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Title: Peripheral Neuropathy Symptoms, Pain, and Functioning in Previously Treated Multiple Myeloma Patients Treated with Selinexor, Bortezomib, and Dexamethasone

Running Head: PN Symptoms, Pain, and Functioning

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To the Editor:

With over 34,000 new cases and ~12,400 deaths from multiple myeloma (MM) anticipated in 2021 in the United States[1] and about twice as many in Europe, there is an unmet medical need for therapies in patients with previously treated MM that have progressed on available agents. Currently, there are few agents with new mechanisms of action approved for early-line treatment. Selinexor (XPOVIO®, Karyopharm Therapeutics Inc.) is a potent, oral, first-in-class, selective inhibitor of nuclear export that specifically blocks exportin 1 (XPO1).[2]

The impact of MM on a patient's health-related quality of life (HRQoL) is well established,[3] with deterioration of physical function, increased fatigue, pain, dyspnea, and anxiety and depression cited as the most common symptoms. Peripheral neuropathy (PN), which can be associated with MM itself[4] and/or certain treatments, includes sensory, motor and, to a lesser extent, autonomic neuropathy. Sensory symptoms are the most frequent and can be characterized as pain, varying in terms of sensation (eg, numbness, tingling, burning) and type (eg, shooting, chronic, electric-shock), and can lead to problems with ambulation and even require the use of a wheelchair.[4] Without proper management, PN and subsequent physical limitations due to PN can become permanent, as well as constraining future treatments.[5]

The BOSTON trial (NCT03110562) was a Phase 3 trial comparing the novel triplet regimen of once weekly oral selinexor with *once* weekly bortezomib and low dose dexamethasone (XVd) versus standard twice weekly bortezomib plus moderate dose dexamethasone (Vd) in adult patients with previously treated MM who received one to three prior anti-MM regimens. This is the first trial of a bortezomib-based triplet therapy (ie, XVd) that showed lower rates of overall and Grade ≥ 2 PN compared with doublet Vd while conferring a longer progression free survival (PFS), and required 37% fewer clinic visits than standard twice weekly Vd.[2]

Recently, the assessment of patient-reported outcomes (PROs) has become an important component in clinical trials as they provide information on the impact of a disease and treatment from the patient's

perspective.[6] To this end, analyses of PROs were included in the BOSTON trial to evaluate patterns in therapy-induced PN symptoms, pain, and function.[2] Patient-reported PN was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Chemotherapy-induced Peripheral Neuropathy (QLQ-CIPN20) validated instrument (secondary HRQoL endpoint). In addition, the EORTC Quality of Life Questionnaire for Cancer-30 item (QLQ-C30) instrument was compared between patients randomized to the XVd arm versus the Vd arm (exploratory endpoint).

At Baseline and Day 1 of each cycle, both the EORTC QLQ-CIPN20 and EORTC QLQ-C30 questionnaires were assessed (Supplementary Material, Figure 1). For this study, analyses focused on physical functioning, role functioning, and pain subscales as pre-specified domains of interest for the EORTC QLQ-C30.

Mixed effects models for repeated measures (MMRM) were fit to the longitudinal data to estimate differences over time. Assessment visits were treated as ordinal in each model. All cycles were 35 days long in the XVd arm; the Vd arm had eight 21-day cycles before switching to 35-day cycles.[2] The only visit that was in common for the two arms was at Day 106 (XVd cycle 4, Vd Cycle 6). Adjusted MMRM model included treatment, time (categorical: Day 22, 36, 43, 64, 71, 85, 106, etc), baseline PRO score, prior PI therapy, number of prior anti-MM regimens, revised international staging system (R-ISS) stage at MM, and prior bortezomib exposure. Meaningful change thresholds (MCTs) derived using anchor- and distribution-based methods for the EORTC QLQ-CIPN20 or estimated from the literature for the EORTC QLQ-C30 were used to identify patients who had experienced a meaningful worsening of symptoms or deterioration in functioning (Supplementary Material).

Time to definitive deterioration (TDD) was defined as the time to which symptoms and function, as measured by the EORTC scales, declined by an identified clinically MCT (time from randomization to the first occurrence of meaningful deterioration that was not followed by subsequent improvement) (Supplementary Material, Table 2 and Table 3). TDD was conducted for the EORTC QLQ-CIPN20

symptom domains and the pre-specified EORTC QLQ-C30 domains and Global Health/Quality of Life (QoL) scale. Cox proportional hazard models compared the hazard rates between arms adjusted for baseline questionnaire score, randomization stratification factors (prior PI therapy, number of prior anti-MM regimens, R-ISS stage at MM) and prior bortezomib exposure.

A total of 402 patients were enrolled in the trial; 388 completed a baseline assessment (191 patients in the XVd arm and 197 patients in the Vd arm). Age, sex, and race was balanced between the two arms (Supplementary Material, Table 1).

