Long-Term Outcomes and Health-Related Quality of Life (HRQOL) by Response Status for Bortezomib, Melphalan, and Prednisone (VMP) ± Daratumumab in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma: ALCYONE

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INTRODUCTION

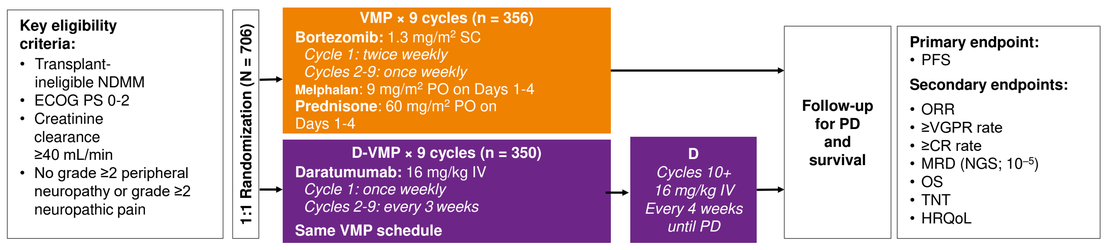
- Patients with multiple myeloma (MM) often experience long-term complications of the disease and adverse events associated with common, continuous therapeutic approaches that can have a negative impact on their health-related quality of life (HRQoL)
- In the primary analysis of the phase 3 ALCYONE study (median follow-up: 16.5 months), addition of daratumumab (a human IgGκ CD38-targeting monoclonal antibody) to bortezomib, melphalan, and prednisone (D-VMP) reduced the risk of disease progression or death by 50% versus VMP alone in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM), without an increase in overall toxicity[1]
  - Progression-free survival (PFS) benefit of D-VMP was accompanied by improved duration and depth of response, including the rates of complete response (CR) or better and minimal residual disease (MRD) negativity (10^{-5} sensitivity threshold), and meaningful improvements in HRQoL[1,2]
  - More recently, a significant overall survival (OS) benefit was also observed with D-VMP versus VMP at a median follow-up of 40.1 months, while PFS remained significantly improved and improvements in duration and depth of response continued, with no new safety concerns[3]
- Subgroup analysis results of ALCYONE examining long-term efficacy outcomes and HRQoL based on response status for D-VMP versus VMP, at a median follow-up of 40.1 months are reported here

METHODS

Study Design

- ALCYONE is a randomized phase 3 study of D-VMP versus VMP in patients with transplant-ineligible NDMM (**Figure 1**)

Figure 1. ALCYONE Study Design



Stratification factors were International Staging System (I vs II vs III), region (Europe vs other), and age (<75 vs ≥75 years). CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; D, daratumumab; D-VMP, daratumumab/bortezomib/melphalan/prednisone; HRQoL, health-related quality of life; IV, intravenous; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral; SC, subcutaneous; TNT, time to next therapy; VGPR, very good partial response.

Endpoints and Assessments

- PFS (primary endpoint): defined as time from randomization to either disease progression, according to International Myeloma Working Group (IMWG) criteria,[4,5] or death
- Secondary efficacy endpoints that were sequentially tested with use of a hierarchical testing approach included overall response rate (ORR), rate of very good partial response (VGPR) or better, rate of CR or better, MRD-negativity rate, and OS
  - Patients were classified by response category based on IMWG response criteria[6]
- MRD-negativity rate (10^{-5} sensitivity threshold) was evaluated in the intent-to-treat (ITT) population (all randomized patients) using clonoSEQ® assay V2.0 (Adaptive Biotechnologies, Seattle, WA, USA)
- Time to next therapy (TNT; time to subsequent antimyeloma therapy) and patient-reported HRQoL; assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30)
- Endpoints assessed at: prespecified interim analyses[1,3], at the time of best response at the beginning of daratumumab monotherapy (cycle 10+) and 1 and 2 years after beginning daratumumab monotherapy

