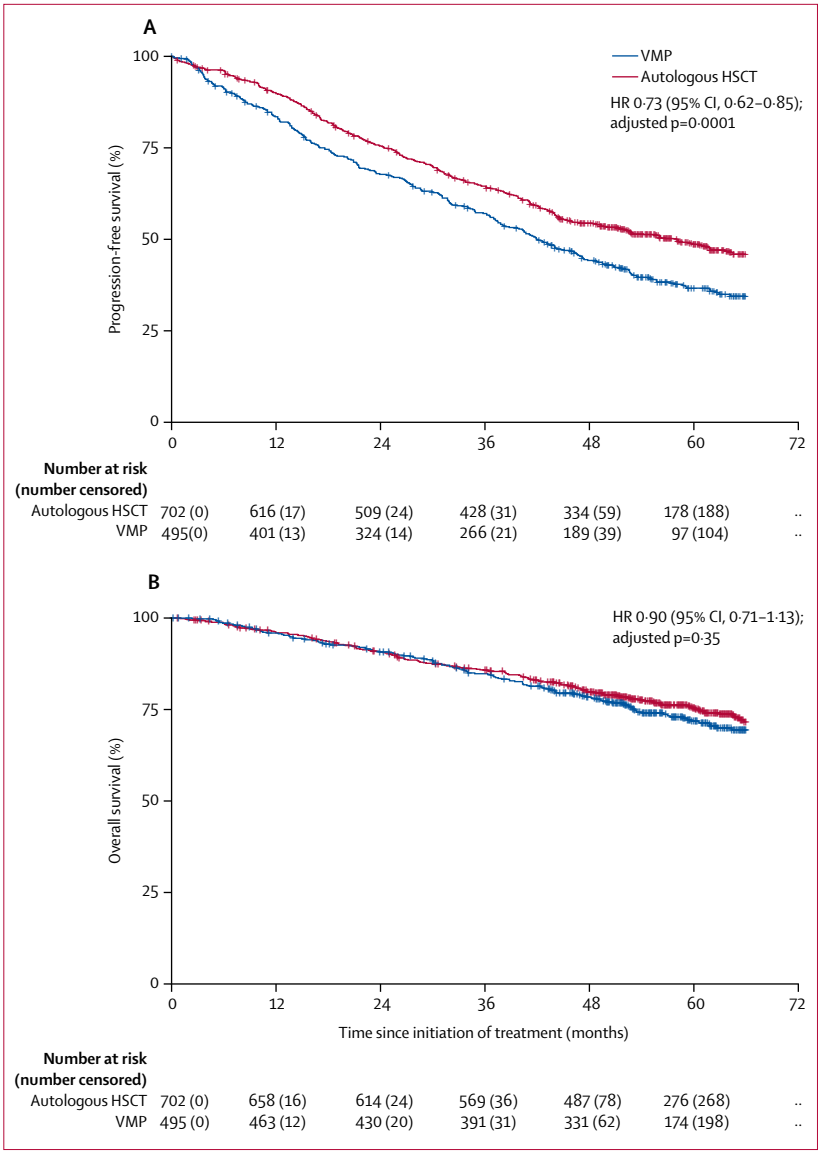

Figure 2: **Final analysis of HSCT versus VMP intensification**
Progression-free survival (A) and overall survival (B) at a median follow-up of 60·3 months (IQR 52·2–67·6; data cutoff Nov 26, 2018) in patients assigned to autologous HSCT and patients assigned to VMP (intention-to-treat population). HR=hazard ratio. HSCT=haematopoietic stem-cell transplantation. VMP=bortezomib–melphalan–prednisone.

At the time of the first randomisation, 485 (41%) of 1197 patients had achieved a very good partial response or higher, with proportions similar between the autologous HSCT group (286 [41%] of 702) and the VMP group (199 [40%] of 495). After intensification therapy, the proportion of patients who achieved at least a very good partial response was significantly higher in the autologous HSCT group (447 [64%] of 702) than in the VMP group (278 [56%] of 495, adjusted p=0·020).

	Autologous HSCT group (n=702)	VMP intensification group (n=495)	Adjusted p values*
Best response	..	..	0·032
Stringent complete response	155 (22%)	106 (21%)	..
Complete response	154 (22%)	94 (19%)	..
Very good partial response	284 (40%)	181 (37%)	..
Partial response	79 (11%)	89 (18%)	..
Stable disease	30 (4%)	25 (5%)	..
Very good partial response or better	593 (84%)	381 (77%)	0·0021

Data are n (%). HSCT=haematopoietic stem-cell transplantation. VMP=bortezomib–melphalan–prednisone. *To control the family-wise error rate at 0·05, p values were adjusted for multiple comparisons according to the Holm procedure.

