Advances in treatments for multiple myeloma (MM) have resulted in improved survival. However, patients who have become refractory to novel agents have a poor prognosis, with a median overall survival (OS) of nine months, or as low as three months in the absence of further treatment after failure of regimens including bortezomib (BORT), thalidomide (THAL) or lenalidomide (LEN).\(^1\) After multiple lines of therapy, the health-related quality of life (HRQoL) of patients with relapsed and/or refractory MM (RRMM) is often compromised,\(^2\) with impairments in physical, emotional, social and cognitive functioning.\(^3\)

Pomalidomide (POM) was recently approved in the US and Europe in combination with dexamethasone for use in patients with RRMM who have received at least two prior treatment regimens, including both LEN and BORT, and have demonstrated disease progression on their last therapy. In the pivotal MM-003 trial, POM+LoDEX provided significant and clinically meaningful improvements in progression-free survival (PFS) and OS compared with high-dose dexamethasone (HiDEX), a commonly used salvage treatment for heavily pre-treated patients at the time the study was initiated.\(^4\) MM-003 was the first study to investigate HRQoL in RRMM patients receiving POM. Here, we present HRQoL results of cross-sectional and longitudinal analyses that were included as pre-specified secondary end points.

The design of MM-003 has been reported previously\(^1\) and is summarized in Figure 1. Enrolled patients were refractory to their last treatment and had failed BORT and LEN after at least two cycles of each (alone or in combination). Patients progressing on HiDEX were allowed to receive POM in a companion MM-003C trial (Figure 1); these patients were not included in the HRQoL analysis after progression from their trial regimen.

Three HRQoL instruments that have been validated previously\(^5\) in patients with RRMM were included as pre-defined end points for non-progressing patients and scored according to their user manuals: the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-MY20, and EQ-5D. The analysis focused on eight pre-selected domains chosen following a workshop discussion with specialists on perceived clinical relevance and on results of multivariate regression analysis comparing domains with the EQ-5D utility index.\(^6\) The domains included five from EORTC QLQ-C30 (Global Health Status, Physical Functioning, Emotional Functioning, Fatigue, and Pain), two from EORTC QLQ-MY20 (Disease Symptoms, Side Effects of Treatment), and the EQ-5D Health Utility value (mapped to a scale with 1 = best health state and 0 = death using a time trade-off methodology).

Patients completed HRQoL questionnaires at baseline, on day 1 of each treatment cycle, and at discontinuation. HRQoL scores were calculated from baseline through to cycle (C) 10 in the cross-sectional analyses. Later cycle data were limited in value due to few remaining patients. Intention-to-treat (ITT) subjects with at least one HRQoL measurement in this period were included in the analyses.

We compared changes in HRQoL scores from baseline and between treatment arms at each cycle by cross-sectional and longitudinal analyses. Cross-sectional descriptive and comparative (between and within treatment arms) analyses used domain scores analyzed as continuous variables. Longitudinal repeated measure mixed effects models were generated to estimate the treatment effect on HRQoL over time and between treatment arms, and adjusted means of score differences from baseline were calculated.

Of the 455 ITT subjects, 433 completed HRQoL measurements and were included in this analysis (POM+LoDEX n=289; HiDEX n=144). Median patient age was 64 years, and over 94% (410/433) had received more than 2 prior therapies; 82% (355 of 433) were refractory to LEN and BORT. Median follow up was ten months. There was no significant difference in patients’ base-line demographics and disease-related characteristics between arms.\(^4\)

Of the 289 patients randomized to receive POM+LoDEX, 17.6% (51 of 289) had EORTC QLQ-C30 and QLQ-MY20 available data at C10 versus 5.5% (8 of 144) of HiDEX patients; 17.3% (50 of 289) of POM+LoDEX patients had EQ-5D data available at C10 versus 4.8% (7 of 144) of HiDEX patients.

Compliance rates up to C10 were generally high (≥77.8% of presenting patients across cycles) and were consistent between treatment groups. Due to the progressive nature of MM, the number of participating patients dropped as the study progressed. Patients in the HiDEX group discontinued from the study earlier than those in the POM+LoDEX group.\(^4\) Reasons for discontinuation were comparable between treatment arms.

In the cross-sectional analysis, mean score improved significantly from baseline (P<0.05, paired t-test) in the POM+LoDEX arm for the Health Utility domain, and dete-
riorated significantly from baseline for Side Effects of Treatment. In the HiDEX arm, no domains showed improvement, and 5 showed deterioration from baseline: Physical Functioning, Health Utility, Fatigue, Disease Symptoms, and Side Effects of Treatment (Figure 2, indicated by ‡).

Between treatment groups, significant differences ($P<0.05$, unpaired $t$-test) in favor of POM+LoDEX were observed in five of the eight pre-selected domains (Physical Functioning, Emotional Functioning, Health Utility, Fatigue, and Side Effects of Treatment) at specific treatment cycles (Figure 2, indicated by *). Trends ($P<0.1$, unpaired $t$-test) were noted in Physical Functioning, Emotional Functioning, Health Utility, Fatigue, and Side Effects of Treatment.

Figure 2. Cross-sectional analysis of mean HRQoL score changes from baseline per treatment cycle. *$P<0.05$ unpaired $t$-test comparing the two treatment groups from baseline; ‡$P<0.05$ paired $t$-test (within group mean change from baseline).
Figure 3. Repeated measure mixed model score changes from baseline (adjusted means). $P$ values indicate unpaired $t$-test comparing treatment groups. *Significant $P$ value ($P<0.05$).
In heavily pre-treated RRMM patients with end-stage disease, maintaining HRQoL may be an important clinical decision factor. The HRQoL domains evaluated here are directly related to quality of survival, and may be helpful in making treatment decisions. Response in MM patients should not be the unique outcome; other end points, such as safety and HRQoL must also be considered, as some patients may derive greater benefit from a lower level of response while achieving prolonged survival without facing unnecessary risk.

POM+LoDEX has become a standard of care treatment in the US for relapsing patients who have received LEN and BORT, and has seen rapid uptake in European countries since its introduction. We show that this treatment combination leads to significant HRQoL improvements that could potentially enhance the lives of patients with RRMM.


References


