Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial

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Lancet 2020; 395: 132–41

Published Online December 9, 2019 https://doi.org/10.1016/S0140-6736(19)32956-3

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Summary

Background Standard-of-care treatment for patients with newly diagnosed multiple myeloma includes combination therapies for patients who are not eligible for autologous stem-cell transplantation. At the primary analysis for progression-free survival of the phase 3 ALCYONE trial, progression-free survival was significantly longer with daratumumab in combination with bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) alone in patients with transplant-ineligible, newly diagnosed multiple myeloma. Here we report updated efficacy and safety results from a prespecified, interim, overall survival analysis of ALCYONE with more than 36 months of follow-up.

Methods ALCYONE was a multicentre, randomised, open-label, active-controlled, phase 3 trial that enrolled patients between Feb 9, 2015, and July 14, 2016, at 162 sites in 25 countries across North America, South America, Europe, and the Asia-Pacific region. Patients were eligible for inclusion if they had newly diagnosed multiple myeloma and were ineligible for high-dose chemotherapy with autologous stem-cell transplantation, because of their age (≥65 years) or because of substantial comorbidities. Patients were randomly assigned in a 1:1 ratio and by permuted block randomisation to receive D-VMP or VMP. An interactive web-based randomisation system was used. Randomisation was stratified by International Staging System disease stage, geographical region, and age. There was no masking to treatment assignments. All patients received up to nine 6-week cycles of subcutaneous bortezomib (1·3 mg/m² of body surface area on days 1, 4, 8, 11, 22, 25, 29, and 32 of cycle one and on days 1, 8, 22, and 29 of cycles two through nine), oral melphalan (9 mg/m² once daily on days 1 through 4 of each cycle), and oral prednisone (60 mg/m² once daily on days 1 through 4 of each cycle). Patients in the D-VMP group also received intravenous daratumumab (16 mg/kg of bodyweight, once weekly during cycle one, once every 3 weeks in cycles two through nine, and once every 4 weeks thereafter as maintenance therapy until disease progression or unacceptable toxicity). The primary endpoint was progression-free survival, which has been reported previously. Results presented are from a prespecified interim analysis for overall survival. The primary analysis population (including for overall survival) was the intention-to-treat population of all patients who were randomly assigned to treatment. The safety population included patients who received any dose of study treatment. This trial is registered with ClinicalTrials.gov, NCT02195479.

Findings 706 patients were randomly assigned to treatment groups (350 to the D-VMP group, 356 to the VMP group). At a median follow-up of 40·1 months (IQR 37·4–43·1), a significant benefit in overall survival was observed for the D-VMP group. The hazard ratio (HR) for death in the D-VMP group compared with the VMP group was 0·60 (95% CI 0·46–0·80; p=0·0003). The Kaplan-Meier estimate of the 36-month rate of overall survival was 78·0% (95% CI 73·2–82·0) in the D-VMP group and 67·9% (62·6–72·6) in the VMP group. Progression-free survival, the primary endpoint, remained significantly improved for the D-VMP group (HR 0·42 [0·34–0·51]; p<0·0001). The most frequent adverse events during maintenance daratumumab monotherapy in patients in the D-VMP group were respiratory infections (54 [19%] of 278 patients had upper respiratory tract infections; 42 [15%] had bronchitis, 34 [12%] had viral upper respiratory tract infections), cough (34 [12%]), and diarrhoea (28 [10%]).

Interpretation D-VMP prolonged overall survival in patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation. With more than 3 years of follow-up, the D-VMP group continued to show significant improvement in progression-free survival, with no new safety concerns.

Funding Janssen Research & Development.

Research in context

Evidence before this study

We searched PubMed for articles published from database inception to Oct 25, 2019. All fields were searched for "newly diagnosed" AND "multiple myeloma" AND "overall survival" AND "monoclonal antibody". Our search identified 60 articles published during this timeframe. Of those, 17 articles were published before the first patient was enrolled in the ALCYONE study in February, 2015, with only one describing a clinical trial of a monoclonal antibody. This study reported results from a phase 2 trial of siltuximab (an interleukin-6 monoclonal antibody) in combination with bortezomib, melphalan, and dexamethasone in transplant-ineligible, newly diagnosed myeloma. This regimen did not show a clinical benefit over standard treatment with bortezomib, melphalan, and dexamethasone alone. Of the 43 articles published after ALCYONE was initiated, four reported results of clinical trials with a monoclonal antibody, but they have yet to show a survival benefit. The primary results of ALCYONE have been previously published and showed a remarkable benefit in progression-free survival for patients treated with daratumumab plus bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone alone; however, overall survival results were not mature at that time.

Added value of this study

Daratumumab in combination with standard-of-care regimens has shown efficacy in both newly diagnosed multiple myeloma and relapsed or refractory multiple myeloma. This updated analysis of the ALCYONE trial shows that the addition of daratumumab to a standard-of-care regimen significantly prolonged survival in patients with multiple myeloma. At a median follow-up of 40·1 months, daratumumab in combination with bortezomib, melphalan, and prednisone showed a 40% reduction in the risk of death versus bortezomib, melphalan, and prednisone alone. The daratumumab regimen continued to show significant progression-free survival benefit and sustained negative status for minimal residual disease, with no new safety concerns.

Implications of all the available evidence

For the first time, a daratumumab-based combination therapy has shown a significant improvement in overall survival. This study and other ongoing studies have shown that daratumumab-based combination regimens enable deep and durable responses, including negative status for minimal residual disease. Although longer-term follow-up of overall survival with daratumumab in other phase 3 studies is ongoing, the current efficacy and safety findings from the ALCYONE study strongly support the addition of daratumumab to standard-of-care regimens for patients with newly diagnosed, transplant-ineligible multiple myeloma.