Table 2: **Best response in the intention-to-treat population assigned to autologous HSCT or VMP intensification**

593 (84%) of 702 patients in the autologous HSCT group and 381 (77%) of 495 in the VMP group achieved as best response a very good partial response or higher (adjusted p=0·0020). Best complete response or higher was reported in 309 (44%) patients in the autologous HSCT group and in 200 (40%) in the VMP group (table 2).

At the data cutoff date for the current analysis (Nov 26, 2018), the number of events of progression or death following the second randomisation was lower than that preplanned for the final comparison between the two treatment groups. Based on this finding, results of the second protocol-specified interim analysis, done on Jan 18, 2018, on a slightly different number of patients than that reported in figure 1 (447 patients randomly assigned to VRD consolidation therapy and 431 patients randomly assigned to no consolidation therapy) are presented here. At this date, the median duration of follow-up was 42·1 months (IQR 32·3–49·2) and 366 events had occurred. 169 (38%) of 447 patients in the VRD consolidation therapy group and 197 (46%) of 431 patients in the no consolidation therapy group experienced disease progression or died. Median progression-free survival was 58·9 months (95% CI 54·0–not estimable) in the VRD group versus 45·5 months (39·5–58·4) in the no consolidation group (HR 0·77, 95% CI 0·63–0·95; adjusted p=0·014; figure 3A). 5-year overall survival was 77·2% (95% CI 68·7–83·6) in the VRD group and 72·2% (95% CI 59·3–81·7) in the no consolidation group (HR 0·99, 0·71–1·39; adjusted p=0·96; figure 3B).

Baseline demographics and disease characteristics of patients assigned to single and double autologous HSCT are shown in the appendix p 5. In the intention-to-treat population, double HSCT significantly improved 5-year progression-free survival (53·5%, 95% CI 46·6–61·3) compared with single HSCT (44·9%, 38·0–53·0; HR 0·74, 95% CI 0·56–0·98; adjusted p=0·036; figure 4A). Double HSCT resulted in significantly improved 5-year overall survival (80·3% [74·5–86·4]) than single HSCT (72·6% [66·5–79·3]; HR 0·62, 95% CI 0·41–0·93; adjusted p=0·022; figure 4B). The HR for disease progression or death favouring double HSCT over single HSCT was not as high in the subgroup of patients with standard-risk cytogenetics (0·83, 95% CI 0·57–1·22) as it was in patients carrying one or more of the three major adverse cytogenetic abnormalities. Median progression-free survival for patients with a high-risk cytogenetic profile was 46·0 months (38·7–not estimable) with double HSCT versus 26·7 months (19·9–49·6) with single HSCT (HR 0·59, 0·34–1·03; p=0·062; appendix p 10). The 5-year overall survival in the high-risk cytogenetic subgroup was 61·3% (45·8–82·1) with double HSCT versus 54·7% (41·1–72·7) with single HSCT (HR 0·70, 0·35–1·42; p=0·32). In the subgroup of patients with del(17p), the HR for progression or death favoured double HSCT over single HSCT (0·24, 0·09–0·66; p=0·0060; appendix p 11). The 5-year overall survival for del(17p)-positive patients was 80·2% (62·4–100) with double HSCT versus 57·1% (39·2–83·2) with single HSCT (HR 0·30, 0·08–1·08; p=0·066; appendix p 12). Comparisons between del(17p)-positive patients and those with standard-risk cytogenetics showed that double HSCT was likely to overcome the adverse effect of del(17p) on progression-free survival (0·70, 0·28–1·74; p=0·44; appendix p 13) and overall survival (1·48, 0·43–5·04; p=0·53; appendix p 14). On a multivariable Cox regression analysis, random allocation to double HSCT was an independent variable that predicted improved progression-free survival and overall survival, together with achievement of best very good partial response or higher, lack of adverse cytogenetics, and revised ISS stage 1 (appendix p 4).