When examining mean scores over time, the EORTC QLQ-CIPN20 Sensory domain scores increased (worsened) for the Vd arm, while scores remained unchanged for the XVd arm for the first several cycles. Specifically, on Day 106, scores in the XVd arm increased by 5.34 points less than scores in the Vd arm (95% confidence interval [CI]: -8.39, -2.29, p-value = 0.006). Additionally, EORTC QLQ-C30 Pain scores worsened for the Vd arm but improved for the XVd arm; on Day 106, a -6.58 difference between arms was observed in favor of the XVd arm (95% CI: -11.36, -1.80; p-value = 0.007). The difference was less pronounced for the EORTC QLQ-CIPN20 Motor domain scores, with a smaller and non-significant difference on Day 106 (-1.81, 95% CI: -4.72, 1.10, p-value = 0.223). For the EORTC QLQ-CIPN20 Autonomic domain scores, there was a similar increase in symptoms for the first few cycles of treatment for both the XVd and Vd arms, with scores in the XVd arm later increasing more than in the Vd arm (Day 106: 4.99, 95% CI: 0.73, 9.25, p-value = 0.022). Ultimately, the trends observed on Day 106 persisted throughout the study across all domains (Table 1; Supplementary Figures 2 and 3).

The number of patients with definitive deterioration in QLQ-CIPN20 sensory symptoms was greater in the Vd arm (86 patients, 45.7%) compared to 51 (27.7%) patients in the XVd arm (Supplementary Table 4). The median TDD was approximately eight months longer in the XVd arm compared to the Vd arm (20.7 months [95% CI: 15.4, not estimable] vs. 12.5 months [95% CI: 7.8, 18.8]), with a corresponding adjusted hazard ratio (HR) of 0.53 (95% CI: 0.38, 0.75; p = 0.0004). The number of patients with definitive deterioration in Motor domain scores was also greater in the Vd arm (83 patients,

43.9%) compared to the XVd arm (65 patients, 35.3%). The median TDD in the XVd arm was 16.2 months compared to 15.1 months in the Vd arm (HR: 0.72, 95% CI: 0.52, 1.00, p = 0.0525). Roughly half of the patients in each treatment arm experienced worsening autonomic symptoms (54.6% and 48.4%, XVd and Vd, respectively) with no significant difference between arms (HR = 1.14, p = 0.3727). While not statistically significant, fewer XVd patients had definitive deteriorations in pain and physical function compared to Vd patients, with similar or extended time to deterioration.

The BOSTON trial is the first study of a bortezomib-based triplet therapy that showed lower rates of overall and Grade ≥2 PN compared with doublet Vd while conferring a longer PFS and fewer clinic visits than standard twice weekly Vd.[2] The underlying hypothesis is that this first-in-class oral treatment (XVd) provides equivalent (or better) PROs on PN symptoms when compared to the Vd treatment arm.

When examining mean scores over time using the EORTC QLQ-C30 and EORTC QLQ-CIPN20, patients who received weekly XVd reported lower sensory symptom and pain scores, but higher autonomic symptom scores. When classifying patients according to whether their scores meaningfully worsened from baseline, patients treated with twice weekly Vd experienced a more rapid rate of sensory symptom worsening and a trend to more rapid worsening of motor symptoms, compared to patients treated with XVd. The improved pain scores in patients treated with XVd may be related to superior disease control. One limitation is the misaligned assessment timepoints which impacted the ability to provide direct time-on-treatment assessments. Each analysis conducted considered timing, however, there was, at times, limited ability to conduct some analyses and complexity to modeling.

As the survival of patients with MM are improving, the need to minimize cumulative side effects such as PN becomes more important to improve QoL. The reduction in PN-related pain and sensory symptoms observed with XVd in this setting of increased PFS, time to next therapy, and patient-preferred oral administration supports a potentially improved patient experience and decreased health care burden and long-term morbidity.

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Table 1. Model-based Change from Baseline to Day 106 on Select EORTC QLQ-CIPN20 and QLQ-C30 Scales

Domain	Least Square Adjusted Mean Change (SE)		XVd versus Vd	
	XVd (N = 191)	Vd (N = 197)	Difference (95% CI)	*P*-value
QLQ-CIPN20				
Sensory	1.59 (1.312)	6.93 (1.265)	-5.34 (-8.39, -2.29)	0.0006
Motor	3.07 (1.247)	4.88 (1.203)	-1.81 (-4.72, 1.10)	0.223
Autonomic	12.39 (1.815)	7.40 (1.746)	4.99 (0.73, 9.25)	0.022
QLQ-C30				
Pain	-4.40 (1.994)	2.18 (1.928)	-6.58 (-11.36, -1.80)	0.007
Physical Function	-3.37 (1.671)	-5.59 (1.612)	2.22 (-1.66, 6.11)	0.262
Role Function	-9.03 (2.284)	-7.09 (2.213)	-1.93 (-7.38, 3.52)	0.487
Global Health/QoL	-3.45 (1.614)	-3.13 (1.544)	-0.32 (-4.15, 3.50)	0.868

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Cancer-30 item Questionnaire; EORTC QLQ-CIPN20 = European Organization for Research and Treatment Chemotherapy-induced Peripheral Neuropathy; SE = standard error; QoL = quality of life.