Introduction

Standard of care for patients with multiple myeloma who are not eligible for autologous stem-cell transplantation historically has included combination therapies such as lenalidomide and dexamethasone, and bortezomib, melphalan, and prednisone, and more recently includes the combination of lenalidomide, bortezomib, and dexamethasone.[1–3]

Daratumumab is a human IgGκ CD38-targeting monoclonal antibody with a direct on-tumour[4–7] and immunomodulatory mechanism of action.[8–10] The addition of daratumumab to standard-of-care regimens in phase 3 studies reduced the risk of disease progression or death by at least 44%, nearly doubled the rate of complete response or better, and at least tripled the percentage of patients who achieved negative status for minimal residual disease (defined as less than one tumour cell per 10^5 white cells) versus standard of care alone in patients with relapsed and newly diagnosed multiple myeloma.[11–14]

At the primary analysis for progression-free survival of the phase 3 ALCYONE trial, progression-free survival was significantly longer with daratumumab in combination with bortezomib, melphalan, and prednisone (D-VMP) versus bortezomib, melphalan, and prednisone (VMP) alone in patients with transplant-ineligible, newly diagnosed multiple myeloma, at a median follow-up of 16·5 months and without an increase in overall toxicity.[11] D-VMP continued to show a significant benefit in progression-free survival with an additional year of follow-up, including in patients at least 75 years of age.[15] A significant benefit in progression-free survival during the subsequent line of therapy was also observed for D-VMP.

Here we report updated efficacy and safety results from a prespecified, interim, overall survival analysis of ALCYONE with more than 36 months of follow-up.

Methods

Study design and participants

ALCYONE was a multicentre, randomised, open-label, active-controlled, phase 3 trial that enrolled patients between Feb 9, 2015, and July 14, 2016, at 162 sites in 25 countries across North America, South America, Europe, and the Asia Pacific region. The study design has been published previously.[11] The independent ethics committee or institutional review board at each site approved the protocol, which is available online and in the appendix (pp 15–362). The trial was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines by the International Conference on Harmonisation Good Clinical Practice.

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For the **study protocol** see https://www.nejm.org/doi/suppl/10.1056/NEJMoa1714678/suppl_file/nejmoa1714678_protocol.pdf

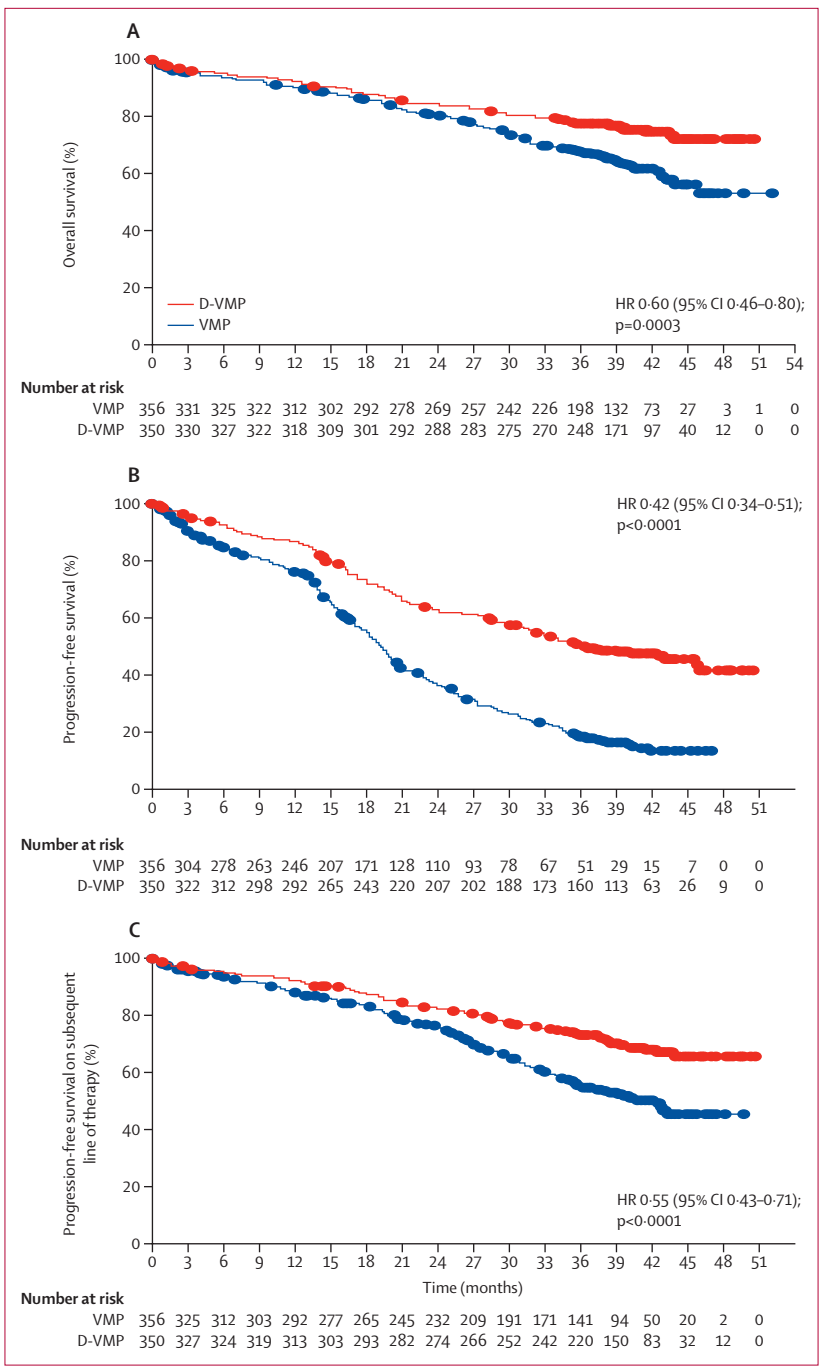

Figure 1: **Survival analyses in the intention-to-treat population**
Kaplan-Meier estimates of overall survival (A), progression-free survival (B), and progression-free survival on the subsequent line of therapy (C) in the intention-to-treat population, which included all patients who were randomly assigned to treatment. D-VMP=daratumumab plus bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. HR=hazard ratio.