Maintenance therapy with lenalidomide was started in 975 (81%) of 1197 patients who were eligible for the first randomisation (599 in the autologous HSCT group and 376 in the VMP group). The median duration of lenalidomide therapy was 34·0 months (IQR 13·3–50·8), and was similar in the autologous HSCT group (34·3 months [14·1–52·2]) and the VMP group (33·4 months [10·9–48·2]). 364 (37%) patients are still under treatment after a median of 53·7 months (46·8–60·9), whereas 611 (63%) have discontinued therapy, most frequently owing to progressive disease (383 [63%]) or treatment-emergent adverse events (170 [28%]). The median progression-free survival from start of lenalidomide maintenance was 50·4 months (95% CI 45·8–57·7) in the overall patient population, and 58·0 months (49·1–not estimable) in the autologous HSCT group versus 43·2 months (38·7–50·1) in the VMP group (HR 0·76, 0·64–0·91; p=0·0030).

167 patients with negative serum and urine immunofixation before starting lenalidomide maintenance were enrolled in the prespecified correlative study of minimal residual disease detection. Median progression-free survival for patients with negative status for minimal residual disease (median not reached, 95% CI 65–not estimable) was significantly improved than for those in whom minimal residual disease was detected

(51·1 months, 32·2–not estimable; HR 0·46, 0·25–0·84; p=0·012).

In the autologous HSCT group, 236 patients with a symptomatic relapse received second-line therapy with a proteasome inhibitor or an immunomodulatory drug, or both; this was followed by salvage autologous HSCT in 40 (17%) patients. In the VMP group, second-line therapy incorporating a proteasome inhibitor or an immunomodulatory drug, or both, or conventional cytotoxic drugs was offered to 209 patients; this was followed by salvage HSCT in 132 (63%) patients.

The most common grade 1–2 and any grade 3 or worse adverse events are listed in table 3. Overall, more patients experienced at least one grade 3 or worse adverse event in the autologous HSCT group than in the VMP group (grade 3: 364 [56%] *vs* 227 [48%]; grade 4 or 5: 529 [81%] *vs* 48 [10%]; p<0·0001). In particular, HSCT was associated with a higher frequency of grade 3 or worse neutropenia (513 [79%] of 652 patients *vs* 137 [29%] of 472 patients in the VMP group), thrombocytopenia (541 [83%] *vs* 74 [16%]), gastrointestinal disorders (80 [12%] *vs* 25 [5%]), mucositis (105 [16%] *vs* none), and infections (192 [30%] *vs* 18 [4%]). The total number of serious adverse events from first randomisation was 557: 368 (66%) in the HSCT group and 189 (34%) in the VMP group. 239 (34%) of 702 patients in the autologous HSCT group, and 135 (27%) of 495 in the VMP group had at least one serious adverse event. Infection and infestation was the most common serious adverse event in the autologous HSCT group (206 [56%] of 368) and the VMP group (70 [37%] of 189). 38 (12%) of 311 deaths from first randomisation were likely to be treatment related: 26 (68%) in the autologous HSCT group and 12 (32%) in the VMP group, most frequently due to infections (eight [21%]), cardiac events (six [16%]), and second primary malignancies (20 [53%]). Seven (1%) patients died within 100 days from HSCT, six due to infections and one because of cardiac failure. Dose reductions related to at least one adverse event were reported in 285 (58%) of 495 patients treated with VMP and 23 (3%) of 702 patients who received high-dose melphalan.

Overall, 86 (5·8%) of 1493 patients developed a second primary malignancy in a median time of 55·6 months (IQR 33·5–66·2) from entry into the study. The incidence of second primary malignancies was 1·4 (95% CI 1·05–1·95) per 100 patient-years in the autologous HSCT group and 1·5 (1·05–2·18) in the VMP group (p=0·88). In both groups, 6% of patients developed a second primary malignancy, with no significant between-treatment difference in the rate of registered haematological (2%) and solid tumours (4%). Details about the type and frequency of second primary malignancies are reported in the appendix (p 6).

