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Health-related Quality of Life in Patients with Newly Diagnosed Multiple Myeloma Who Are Ineligible for Stem Cell Transplantation: Results from the ALCYONE Trial

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INTRODUCTION

- Multiple myeloma (MM) primarily affects elderly individuals with a median age at the time of diagnosis of approximately 70 years [1]
- Treatment approaches for newly diagnosed MM patients depend on "fitness," with chronological age still being an important discriminator for selecting therapy [2]
- Advances in MM over the past several years have improved survival outcomes for patients, but MM remains an incurable disease [3]
- Key areas of health-related quality of life (HRQoL) affected by MM were emotional state, independence, mobility, physical activity, relationships, social and leisure activities, and work [4]
- Here we present the analyses of the HRQoL outcomes from the ALCYONE clinical trial
  - In May 2018, the FDA approved daratumumab in combination with bortezomib, melphalan, and prednisone (D-VMP) for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT)

Hypothesis: Treatment for newly diagnosed multiple myeloma improves HRQoL

METHODS

Clinical Trial Design

- Multicenter (global), randomized, open-label, active-controlled, phase 3 trial enrolled patients from February 9, 2015 through July 14, 2016 with MM [5]
  - Key eligibility criteria
    - Newly diagnosed, documented MM
    - Not eligible for high-dose chemotherapy with ASCT because of coexisting conditions or age (≥65 years)
- Treatment arms, randomized 1:1:
  - VMP: bortezomib 1.3 mg/m^2 SC (Cycle 1: twice weekly; Cycles 2-9: once weekly), melphalan 9 mg/m^2 PO (on Days 1-4), and prednisone 60 mg/m^2 PO (on Days 1-4)
  - D-VMP: intravenous daratumumab dose 16 mg/kg (administered once weekly in Cycle 1, every 3 weeks in Cycles 2 through 9, and every 4 weeks thereafter until disease progression or unacceptable toxic effects)
    - Same VMP dosing schedule as in VMP arm
- Primary endpoint: progression-free survival (PFS) = time from randomization to either progressive disease or death
  - Exploratory endpoint: patient-reported HRQoL as measured by patient-reported outcome (PRO) instruments

PRO Instruments

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30)
  - 30 items
    - Scales: physical, role, emotional, cognitive, and social functioning, global health status (GHS), pain, fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties
    - Recall: 1 week ("past week")
    - Response scale: 4-point verbal rating scale (Items 1-28) and 7-point numeric rating scale (Items 29-30; GHS items)
    - Scoring: 0-100; higher score represents better HRQoL (GHS), better functioning, and more/worse symptomology
  - Data collected using an electronic site tablet (ePRO) device at baseline (Cycle 1, Day 1), Month 3, Month 6, Month 9, and Month 12 during treatment then every 6 months until disease progression
- EuroQol five-dimensional descriptive system (EQ-5D-5L) with visual analog scale (VAS)

Statistical Analysis

- Intent-to-treat (ITT) for descriptive analysis; baseline and ≥1 post-baseline PRO assessment for PRO analysis
  - No imputation of missing data and no adjustments made for multiplicity
  - Analysis only conducted with on-treatment data; baseline through Month 12
  - Data censored due to progression or discontinuation of therapy
- Treatment differences: repeated measures, mixed-effects model with a missing at random data assumption
  - Fixed effects: baseline PRO score, treatment group, time, treatment by time interaction, and stratification factors. Random effect: subject
- Meaningful change set at a change of 10 points for all EORTC scales
  - Between 5 and 10 points on the 1 to 100 scales of the EORTC QLQ-C30 noticed by patients and regarded as "significant changes" [6]

RESULTS

Study Population

- The ITT population included subjects randomized to D-VMP (n=350) and VMP (n=356)
  - Mean age was 71 years, there were slightly more females than males (53.7% vs 46.3%), and approximately half of the sample had a baseline ECOG score of 1 (50.3%)