See Online for appendix

All patients provided written informed consent. Data were compiled and maintained by the sponsor, but authors were given access to the data and were not restricted by confidentiality agreements. The sponsor and authors vouch for the accuracy and completeness of the data from the prespecified interim analysis and for adherence of the trial to the protocol.

Complete eligibility criteria have been published previously.[11] Briefly, patients were eligible for inclusion if they had newly diagnosed multiple myeloma and were ineligible for high-dose chemotherapy with autologous stem-cell transplantation, because of their age (≥65 years) or because of substantial comorbidities (appendix p 4).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio and by permuted block randomisation to receive D-VMP or VMP. An interactive web-based randomisation system (IRT, Signant Health, Wayne, PA, USA) was used, and each patient was assigned a unique number. Randomisation was stratified by International Staging System (ISS) disease stage (I *vs* II *vs* III, with higher stages indicating a poorer prognosis), geographical region (Europe *vs* other), and age (<75 years *vs* ≥75 years). ISS stages were determined on the basis of albumin and β_2 microglobulin concentrations. There was no masking to treatment assignments.

Procedures

All patients received up to nine 6-week cycles of subcutaneous bortezomib (1·3 mg/m² of body surface area on days 1, 4, 8, 11, 22, 25, 29, and 32 of cycle one and on days 1, 8, 22, and 29 of cycles two through nine), oral melphalan (9 mg/m² once daily on days 1 through 4 of each cycle), and oral prednisone (60 mg/m² once daily on days 1 through 4 of each cycle). Patients in the D-VMP group also received intravenous daratumumab (16 mg/kg of bodyweight, once weekly during cycle one, once every 3 weeks in cycles two through nine, and once every 4 weeks thereafter until disease progression or unacceptable toxicity). To mitigate infusion-related reactions, daratumumab was administered with 20 mg oral or intravenous dexamethasone, which was substituted for prednisone on day 1 of cycles one through nine (appendix p 4).

Outcomes

The primary endpoint of the ALCYONE trial was progression-free survival, which has been reported previously.[11] Secondary endpoints were rate of complete response, negative status for minimal residual disease (defined as <1 tumour cell per 100 000 white blood cells),[16] time to progression, progression-free survival on the subsequent line of therapy, overall survival, overall response rate, and safety (appendix pp 5–6). Secondary endpoints were tested sequentially with the use of a hierarchical testing approach, each with an overall two-sided α level of 0·05: overall response rate, rate of very good partial response or better, rate of complete response or better, and rate of negative status for minimal residual disease. Criteria for a stringent complete response included the criteria for a complete response plus a normal free light chain ratio and absence of clonal

	D-VMP group (n=350)	VMP group (n=356)	Odds ratio (95% CI)	p value
Overall response (%; 95% CI)	318 (90·9%; 87·3–93·7)	263 (73·9%; 69·0–78·4)	3·55 (2·30–5·49)	<0·0001
Best overall response				
Complete response or better	160 (46%)	90 (25%)	2·50 (1·82–3·45)	<0·0001
Stringent complete response	81 (23%)	28 (8%)	..	..
Complete response	79 (23%)	62 (17%)	..	..
Very good partial response or better	255 (73%)	177 (50%)	2·71 (1·98–3·71)	<0·0001
Very good partial response	95 (27%)	87 (24%)	..	..
Partial response	63 (18%)	86 (24%)	..	..
Stable disease	20 (6%)	76 (21%)	..	..
Progressive disease	0	2 (1%)	..	..
Response could not be measured	12 (3%)	15 (4%)	..	..
Negative status for minimal residual disease	99 (28%)	25 (7%)	5·23 (3·27–8·36)	<0·0001
Sustained negative status for minimal residual disease				
≥6 months	55 (16%)	16 (5%)	3·96 (2·22–7·06)	<0·0001
≥12 months	49 (14%)	10 (3%)	5·63 (2·80–11·31)	<0·0001

D-VMP=daratumumab in combination with bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. The p value for response rates was calculated using the Cochran–Mantel–Haenszel χ^2 test.

Table 1: **Summary of best overall responses and minimal residual disease status in the intention-to-treat population**

plasma cells, as assessed by immunohistochemical or immunofluorescence analysis or by two-colour to four-colour flow cytometry. The p value for minimal residual disease negativity and sustained minimal residual disease negativity was calculated with Fisher's exact test. Progression-free survival on the subsequent line of therapy is defined as the time from randomisation to disease progression on the next line of therapy or death, whichever comes first. International Myeloma Working Group criteria[16] were used to define all efficacy responses, including progressive disease and negative status for minimal residual disease. Minimal residual disease status was assessed in bone marrow samples with the Adaptive clonoSEQ assay (version 2.0; Adaptive Biotechnologies, Seattle, WA, USA) after randomisation. Efficacy responses were assessed as described previously (appendix pp 5–6).[11] Cytogenetic risk was assessed locally by fluorescence in situ hybridisation or karyotype testing. Patients had high cytogenetic risk if they had at least one of the following abnormalities: del17p, t(4;14), or t(14;16). Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).[17]