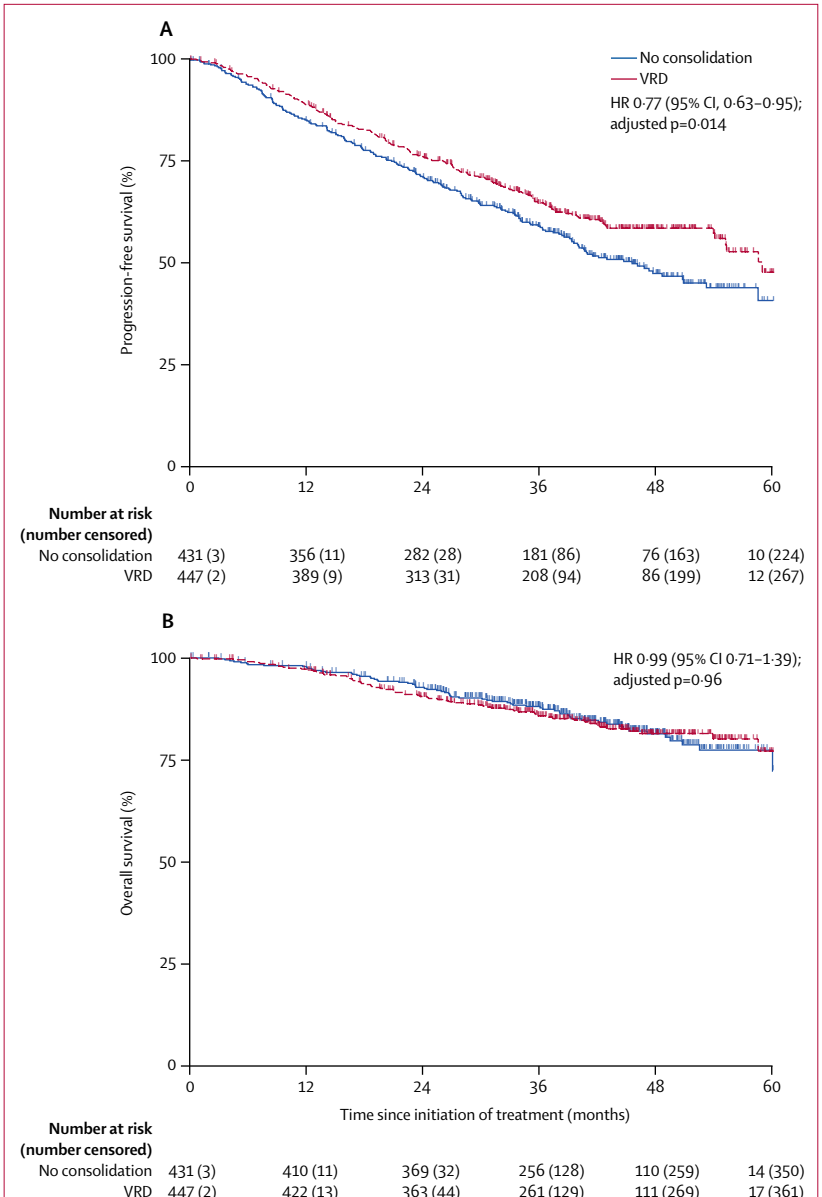

Figure 3: **Second interim analysis of VRD consolidation therapy versus no consolidation**
Progression-free survival (A) and overall survival (B) at a median follow-up of 42·1 months (IQR 32·3–49·2; data cutoff Jan 18, 2018) in patients assigned to VRD consolidation therapy and patients assigned to no consolidation therapy (intention-to-treat population). HR=hazard ratio. VRD=bortezomib–lenalidomide–dexamethasone.

Discussion

In this multicentre, open-label, phase 3 study—to the best of our knowledge, the largest of its kind—we compared HSCT with VMP and VRD consolidation therapy with no consolidation for previously untreated patients with multiple myeloma aged up to 65 years. The study met one of its primary endpoints since autologous HSCT significantly improved progression-free survival compared with VMP, supporting the value of HSCT even in the era of highly active novel agents. The improved progression-free survival with autologous HSCT over VMP was maintained across all prespecified prognostic subgroups, including patients with predicted unfavourable outcomes. Patients randomly allocated to receive four cycles of VMP after