Statistical Analyses

- Results from prespecified interim analyses are reported[3] as well as post hoc, subgroup analyses of the ITT population examining efficacy endpoints by response status for D-VMP versus VMP
- Time to event variables and response rates were evaluated using the Kaplan–Meier method and stratified Cochran–Mantel–Haenszel test, respectively
- The EORTC QLQ-C30 scales change from baseline were summarized descriptively by treatment group
  - Clinically meaningful improvements: a ≥10-point increase in the EORTC QLQ-C30 function scales and a decrease for symptom scales[7,8]

RESULTS

Patients and Treatments

- A total of 706 patients in ALCYONE (D-VMP, n=350; VMP, n=356) were randomized
- Patient demographics and baseline characteristics of the ITT population were previously published and were well-balanced between treatment groups (**Table 1**)
  - Median (range) age was 71.0 (40-93) years, and 46.3% of patients were male
- ECOG performance status scores of 0, 1, and 2 were reported in 25.1%, 50.3%, and 24.6% of patients, respectively
- At the time of clinical cutoff for the updated analysis (June 24, 2019), all patients who received study treatment had either completed or discontinued the first 9 treatment cycles; 146 (42%) of 350 patients in the D-VMP group continued to receive daratumumab monotherapy

Summary of Efficacy in the Overall ITT Population

- At a median follow-up of 40.1 months, **D-VMP reduced the risk of disease progression or death by 58% versus VMP** (median PFS: D-VMP, 36.4 months vs VMP, 19.3 months; hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.34-0.51; P <0.0001)
- D-VMP improved ORR (91% vs 74%) and the rates of CR or better (46% vs 25%), VGPR or better (73% vs 50%), MRD-negativity (28% vs 7%; all P <0.0001), and the rate of CR or better with MRD-negativity (27% vs 7%) versus VMP
- **A significant OS benefit was observed with D-VMP versus VMP, with a 40% reduction in the risk of death** (median OS: D-VMP, not reached [NR] vs VMP, NR; HR, 0.60; 95% CI, 0.46-0.80; P=0.0003); 36-month survival rates were 78% and 68% with D-VMP and VMP, respectively
- PFS remained significantly improved and improvements in duration and depth of response continued, while a significant OS benefit was observed with D-VMP versus VMP after >3 years of follow-up

Efficacy by Response Status

- PFS, TNT, and OS were prolonged, with deeper responses in both treatment groups (**Table 2**)
- **Median PFS was prolonged for D-VMP versus VMP in patients with a best response of partial response (PR), VGPR, and ≥CR** (**Figure 2** and **Table 2**)
  - All patients who achieved ≥CR with MRD-negativity demonstrated prolonged PFS, regardless of treatment
- Median TNT was increased with D-VMP versus VMP in patients with a best response of PR and improved with D-VMP versus VMP in patients with a best response of VGPR, ≥CR, or ≥CR with MRD negativity (**Table 2**)
- A trend toward improved median OS was observed with D-VMP versus VMP across response categories (**Table 2**)
  - For patients achieving ≥CR with MRD-negativity, 36-month survival rates were high (D-VMP, 89.3% vs VMP, 96.0%)

Table 1. Demographic and Baseline Disease Characteristics of Patients

Characteristic	D-VMP (n=350)	VMP (n=356)
Age		
Median (range), years	71.0 (40-93)	71.0 (50-91)
Distribution, n (%)		
<65 years	36 (10.3)	24 (6.7)
65-74 years	210 (60.0)	225 (63.2)
≥75 years	104 (29.7)	107 (30.1)
Male, n (%)	160 (45.7)	167 (46.9)
ECOG performance status,[a] n (%)		
0	78 (22.3)	99 (27.8)
1	182 (52.0)	173 (48.6)
2	90 (25.7)	84 (23.6)
ISS stage,[b] n (%)		
I	69 (19.7)	67 (18.8)
II	139 (39.7)	160 (44.9)
III	142 (40.6)	129 (36.2)
Cytogenetic profile[c]		
n	314	302
Standard risk, n (%)	261 (83.1)	257 (85.1)
High risk, n (%)	53 (16.9)	45 (14.9)
Median time since diagnosis of MM (range), months	0.76 (0.1-11.4)	0.82 (0.1-24.8)