Summary of Clinical Results

- At a median follow-up of 16.5 months, median PFS was significantly improved with D-VMP vs. VMP (HR: 0.50; 95% CI: 0.38, 0.65; p<0.001); the 18-month PFS rate was 71.6% (95% CI: 65.5, 76.8) in the D-VMP group and 50.2% (95% CI: 43.2, 56.7) in the VMP group [5]
- Disease progression or death occurred in 88 patients (25.1%) in the D-VMP group versus 143 patients (40.2%) in the VMP group
- During the first nine cycles, 19.4% of the patients in the D-VMP group and 33.1% of the patients in the VMP group discontinued treatment
- Median (range) cumulative bortezomib dose received was 46.9 mg/m^2 (1.3-55.3) versus 42.2 mg/m^2 (2.6-55.0) for D-VMP versus VMP, respectively

PRO Compliance

- Compliance rates were >90% at baseline and exceeded 70% through Month 12 [Table 1]
- Slightly higher compliance in the D-VMP arm was observed during treatment

Table 1. EORTC QLQ-C30 Compliance During Treatment (ITT)

	D-VMP n=350	VMP n=356	Total N=706
Baseline	316 / 350 (90.3%)	327 / 356 (91.9%)	643 / 706 (91.1%)
Month 3	281 / 326 (86.2%)	259 / 324 (79.9%)	540 / 650 (83.1%)
Month 6	250 / 317 (78.9%)	219 / 286 (76.6%)	469 / 603 (77.8%)
Month 9	240 / 300 (80.0%)	192 / 258 (74.4%)	432 / 558 (77.4%)
Month 12	230 / 288 (79.9%)	180 / 242 (74.4%)	410 / 530 (77.4%)

Compliance is defined as the number of forms received as a percentage of the number of forms expected. Forms are expected from all subjects who are on study treatment by certain month cut-off. Percentages calculated with the number of expected forms in each group as the denominator.

Baseline EORTC QLQ-C30 Mean Values

- Overall, subjects reported high cognitive and social functioning and low GHS, physical, and role functioning, in addition to high levels of pain and fatigue and very little nausea/vomiting and diarrhea [Table 2]
  - Reference data provided by EORTC for the QLQ-C30: all stages of MM, all ages [7]
- At baseline, the EORTC QLQ-C30 mean values were similar between treatment arms

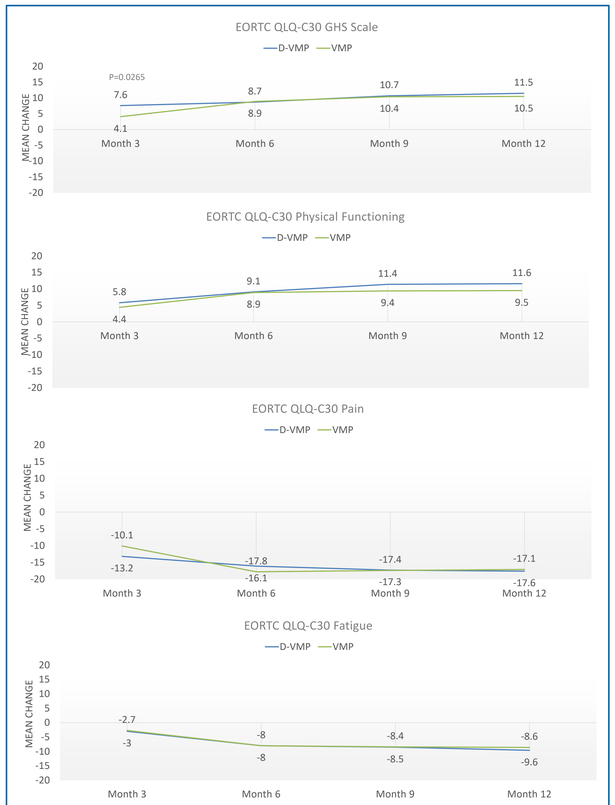
Table 2. Baseline EORTC QLQ-C30 Mean Values by Treatment Group (ITT)