Statistical analysis

The primary analysis population (including for overall survival) was the intention-to-treat population of all patients who were randomly assigned to treatment. The safety population included patients who received any dose of study treatment. Sample size assumptions have been previously described.[11] Briefly, 350 patients per treatment group were estimated to provide 85% power to detect a 27·6% lower risk of disease progression or death in the D-VMP group versus the VMP group.[11] The primary endpoint and other time-to-event variables were estimated using the Kaplan-Meier method. A Cox regression model was used to estimate treatment effect, presented as hazard ratios (HRs) with two-sided 95% CIs. Binary endpoints, such as overall response rate, were assessed using the stratified Cochran–Mantel–Haenszel test. For progression-free survival, patients were censored at the date of last disease assessment, before subsequent antimyeloma therapy or at withdrawal of consent to study participation (whichever came first). For progression-free survival on the subsequent line of therapy, patients were censored at the start of subsequent antimyeloma therapy or the date of last follow-up (whichever came first). For overall survival, patients were censored at the last date at which they were known to be alive. For progression-free survival and progression-free survival on the subsequent line of therapy, results were stratified according to ISS staging, geographical region, and patient age as per randomisation.

The significance of progression-free survival was established at the second interim analysis for progression-free survival,[11] but testing of overall survival continued as planned. The first interim analysis, with a purpose to evaluate safety only, was performed after a total of approximately 100 patients had been treated for at least two cycles or discontinued the study treatment. The final analysis of overall survival will occur after 330 deaths have been observed; the current analysis, occurring after 209 deaths (ie, 63% of planned events) were observed, is a prespecified interim analysis for overall survival. Analyses of progression-free survival and overall survival were also performed in prespecified subgroups (including by patient age and cytogenetic risk status). Analyses of sustained negative status for minimal residual disease, progression-free survival and overall survival by sustained negative status for minimal

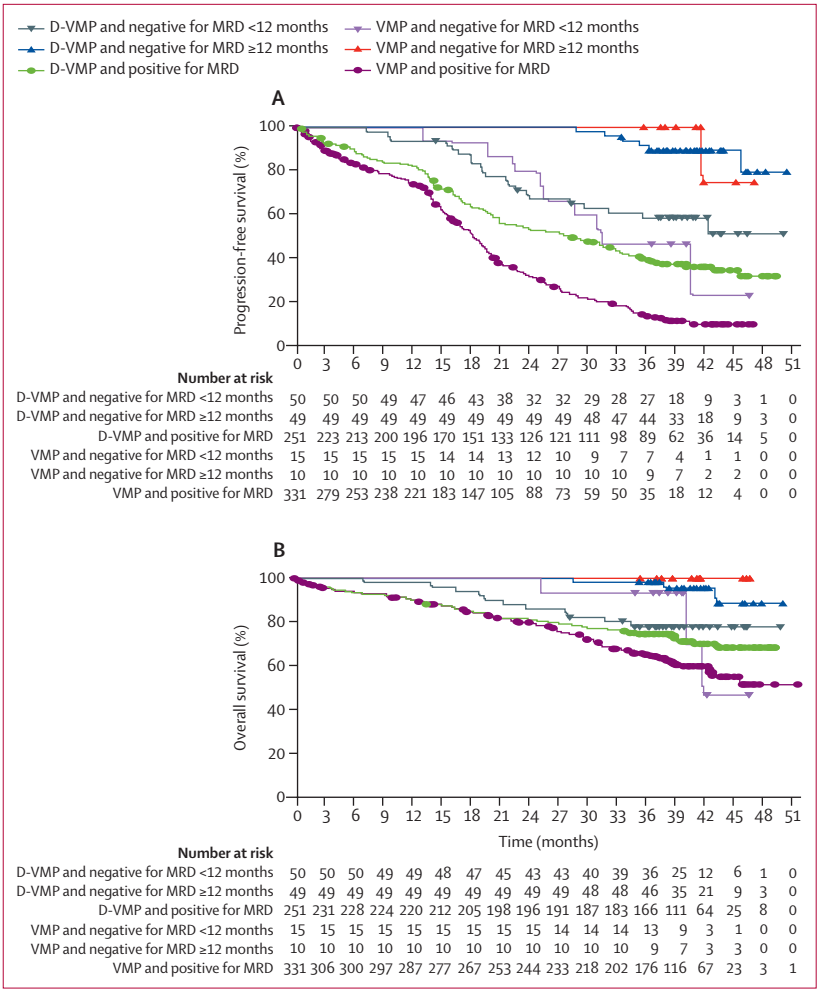

Figure 2: **Survival analyses by MRD status**
Kaplan-Meier estimates of progression-free survival (A), and overall survival (B) among patients in the intention-to-treat population by minimal residual disease status. D-VMP=daratumumab in combination with bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. MRD=minimal residual disease.

residual disease, and overall survival by type of subsequent therapy were considered post hoc. Results describing subsequent therapies and outcomes are descriptive. SAS (version 9.4; SAS Institute, Cary, NC, USA) was the program used for statistical analyses. This trial is registered with ClinicalTrials.gov, NCT02195479.

Role of the funding source

The funders designed the trial, collected the data, and analysed and interpreted the data in collaboration with the authors. Professional medical writers who were funded by the sponsor prepared the manuscript. 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

706 patients were randomly assigned to treatment groups (350 to the D-VMP group, 356 to the VMP group). Patient demographics and baseline disease characteristics were well balanced between groups (appendix p 10).[11] Median age was 71 years (range 40–93); 211 (30%) of 706 patients were at least 75 years of age. 271 (38%) patients had ISS stage III disease and 98 (14%) had a high-risk cytogenetic profile.

Among the patients who were randomly assigned, four in the D-VMP group and two in the VMP group did not receive at least one dose of study treatment (appendix p 7). At the time of clinical cutoff for the updated analysis on June 24, 2019, all 700 patients who received study treatment had either completed or discontinued the first nine treatment cycles and 146 (42%) of 350 in the D-VMP group continued to receive daratumumab monotherapy. The most common reason for patients to discontinue treatment in both groups was progressive disease.