D-VMP, daratumumab/bortezomib/melphalan/prednisone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; MM, multiple myeloma; VMP, bortezomib/melphalan/prednisone. [a]ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]The ISS disease stage is based on the combination of serum β2-microglobulin and albumin levels. Higher stages indicate more advanced disease. [c]Cytogenetic risk was assessed by fluorescence in situ hybridization or karyotype testing; high risk was defined as the presence of t(4;14), t(14;16), or del17p.

RESULTS *(CONTD.)*

Table 2. Efficacy by Response Status

Response category	D-VMP (n=350)	VMP (n=356)	HR (95% CI)	P value
PR, n (%)	63 (18.0)	86 (24.2)		
Median PFS, mo	17.1	16.1	0.58 (0.40-0.85)	0.0043
Median TNT, mo	23.6	20.7	0.74 (0.50-1.11)	0.1429
OS				
Median, mo	NR	NR	0.69 (0.39-1.21)	0.1879
36-mo survival rate, %	71.4	63.5	–	–
VGPR, n (%)	95 (27.1)	87 (24.4)		
Median PFS, mo	25.6	19.5	0.57 (0.40-0.81)	0.0014
Median TNT, mo	43.8	27.5	0.54 (0.36-0.81)	0.0027
OS				
Median, mo	NR	46.2	0.68 (0.40-1.15)	0.1463
36-mo survival rate, %	75.4	68.8	–	–
CR or better, n (%)	160 (45.7)	90 (25.3)		
Median PFS, mo	NR	34.6	0.41 (0.28-0.61)	<0.0001
Median TNT, mo	NR	44.4	0.38 (0.23-0.63)	<0.0001
OS				
Median, mo	NR	NR	0.86 (0.44-1.69)	0.6673
36-mo survival rate, %	89.3	88.5	–	–
CR or better + MRD negative, n (%)	94 (26.9)	25 (7.0)		
Median PFS, mo	NR	41.8	0.57 (0.27-1.20)	0.1314
Median TNT, mo	NR	44.4	0.38 (0.16-0.88)	0.0197
OS				
Median, mo	NR	NR	1.07 (0.30-3.78)	0.9202
36-mo survival rate, %	89.3	96.0	–	–

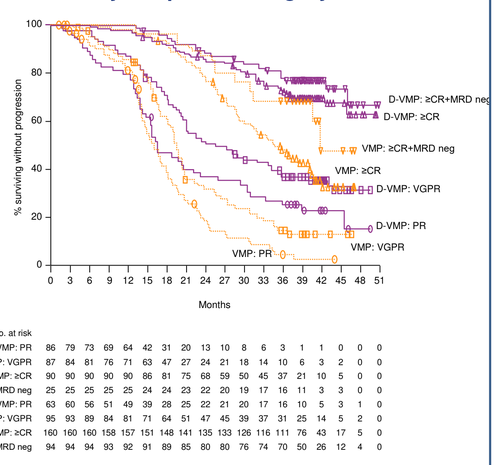
CR, complete response; D-VMP, daratumumab/bortezomib/melphalan/prednisone; HR, hazard ratio; MRD, minimal residual disease; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; TNT, time to next therapy; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone.