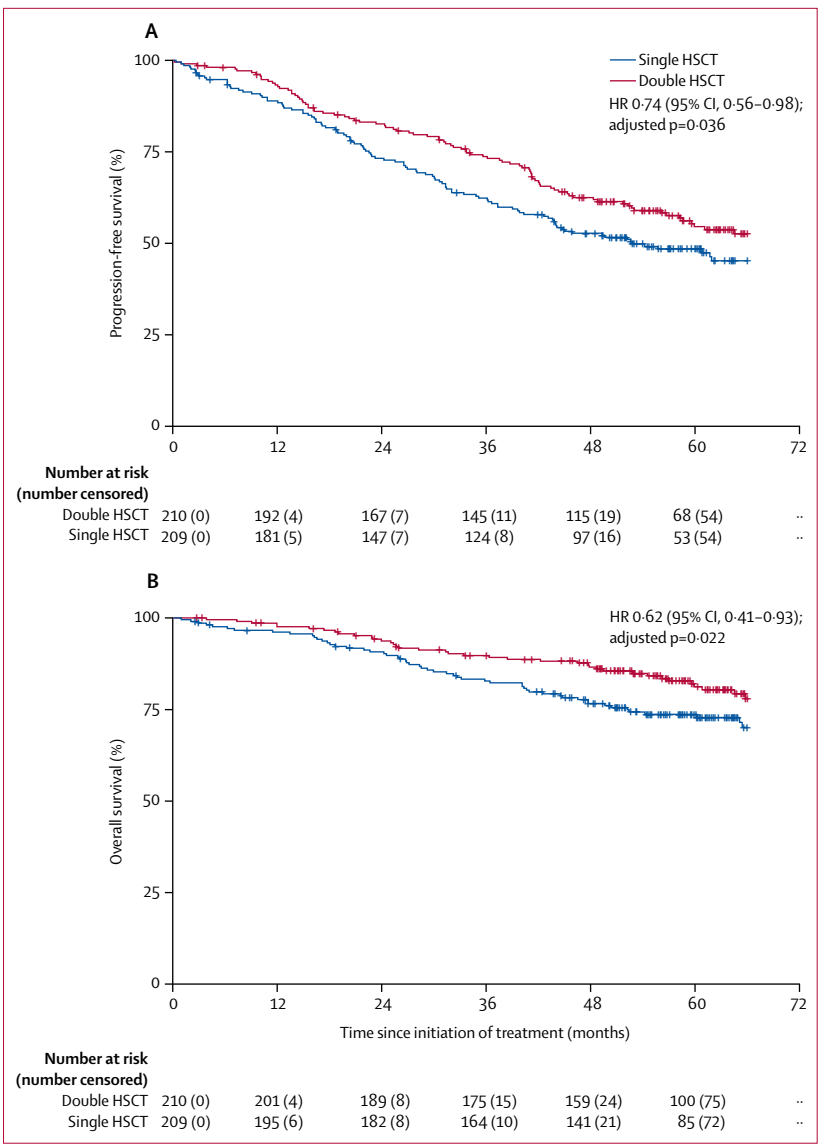

Figure 4: **Final analysis of single autologous HSCT versus double HSCT**
Progression-free survival (A) and overall survival (B) at a median follow-up of 60·3 months (IQR 52·2–67·6; data cutoff Nov 26, 2018) in patients assigned to single HSCT and patients assigned to double HSCT (intention-to-treat population). HR=hazard ratio. HSCT=haematopoietic stem-cell transplantation.

three or four cycles of previous VCD induction therapy, with or without two cycles of VRD consolidation therapy, and lenalidomide maintenance had a median progression-free survival (42 months) longer than that previously reported in the VISTA study[4] and consistent with that seen with VRD in the SWOG S0777 study.[5] However, differences in the age distribution, number of preplanned treatment cycles, and number of bortezomib doses prevent any formal comparison with these studies.

In our analysis, the estimated 5-year rate of overall survival was similar for patients in the autologous HSCT group and the VMP group (75% *vs* 72%). Although this suggests that delaying HSCT to a later time is not harmful, a substantial proportion of patients may become ineligible for high-dose melphalan at first relapse, as reflected by the 63% of patients in the VMP group who underwent salvage HSCT. At the time that this analysis was performed, the follow-up was fairly short and longer-term observation might be needed to detect any overall survival advantage, as seen in other trials.[24] Additionally, effective therapies given at the time of relapse might have ultimately led to similar outcomes between the two treatment groups.

An additional primary endpoint of our study was progression-free survival after the second randomisation to receive consolidation or no consolidation therapy. Data from the second preplanned interim analysis showed that the endpoint was met, since VRD consolidation therapy significantly improved progression-free survival compared with no consolidation therapy. More patients who received consolidation treatment followed by lenalidomide maintenance achieved at least complete response than those who did not receive consolidation but were treated with lenalidomide maintenance (55% *vs* 40%). In a recently published phase 3 study conducted in the USA by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 trial)[25] no difference in progression-free survival was observed by comparing double HSCT with single HSCT with or without VRD consolidation therapy (all three treatment groups received subsequent lenalidomide maintenance). Differences in the design of these studies may account for their conflicting results. In our study, planned induction therapy before the first randomisation included three or four cycles of VCD, reflecting the current European practice of administering a short-term bortezomib-based treatment. Whether prolonged exposure to induction therapy for up to 1 year, and the predominant use of VRD, as in the BMT CTN 0702 trial,[25] may have reduced the probability of further benefit with VRD consolidation therapy, differently from what we observed in our study, remains an open question.