	D-VMP Mean (SD)	VMP Mean (SD)	Reference Population of Patients with MM Mean (SD)
GHS	50.74 (20.996)	52.40 (22.691)	55.70 (22.8)
Physical functioning	59.96 (26.756)	63.65 (25.701)	67.7 (23.4)
Role functioning	57.54 (34.250)	61.06 (33.192)	60.1 (33.4)
Emotional functioning	69.70 (24.735)	71.10 (22.304)	71.3 (22.7)
Cognitive functioning	80.49 (21.998)	83.38 (19.948)	78.1 (23.8)
Social functioning	70.41 (28.468)	70.64 (28.651)	63.2 (31.0)
Pain	46.10 (33.130)	43.12 (31.429)	47.1 (33.6)
Fatigue	42.48 (25.661)	41.05 (25.798)	48.7 (26.7)
Nausea/vomiting	5.38 (12.425)	5.45 (13.566)	10.5 (19.2)
Dyspnea	18.35 (24.930)	19.37 (24.742)	26.0 (27.3)
Insomnia	29.54 (30.044)	27.93 (31.135)	28.9 (30.6)
Appetite loss	22.26 (28.116)	21.81 (26.623)	23.2 (30.2)
Constipation	23.00 (31.517)	18.86 (27.404)	23.2 (29.9)
Diarrhea	5.91 (17.015)	5.40 (15.270)	9.6 (19.4)
Financial difficulties	18.88 (26.534)	17.33 (24.743)	16.1 (26.6)

Higher values (closer to 100) represent better global health status, better functioning, and more/worse symptoms. Lower values (closer to 0) represent worse global health status, worse functioning, and less/better symptoms.

Treatment Effects

- As an overview, results are presented for GHS, physical functioning, pain, and fatigue as concepts relevant to patients with MM
- At Month 3, the mean (95% CI) change from baseline for the EORTC QLQ-C30 GHS subscale was 7.6 (5.3, 9.8) for D-VMP and 4.1 (1.8, 6.5) for VMP (p=0.0265) [Figure 1]
  - Mean change was >10 points starting at Month 9, indicating meaningful change for patients
- Functional and symptom scales demonstrated improvement with no statistical differences between treatment arms
- Within-group mean changes in physical functioning, pain, and fatigue symptom scales achieved a meaningful improvement (decline in symptom) from baseline [Figure 1]
- Supportive results were observed with the EQ-5D-5L VAS
  - Statistically significant differences in the mean change from baseline were observed at Month 3 (D-VMP: 6.8 [95% CI: 4.9, 8.7], VMP: 3.7 [95% CI: 1.7, 5.7]; p=0.0151)

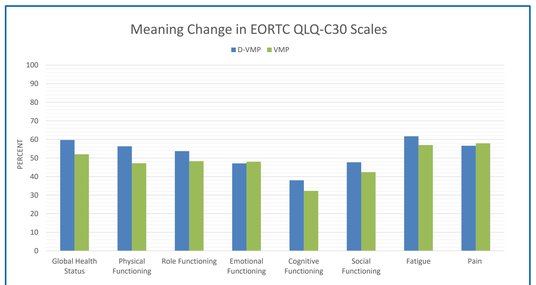


p<0.05 at Month 3 for EORTC QLQ-C30 GHS comparing D-VMP and VMP; all other treatment comparisons were non-significant
GHS and Physical Functioning: positive change = improvement
Pain and Fatigue: negative change = improvement

Figure 1. Change from Baseline: Mixed Models for Repeated Measures (Missing at Random)

PRO Response Rates

- Patients treated with D-VMP had higher response rates for a majority of the EORTC QLQ-C30 endpoints compared to VMP alone [Figure 2]
  - GHS: 59.7% of the subjects treated with D-VMP compared to 52% in the VMP arm; (odds ratio [OR]: 1.37; 95% CI: 1.02, 1.85)
  - Physical functioning: 56.3% of the subjects treated with D-VMP compared to 47.2% in the VMP arm (OR: 1.44; 95% CI: 1.07, 1.94)



Responder defined as having a ≥10-point improvement.

Figure 2. Percentage of PRO Responders for the EORTC QLQ-C30 during Treatment

Limitations

- Clinical trial design was open label
- Analyses censored due to progression or discontinuation from treatment

CONCLUSIONS

- **Patients experienced meaningful improvement in HRQoL over the course of therapy, with more patients achieving meaningful change when treated with D-VMP**
- **Improvements in HRQoL were consistent with the clinical benefit that showed superior PFS of D-VMP over VMP alone**

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DISCLOSURES

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