At a median follow-up of 40·1 months (IQR 37·4–43·1), 83 (24%) of 350 patients in the D-VMP group and 126 (35%) of 356 patients in the VMP group had died. The HR for death in the D-VMP group compared with the VMP group was 0·60 (95% CI 0·46–0·80; p=0·0003; figure 1A), crossing the prespecified stopping boundary of p=0·0317 and representing a 40% reduction in the risk of death. The Kaplan-Meier estimate of the 36-month rate of overall survival was 78·0% (95% CI 73·2–82·0) in the D-VMP group and 67·9% (62·6–72·6) in the VMP group. Median overall survival was not reached in either group and follow-up is ongoing. A sensitivity analysis (in the per-protocol population, including all patients who were randomly assigned and met all eligibility criteria) of 344 patients in the D-VMP group and 351 in the VMP group noted consistent results for overall survival (HR 0·61 [0·46–0·80]; p=0·0004).

Disease progression or death had occurred in 176 (50%) of 350 patients in the D-VMP group and 265 (74%) of 356 patients in the VMP group; most of these events were progressive disease (142 [41%] in the D-VMP group and 230 [65%] in the VMP group). The HR for disease progression or death in the D-VMP group compared with the VMP group was 0·42 (95% CI 0·34–0·51; p<0·0001; figure 1B). The Kaplan-Meier estimate of the 36-month rate of progression-free survival was 50·7% (45·1–55·9) in the D-VMP group and 18·5% (14·4–23·1) in the VMP group. Median progression-free survival was 36·4 months (95% CI 32·1–45·9) in the D-VMP group versus 19·3 months (18·0–20·4) in the VMP group.

Overall response rate was 90·9% (95% CI 87·3–93·7) for 350 patients in the D-VMP group and 73·9% (69·0–78·4) for 356 patients in the VMP group (p<0·0001; table 1). Rates of very good partial response or better (73% in the D-VMP group *vs* 50% in the VMP group; p<0·0001) and complete response or better (46% in the D-VMP group *vs* 25% in the VMP group; p<0·0001) were also significantly higher in the D-VMP group than in the VMP group. The rate of negative status for minimal residual disease was four times greater in the D-VMP

	Age <75 years				Age ≥75 years			
	D-VMP group (n=246)	VMP group (n=249)	Odds ratio (95% CI)	p value	D-VMP group (n=104)	VMP group (n=107)	Odds ratio (95% CI)	p value
Overall response (%; 95% CI)	227 (92·3%; 88·2–95·3)	188 (75·5%; 69·7–80·7)	3·88 (2·24–6·72)	<0·0001	91 (87·5%; 79·6–93·2)	75 (70·1%; 60·5–78·6)	2·99 (1·46–6·10)	0·0021
Best overall response								
Complete response or better	117 (48%)	64 (26%)	2·62 (1·80–3·83)	<0·0001	43 (41%)	26 (24%)	2·20 (1·22–3·96)	0·0085
Stringent complete response	58 (24%)	20 (8%)	..	..	23 (22%)	8 (8%)	..	..
Complete response	59 (24%)	44 (18%)	..	..	20 (19%)	18 (17%)	..	..
Very good partial response or better	183 (74%)	125 (50%)	2·88 (1·97–4·21)	<0·0001	72 (69%)	52 (49%)	2·38 (1·36–4·18)	0·0024
Very good partial response	66 (27%)	61 (25%)	..	..	29 (28%)	26 (24%)	..	..
Partial response	44 (18%)	63 (25%)	..	..	19 (18%)	23 (22%)	..	..
Stable disease	12 (5%)	49 (20%)	..	..	8 (8%)	27 (25%)	..	..
Progressive disease	0	2 (1%)	..	..	0	0	..	..
Response could not be measured	7 (3%)	10 (4%)	..	..	5 (5%)	5 (5%)	..	..

D-VMP=daratumumab in combination with bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. The p value for response rates was calculated using the Cochran–Mantel–Haenszel χ^2 test.

Table 2: **Summary of best overall responses by age subgroup in the intention-to-treat population**

	Standard cytogenetic risk				High cytogenetic risk			
	D-VMP group (n=261)	VMP group (n=257)	Odds ratio (95% CI)	p value	D-VMP group (n=53)	VMP group (n=45)	Odds ratio (95% CI)	p value
Overall response (%; 95% CI)	238 (91·2%; 87·1–94·3)	184 (71·6%; 65·7–77·0)	4·11 (2·47–6·81)	<0·0001	49 (92·5%; 81·8–97·9)	33 (73·3%; 58·1–85·4)	4·45 (1·32–15·01)	0·0111
Best overall response								
Complete response or better	126 (48%)	66 (26%)	2·70 (1·86–3·91)	<0·0001	22 (42%)	11 (24%)	2·19 (0·92–5·25)	0·0764
Stringent complete response	66 (25%)	25 (10%)	..	..	10 (19%)	1 (2%)	..	..
Complete response	60 (23%)	41 (16%)	..	..	12 (23%)	10 (22%)	..	..
Very good partial response or better	191 (73%)	125 (49%)	2·88 (2·00–4·16)	<0·0001	39 (74%)	20 (44%)	3·48 (1·49–8·13)	0·0035
Very good partial response	65 (25%)	59 (23%)	..	..	17 (32%)	9 (20%)	..	..
Partial response	47 (18%)	59 (23%)	..	..	10 (19%)	13 (29%)	..	..
Stable disease	17 (7%)	62 (24%)	..	..	0	9 (20%)	..	..
Progressive disease	0	2 (1%)	..	..	0	0	..	..
Response could not be measured	6 (2%)	9 (4%)	..	..	4 (8%)	3 (7%)	..	..