The role of preplanned double HSCT is still an area of debate in the era of novel agents for myeloma therapy and was evaluated as a secondary endpoint of our study. Results of the final analysis of single versus double HSCT showed a significantly longer progression-free survival (HR 0·74) and overall survival (HR 0·62) with double HSCT, which was an independent factor favourably affecting these outcomes. The magnitude of benefit with double HSCT, as measured by the HR for disease progression or death, was higher for patients with high-risk cytogenetics. This finding might influence the interpretation of the superiority of double over single HSCT in the overall patient population. A longer-term follow-up will be required to evaluate the benefit, if any, with double HSCT in patients with standard-risk cytogenetics. Consistent with previous reports,[26,27] patients with del(17p) were likely to benefit the most from an intensive treatment strategy that included bortezomib and two sequential courses of high-dose melphalan, as reflected by the HR for disease

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	Autologous HSCT group (n=652)				VMP intensification group (n=472)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
At least one adverse event	541 (83%)	364 (56%)	522 (80%)	7 (1%)	406 (86%)	227 (48%)	48 (10%)	0
Haematological	345 (53%)	186 (29%)	519 (80%)	2 (<1%)	231 (49%)	143 (30%)	42 (9%)	0
Anaemia	331 (51%)	101 (15%)	5 (1%)	1 (<1%)	123 (26%)	2 (<1%)	0	0
Neutropenia	11 (2%)	39 (6%)	473 (73%)	1 (<1%)	84 (18%)	113 (24%)	24 (5%)	0
Thrombocytopenia	16 (2%)	72 (11%)	467 (72%)	2 (<1%)	113 (24%)	50 (11%)	24 (5%)	0
Non-haematological	435 (67%)	264 (40%)	44 (7%)	7 (1%)	370 (78%)	134 (28%)	7 (1%)	0
Cardiac	39 (6%)	15 (2%)	2 (<1%)	1 (<1%)	27 (6%)	12 (3%)	0	0
Gastrointestinal	212 (33%)	79 (12%)	1 (<1%)	0	123 (26%)	24 (5%)	1 (<1%)	0
Diarrhoea	113 (17%)	34 (5%)	1 (<1%)	0	40 (8%)	15 (3%)	1 (<1%)	0
Nausea/vomiting	97 (15%)	27 (4%)	0	0	52 (11%)	8 (2%)	0	0
Anorexia	12 (2%)	26 (4%)	0	0	4 (1%)	0	0	0
Mucositis	137 (21%)	94 (14%)	11 (2%)	0	8 (2%)	0	0	0
General disorders	103 (16%)	13 (2%)	0	0	140 (30%)	19 (4%)	1 (<1%)	0
Pain	23 (4%)	3 (<1%)	0	0	57 (12%)	7 (1%)	1 (<1%)	0
Fatigue	53 (8%)	9 (1%)	0	0	80 (17%)	8 (2%)	0	0
Oedema	15 (2%)	0	0	0	15 (3%)	3 (1%)	0	0
Infections	150 (23%)	160 (25%)	27 (4%)	5 (1%)	119 (25%)	17 (4%)	1 (<1%)	0
Febrile neutropenia	35 (5%)	113 (17%)	8 (1%)	0	1 (<1%)	2 (<1%)	0	0
Respiratory	22 (3%)	9 (1%)	7 (1%)	1 (<1%)	40 (8%)	6 (1%)	1 (<1%)	0
Sepsis	6 (1%)	10 (2%)	11 (2%)	4 (1%)	0	0	0	0
Fever/FUO	51 (8%)	2 (<1%)	0	0	31 (7%)	2 (<1%)	0	0
Other	37 (6%)	26 (4%)	1 (<1%)	0	49 (10%)	7 (1%)	0	0
Laboratory investigations	54 (8%)	36 (6%)	4 (1%)	0	29 (6%)	10 (2%)	1 (<1%)	0
Hepatic	16 (2%)	17 (3%)	0	0	15 (3%)	5 (1%)	0	0
Hyperglycaemia	9 (1%)	4 (1%)	1 (<1%)	0	9 (2%)	3 (1%)	0	0
Electrolytes	27 (4%)	16 (2%)	3	0	5 (1%)	1 (<1%)	1 (<1%)	0
Nervous system disorders	79 (12%)	16 (2%)	0	0	202 (43%)	67 (14%)	3 (1%)	0
Peripheral neuropathy	62 (10%)	9 (1%)	0	0	197 (42%)	65 (14%)	3 (1%)	0
Other	20 (3%)	7 (1%)	0	0	9 (2%)	2 (<1%)	0	0
Cutaneous disorders	39 (6%)	2 (<1%)	0	0	89 (19%)	10 (2%)	0	0
Vascular disorders	7 (1%)	1 (<1%)	0	0	9 (2%)	1 (<1%)	0	0
Renal disorders	7 (1%)	3 (<1%)	0	0	8 (2%)	3 (1%)	0	0
Respiratory	18 (3%)	1 (<1%)	2 (<1%)	1 (<1%)	16 (3%)	1 (<1%)	0	0
Other	11 (2%)	1 (<1%)	0	0	20 (4%)	4 (1%)	0	0