Table 3. Clinically Meaningful Improvements[a] in EORTC QLQ-C30 Scales at Month 12 by Response Status

Response category	D-VMP (n=350)	VMP (n=356)	Odds ratio (95% CI)[b]
PR, n (%)	63 (18.0)	86 (24.2)	
EORTC QLQ-C30 scales, n (%)[c]			
Global health status	16 (41.0)	28 (58.3)	0.50 (0.21-1.17)
Physical functioning	17 (43.6)	24 (50.0)	0.77 (0.33-1.81)
Fatigue	22 (56.4)	27 (56.3)	1.01 (0.43-2.36)
Pain	19 (48.7)	26 (54.2)	0.80 (0.34-1.87)
VGPR, n (%)	95 (27.1)	87 (24.4)	
EORTC QLQ-C30 scales, n (%)			
Global health status	35 (57.4)	28 (51.9)	1.25 (0.60-2.61)
Physical functioning	34 (55.7)	29 (53.7)	1.09 (0.52-2.27)
Fatigue	33 (54.1)	33 (61.1)	0.75 (0.36-1.58)
Pain	34 (55.7)	35 (64.8)	0.68 (0.32-1.45)
CR or better, n (%)	160 (45.7)	90 (25.3)	
EORTC QLQ-C30 scales, n (%)			
Global health status	63 (52.9)	35 (54.7)	0.93 (0.51-1.72)
Physical functioning	69 (58.0)	29 (45.3)	1.67 (0.90-3.07)
Fatigue	71 (59.7)	36 (56.3)	1.15 (0.62-2.13)
Pain	82 (68.9)	34 (53.1)	1.96 (1.05-3.66)
CR or better + MRD negative, n (%)	94 (26.9)	25 (7.0)	
EORTC QLQ-C30 scales, n (%)			
Global health status	42 (57.5)	8 (53.3)	1.19 (0.39-3.62)
Physical functioning	43 (58.9)	7 (46.7)	1.64 (0.54-5.00)
Fatigue	46 (63.0)	9 (60.0)	1.14 (0.36-3.54)
Pain	52 (71.2)	11 (73.3)	0.90 (0.26-3.15)

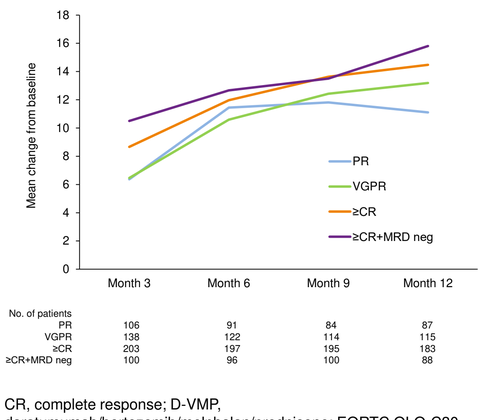
CR, complete response; D-VMP, daratumumab/bortezomib/melphalan/prednisone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone. [a]Shown are the number of patients with clinically meaningful improvements in EORTC QLQ-C30 scales. Clinically meaningful improvements were defined as a ≥10-point increase in the EORTC QLQ-C30 function scales and a decrease for symptom scales.[7,8] [b]Mantel–Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for D-VMP. [c]Percentages for EORTC QLQ-C30 subscales calculated with the number of 10-point improvement patients divided by the number of patients in each visit and each subscale.

Figure 2. PFS by Response Category



CR, complete response; D-VMP, daratumumab/bortezomib/melphalan/prednisone; MRD, minimal residual disease; PFS, progression-free survival; PR, partial response; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone

Figure 3. EORTC QLQ-C30 Global Health Status Over Time by Response Status



CR, complete response; D-VMP, daratumumab/bortezomib/melphalan/prednisone; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone.

- In the pooled study population (D-VMP and VMP patients), global health status improved with deepening responses from Months 3 to 12 (**Figure 3**)
- More patients achieved deeper responses with D-VMP and for these patients clinically meaningful improvements in global health status, physical functioning, fatigue, and pain were observed (**Table 3**)

CONCLUSIONS

- More patients with transplant-ineligible NDMM achieved deeper responses with D-VMP versus VMP, which led to better outcomes of PFS, TNT, and OS
- Deeper responses with D-VMP were associated with clinically meaningful improvements in HRQoL
- These findings suggest that the addition of daratumumab to VMP achieves and maintains deep responses for patients with transplant-ineligible NDMM, leading to better outcomes and HRQoL. This analysis continues to support the use of daratumumab-based regimens for treatment of patients with NDMM

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