D-VMP=daratumumab in combination with bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. The p value for response rates was calculated using the Cochran–Mantel–Haenszel χ^2 test.

Table 3: **Summary of best overall responses by cytogenetic risk in the intention-to-treat population**

group than in the VMP group (28% in the D-VMP group *vs* 7% in the VMP group; p<0·0001; table 1). Compared with the VMP group, more patients in the D-VMP group remained negative for minimal residual disease after 6 months (55 [16%] in the D-VMP group *vs* 16 [5%] in the VMP group; p<0·0001) and after 12 months (49 [14%] in the D-VMP group vs 10 [3%] in the VMP group; p<0·0001; table 1). Sustained negative status for minimal residual disease for at least 12 months was associated with significantly improved progression-free survival and overall survival (figure 2). Patients who did not sustain negative status for minimal residual disease for at least 12 months frequently had a missing or indeterminate sample (21 in the D-VMP group and seven in the VMP group), or became positive for minimal residual disease before disease progression or death (17 in the D-VMP group and seven in the VMP group; appendix p 11).

Prespecified subgroup analyses of overall survival showed favourable results for the D-VMP group over the VMP group across all subgroups; the benefit was less

	D-VMP group	VMP group
Patients receiving subsequent therapy	115/350 (33%)	202/356 (57%)
Regimen containing proteasome inhibitor without immunomodulatory drug as first subsequent therapy	14/115 (12%)	28/202 (14%)
Median overall survival, months (95% CI)	NR (20·4–NR)	42·9 (31·4–NR)
36-month rate of overall survival (95% CI)	71·4% (40·6–88·2)	57·1% (37·1–72·9)
Regimen containing immunomodulatory drug without proteasome inhibitor as first subsequent therapy	55/115 (48%)	108/202 (54%)
Median overall survival, months (95% CI)	NR (43·6–NR)	NR (37·7–NR)
36-month rate of overall survival (95% CI)	67·2% (53·1–77·9)	62·3% (52·3–70·8)
Regimen containing proteasome inhibitor and immunomodulatory as first subsequent therapy	29/115 (25%)	25/202 (12%)
Median overall survival, months (95% CI)	NR (39·8–NR)	46·2 (39·1–NR)
36-month rate of overall survival (95% CI)	82·3% (62·6–92·2)	76·0% (54·2–88·4)
Regimen containing daratumumab as first subsequent therapy	1/115 (1%)	21/202 (10%)
Median overall survival, months (95% CI)	NR	NR
36-month rate of overall survival (95% CI)	NR	100·0% (100·0–100·0)
Other regimens as first subsequent therapy	16/115 (14%)	20/202 (10%)
Median overall survival, months (95% CI)	41·5 (24·6–NR)	NR (31·5–NR)
36-month rate of overall survival (95% CI)	66·7% (37·5–84·6)	74·4% (48·9–88·5)

Proteasome inhibitors include bortezomib, carfilzomib, marizomib, ixazomib, and oprozomib. Immunomodulatory drugs include thalidomide, lenalidomide, and pomalidomide. D-VMP=daratumumab in combination with bortezomib, melphalan, and prednisone. VMP=bortezomib, melphalan, and prednisone. NR=not reached.

Table 4: **Subsequent lines of therapy and outcomes**

	Any grade	Grade 3 or 4
Haematological adverse events		
Anaemia	25 (9%)	12 (4%)
Neutropenia	15 (5%)	6 (2%)
Thrombocytopenia	13 (5%)	5 (2%)
Non-haematological adverse events		
Upper respiratory tract infection	54 (19%)	2 (1%)
Bronchitis	42 (15%)	3 (1%)
Viral upper respiratory tract infection	34 (12%)	0
Cough	34 (12%)	0
Diarrhoea	28 (10%)	0
Arthralgia	24 (9%)	0
Urinary tract infection	22 (8%)	4 (1%)
Back pain	22 (8%)	2 (1%)
Pyrexia	19 (7%)	0
Pneumonia	17 (6%)	10 (4%)
Peripheral oedema	17 (6%)	0
Hypertension	16 (6%)	8 (3%)
Asthenia	15 (5%)	1 (<1%)
Pain in extremity	15 (5%)	0
Fatigue	13 (5%)	1 (<1%)
Nausea	10 (4%)	0

Daratumumab monotherapy was provided to 278 patients after treatment cycle nine. Adverse events of any grade were reported in at least ten patients, and adverse events of grade 3 or 4 were reported in at least three patients.

Table 5: **Most common adverse events during maintenance daratumumab monotherapy in the safety population**

pronounced in patients with high cytogenetic risk compared with patients with standard cytogenetic risk (appendix pp 8–9). Responses were consistently improved in the D-VMP group regardless of age or cytogenetic risk status (tables 2, 3).

115 (33%) of 350 patients in the D-VMP group and 202 (57%) of 356 patients in the VMP group received subsequent therapy. Of these, seven in the D-VMP group and 25 in the VMP group did not have disease progression beforehand. For patients who had disease progression, 108 (76%) of 142 in the D-VMP group and 177 (77%) of 230 in the VMP group received a subsequent line of therapy. 102 (29%) of 350 patients in the D-VMP group and 152 (43%) of 356 patients in the VMP group had disease progression or death on the subsequent line of therapy (HR 0·55 [95% CI 0·43–0·71]; p<0·0001; figure 1C). Median progression-free survival on the subsequent line of therapy was 42·3 months (35·8–not reached) in the VMP group, but it was not reached in the D-VMP group. The Kaplan-Meier estimate of the 36-month rate of progression-free survival on the subsequent line of therapy was 73·2% (68·1–77·7) in the D-VMP group and 55·2% (49·4–60·6) in the VMP group.