Data are n (%). The table includes grade 1 or 2 adverse events occurring in at least 10% of patients and grade 3, 4, or 5 events in any patient. FUO=fever of unknown origin. HSCT=haematopoietic stem-cell transplantation. VMP=bortezomib–melphalan–prednisone.

Table 3: **Adverse events in patients assigned to autologous HSCT or VMP intensification**

progression (0·24) or death (0·30) observed in this subgroup of patients compared with del(17p)-positive patients randomly assigned to the single HSCT group. These findings were not confirmed in the BMT CTN 0702 trial, but the rate of non-adherence to the second planned HSCT, which was as high as 32% (*vs* 20% in the EMN02/HO95 trial), and the many differences between the two studies, including also the definition of high-risk disease, may partly account for the conflicting results. Preliminary analyses of highly active four-drug regimens have recently reported enhanced rates of complete response and negative minimal residual disease status.[28,29] Whether these newer treatments might improve, or overcome, the poor prognosis imparted by high-risk cytogenetic abnormalities and ultimately abrogate the preferential use of double HSCT in this setting, as suggested by our analysis, needs to be addressed in future trials.

In our study, lenalidomide maintenance was planned until progressive disease or undue toxicity, although the optimal length of treatment is still debated. Median duration of treatment (34 months), discontinuation rate due to treatment-related adverse events (28%), risk of second primary malignancy (6%), and median progression-free survival after autologous HSCT (58 months) were consistent with those reported in other phase 3 studies.[24,30] Patients with undetectable minimal residual disease by flow cytometry before starting maintenance therapy had a reduced risk of disease

progression or death compared with those in whom minimal residual disease was detected.

Our study has some limitations. When the trial was designed, VCD was one of the most frequently used induction regimens in Europe and the USA for HSCT-eligible patients with multiple myeloma, whereas it is now considered a less optimal treatment option than VRD or bortezomib–thalidomide–dexamethasone. This finding might have ultimately affected the rates of response. The number of patients enrolled in the correlative substudy of minimal residual disease assessment by flow cytometry was limited and prevented a comprehensive analysis of the intention-to-treat population aimed at revealing more subtle differences in the response between treatment groups. The sample size of subgroups of patients with and without cytogenetic abnormalities was not powered for the comparison of double versus single HSCT and results warrant further confirmation. Finally, the analysis of quality of life reports is ongoing and data are not yet available.

In conclusion, upfront autologous HSCT significantly prolonged progression-free survival compared with VMP, a gain retained across all prognostic subgroups of patients. At a fairly short median follow-up of approximately 5 years, overall survival was similar between the two treatment groups. Consolidation therapy with VRD significantly improved progression-free survival, but not overall survival, compared with no consolidation. Double HSCT was superior to single HSCT in terms of progression-free survival and overall survival in the intention-to-treat population, although del(17p)-positive patients were likely to benefit most from this intensive treatment strategy. Four-drug regimens including a monoclonal antibody combined with a proteasome inhibitor and an immunomodulatory drug are currently being evaluated in clinical trials as induction therapy before, and consolidation after, autologous HSCT, through serial assessments of minimal residual disease.[28] Final results from these studies should be awaited before a shift from routine use of upfront autologous HSCT to delayed HSCT or alternative treatment strategies driven by minimal residual disease status can be offered to patients with newly diagnosed multiple myeloma who are fit for high-dose chemotherapy.