First subsequent therapies for patients in both treatment groups are summarised in the appendix (p 12). Among the 317 patients who received second-line therapy, an immunomodulatory drug-containing regimen without a proteasome inhibitor was the most common first subsequent therapy (55 [48%] of 115 patients in the D-VMP group and 108 [54%] of 202 in the VMP group; table 4). The most common immunomodulatory drug-containing regimen was lenalidomide and dexamethasone. Other common subsequent therapies included a proteasome inhibitor plus an immunomodulatory drug (29 [25%] patients in the D-VMP group and 25 [12%] in the VMP group) and a proteasome inhibitor-containing regimen without an immunomodulatory drug (14 [12%] patients in the D-VMP group and 28 [14%] in the VMP group). The most common proteasome inhibitor plus immunomodulatory drug combination regimen was carfilzomib, lenalidomide, and dexamethasone, and the most common proteasome inhibitor-containing regimen without an immunomodulatory drug was bortezomib and dexamethasone (appendix p 12). 21 (10%) patients in the VMP group and one (1%) in the D-VMP group received a daratumumab-containing regimen as first subsequent therapy. 13 (4%) patients received daratumumab plus lenalidomide and dexamethasone, five (2%) received daratumumab plus bortezomib and dexamethasone, two (1%) received daratumumab plus carfilzomib and dexamethasone, and two (1%) received daratumumab monotherapy. Improved overall survival was observed for most categories of subsequent therapy for the D-VMP group compared with the VMP group (table 4).

No new safety concerns were identified in the D-VMP group with longer follow-up. At the clinical cutoff date,

all patients in the VMP group had completed treatment. An updated summary of the most common adverse events occurring overall and during cycles one through nine for both treatment groups is included in the appendix (p 13). During cycles one through nine, the most common (>15% of patients in either group) grade 3 or 4 treatment-emergent adverse events were neutropenia (138 [40%] of 346 patients in the D-VMP group and 138 [39%] of 354 in the VMP group), thrombocytopenia (119 [34%] patients in the D-VMP group and 134 [38%] in the VMP group), and anaemia (53 [15%] patients in the D-VMP group and 70 [20%] in the VMP group). The most common (≥10% of patients) adverse events during daratumumab monotherapy after the first nine treatment cycles in patients in the D-VMP group were upper respiratory tract infection, bronchitis, viral upper respiratory tract infection, cough, and diarrhoea (table 5). The most common grade 3 or 4 adverse events during this period were anaemia (12 [4%] of 278 patients), pneumonia (ten [4%]), hypertension (eight [3%]), neutropenia (six [2%]), and thrombocytopenia (five [2%]).

During cycles one through nine, the incidence of grade 3 or 4 infections was higher in the D-VMP group than in the VMP group (75 [22%] of 346 patients in the D-VMP group *vs* 53 [15%] of 354 in the VMP group). Pneumonia was the most common grade 3 or 4 infection (38 [11%] patients in the D-VMP group and 15 [4·2%] in the VMP group). Six (2%) patients in the D-VMP group and six (2%) in the VMP group discontinued treatment because of infections; three (1%) patients in the D-VMP group and one (<1%) in the VMP group discontinued treatment due to pneumonia. Serious adverse events occurred during cycles one through nine in 132 (38%) patients in the D-VMP group and in 117 (33%) patients in the VMP group; pneumonia was the most common (33 [10%] patients in the D-VMP group and 12 [3%] in the VMP group). During daratumumab monotherapy, 30 (11%) of 278 patients in the D-VMP group had grade 3 or 4 infections (ten [4%] had grade 3 or 4 pneumonia) and 60 (22%) had a serious adverse event. Overall, 83 (24%) of 346 patients in the D-VMP group and 126 (36%) of 354 in the VMP group died during the study. The incidence of invasive second primary malignancy was similar in the D-VMP group and the VMP group (17 [5%] in the D-VMP group and 16 [5%] in the VMP group). The rate of discontinuation of treatment due to adverse events was lower in the D-VMP group than in the VMP group (24 [7%] patients discontinued treatment in the D-VMP group compared with 33 [9%] in the VMP group).

Discussion

For the first time, we show that the addition of daratumumab to a standard-of-care regimen significantly prolonged survival in patients with multiple myeloma. Daratumumab in combination with VMP prolonged overall survival in patients with transplant-ineligible, newly diagnosed myeloma, with a 40% reduction in the risk of death versus VMP alone after a median follow-up of 40 months. Patients in the D-VMP group continued to have a significant progression-free survival benefit over the VMP group. Responses with daratumumab continued to improve over time from the primary analysis (which had a median follow-up of 16·5 months),[11] with slight improvements in rates of stringent complete response (from 63 [18%] of 350 patients in the primary analysis to 81 [23%] of 350 patients) and complete response or better (from 149 [43%] patients in the primary analysis to 160 [46%]). Similarly, negative status for minimal residual disease in the D-VMP group increased from 78 (22%) of 350 patients in the primary analysis[11] to 99 (28%) of 350 in this analysis, and significantly more patients receiving daratumumab remained negative for minimal residual disease for at least 12 months. Patients with sustained negative status of at least 12 months for minimal residual disease had improved progression-free and overall survival compared with patients who had sustained negative status for minimal residual disease for less than 12 months (figure 2). A potential limitation of this study is that after completion of nine cycles of therapy with VMP, patients in the D-VMP group continued to receive daratumumab monotherapy while patients in the VMP group did not receive further treatment, per the approved VMP dosing schedule.

In prespecified subgroup analyses, a benefit in overall survival was observed in the D-VMP group over the VMP group across all subgroups analysed, with the exception of patients with high cytogenetic risk; follow-up in these patients is ongoing. For most types of subsequent therapy received, overall survival was improved in the D-VMP group compared with the VMP group (table 4). Additionally, 21 (10%) of 202 patients in the VMP group received a daratumumab-containing regimen as a first subsequent therapy; at 36 months, all of these patients remained alive.

No new safety concerns were identified for patients in the D-VMP group who received daratumumab monotherapy after cycle nine. During daratumumab monotherapy, respiratory infections were the most common adverse event, but were generally grade 1 or 2 (table 5).

Comparison with other studies are not fully appropriate due to differences not only in backbone regimens and control arm treatment, but because patient populations are not identical. In the FIRST trial of lenalidomide and dexamethasone versus melphalan, prednisone, and thalidomide,[18] the HR for death for continuous lenalidomide and dexamethasone versus a comparator group of fixed-duration melphalan, prednisone, and thalidomide for 72 weeks was 0·78, while in the VISTA trial of bortezomib, melphalan, and prednisone versus melphalan and prednisone alone the HR was 0·695.[19] In the SWOG S0777 trial of bortezomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with newly

diagnosed multiple myeloma,[20] the HR was 0·709 although the patient population in this trial included newly diagnosed patients who may have been transplant-eligible but did not have an intent for immediate stem-cell transplant. Longer-term follow-up of overall survival data from ALCYONE will provide a greater understanding of the potential effect of D-VMP relative to other therapies for newly diagnosed multiple myeloma.

Treatment of patients with transplant-ineligible, newly diagnosed multiple myeloma with D-VMP results in a significant reduction in the risk of death compared with initial treatment with VMP alone. This is the first report of an overall survival benefit with daratumumab in patients with multiple myeloma, and additional studies of daratumumab-based combinations, including daratumumab plus lenalidomide and dexamethasone and daratumumab plus bortezomib, lenalidomide, and dexamethasone in this patient population are underway. These findings continue to support the use of daratumumab-based regimens for front-line treatment in patients with transplant-ineligible, newly diagnosed multiple myeloma.

For the **data sharing policy** see https://www.janssen.com/clinical-trials/transparency

For the **Yale Open Data Access Project site** see http://yoda.yale.edu

Contributors

All authors participated in the drafting and revising of the manuscript and approved the final version for submission. MAD, TF, AJ, RK, M-VM, MQ, JS-M, and JU participated in the conception and design of the work being described in the publication, acquisition or collection of data, and analysis or interpretation of data. JB, CD, SG, GI, SK, ZN, LP, SW, and S-SY participated in the acquisition or collection of data, and analysis or interpretation of data. PC, MCa, MCo, AC, MG, AML, PL, and TS participated in the acquisition or collection of data. KS participated in the conception and design of the work being described in the publication. YC, MK, AK, and JW participated in the analysis or interpretation of data.

Declaration of interests

M-VM received honoraria from Amgen, Celgene, Janssen, and Takeda, and served as a consultant or in an advisory role for Amgen, GlaxoSmithKline, Celgene, Janssen, Takeda, and AbbVie. MCo received honoraria from AbbVie, GlaxoSmithKline, Bristol-Myers Squibb, Adaptive Biotechnologies, Takeda, Janssen, Celgene, and Amgen; served as a consultant or in an advisory role for AbbVie, GlaxoSmithKline, Bristol-Myers Squibb, Adaptive Biotechnologies, Takeda, Janssen, Celgene, and Amgen; received research support from Janssen and Celgene; and served on a speaker's bureau for Janssen and Celgene. JB received honoraria from Janssen, Celgene, Amgen, and Takeda. MAD received honoraria from Janssen, Celgene, Takeda, Amgen, and Bristol-Myers Squibb, and served as a consultant or in an advisory role for Janssen, Celgene, Takeda, Amgen, and Bristol-Myers Squibb. KS received honoraria from Janssen, Celgene, Novartis, Bristol-Myers Squibb, Ono, Takeda, and Sanofi Aventis; served as a consultant or in an advisory role for Janssen, Celgene, Novartis, Bristol-Myers Squibb, Ono, Takeda, and Sanofi Aventis; and is employed by SRL. AJ received honoraria from AbbVie, Adaptive Biotechnologies, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, SkylineDx, and Takeda, and served as a consultant or in an advisory role for AbbVie, Adaptive Biotechnologies, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Karyopharm, SkylineDx, and Takeda. SK received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda; served as a consultant or in an advisory role for Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda; and received research funding from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda. CD served as a consultant or in an advisory role for Janssen. PL received honoraria from Janssen, Celgene, Takeda, and Amgen, and served as a consultant or in an advisory role for Janssen, Celgene, Takeda, and Amgen. MCa received honoraria from Chugai, Janssen, Celgene, Jazz, Takeda, and Amgen, and received research funding from Janssen and Celgene. SG received research funding from Affimed. MG has received honoraria from Janssen and Amgen; research funding from Novartis; and travel, accommodations, and expenses from Takeda, Novartis, and Amgen. JS-M received honoraria from Janssen, Celgene, Amgen, Bristol-Myers Squibb, Novartis, Sanofi, and Roche. MK, YC, JW, AK, JU, SW, MQ, and RK are employed by Janssen. All other authors declare no competing interests.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available online. As noted on this site, requests for access to study data can be submitted through the Yale Open Data Access Project site.

Acknowledgments

This study was sponsored by Janssen Research & Development. We thank the patients who volunteered to participate in this trial, their families, and the staff members at the trial sites who cared for them; the members of the data and safety monitoring committee (Heinz Ludwig, Sigurdur Kristinsson, and Stephen George); representatives of the sponsor who were involved in data collection and analyses; and Elise Blankenship and Melissa Brunckhorst of MedErgy, for editorial assistance in the development of an earlier draft of the manuscript.

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