Contributors

The lead authors (MC, MBo, and PS) designed the study and wrote the report. FG, MBe, LPa, MTP, MAD, SZ, EZ, GAP, FP, VMo, MGa, VMa, BG, MH ABe, LPo, PY, MGr, AC, SB, MO, IDV, RZ, AML, NFA, ABr, APas, GBe, M-DL, GBo, HL, SA, AMM, KLW, RB, RH, MD, PAvdB, TCdT, CD, GS, AW, PG, U-HM, MvMK, MM, CM, AMC, APal, SC, and AS were study investigators. RT collated the data. LD, BvdH, and LPa analysed the data. SO and VHJvdV did the assessment of minimal residual disease. MC and PS were coprincipal investigators of the study. All authors contributed to the review of the manuscript and approved the final version before submission.

Declaration of interests

MC has received honoraria from Janssen, Celgene, Amgen, Bristol-Myers Squibb, Takeda, AbbVie, Sanofi, and Adaptive Biotechnologies, and is a member of speakers' bureaus for Janssen and Celgene. FG has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Takeda, Roche, AbbVie, Adaptive Biotechnologies, and Seattle Genetics. MBe has received honoraria from Celgene, Janssen, Sanofi, Takeda, and Amgen, and is a member of speakers' bureaus for Celgene, Janssen, Takeda, and Amgen. LPa has received honoraria from Celgene, Janssen, Takeda, and Amgen. MTP has received honoraria from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Amgen, Takeda, and Sanofi. MAD has received honoraria from Amgen, Takeda, Celgene, Bristol-Myers Squibb, and Janssen. SZ has received honoraria from Celgene, Sanofi, Takeda, and Janssen, and research funding from Celgene, Takeda, and Janssen. SO has received honoraria from Amgen, Celgene, Janssen, Adaptive Biotechnologies, and Takeda. VHJvdV is one of the inventors on the EuroFlow-owned patent "Methods for flow cytometric detection of minimal residual disease in leukemia and lymphoma (US61/659,524)", licensed to Cytognos. EZ has received honoraria from Janssen, Bristol-Myers Squibb, Amgen, and Takeda. GAP has received honoraria from Amgen, Celgene, Janssen, and Novartis. MGa has received honoraria from Bristol-Meyers-Squibb, Celgene, Janssen, and Takeda. BG has received honoraria from Amgen, Celgene, and Janssen. Abe has received honoraria from Janssen, Celgene, and Amgen. SB has received honoraria from Celgene and Janssen. MO has received honoraria from Celgene and Janssen. AML has received research funding from Novartis, Janssen, Abbvie, Roche, Amgen, and Celgene; has received honoraria from Abbvie, Amgen, Takeda, and Servier; and has acted as a consultant for Incyte, Bristol-Meyers Squibb, Pfizer, Beigene, Oncopeptide, Verastem, Karyiopharm, Archigen, Biopharma, Debiopharm, Morphosys, Fibrogen, and Onconova. ABr has received honoraria from Celgene, Janssen, Amgen, and Takeda. Gbe has received honoraria from Novartis, Celgene, and Amgen. M-DL has received honoraria and travel support from Janssen. HL has received honoraria from Janssen, Celgene, Amgen, Sanofi, and Seattle Genetics; is a member of speakers' bureaus for Janssen, Celgene, Amgen, Sanofi, and Seattle Genetics; and has received research funding from Amgen and Takeda. SA has received honoraria from Amgen, Celgene, and Janssen. RH has received honoraria and research funding from Amgen, Takeda, Celgene, Janssen, Abbvie, Novartis, PharmaMar, and Bristol-Myers Squibb. TCdT has received honoraria from Celgene, Janssen, and Amgen. AW has received honoraria from Janssen and Takeda. U-HM has received honoraria from Amgen, Sanofi, Janssen, Takeda, and Celgene. MM has received honoraria from Celgene, Servier, Jansen-Cilag, and Gilead, and has received research funding from Celgene. APal has received honoraria from Roche, Janssen, Celgene, and Takeda. AS has acted as a consultant for Celgene, Janssen, Secura Bio, Specialised Therapeutics Australia, AbbVie, Servier, Haemalogix, and Sanofi; is a member of speakers' bureaus for Celgene, Janssen, and Takeda; has received research funding from Celgene, Janssen, Amgen, Takeda, Servier, and Haemalogi; and has received honoraria from Celgene, Janssen, Amgen, Takeda, Secura Bio, Specialised Therapeutics Australia, AbbVie, Servier, Haemalogix, and Sanofi. MBo has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie, and has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma. PS has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, and Takeda, and has received research funding from Amgen, Celgene, Janssen, Karyopharm, SkylineDx, and Takeda. All interests declared are outside of the submitted work. All other authors declare no competing interests.

Data sharing

No data will be made available for sharing.

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