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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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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.26282

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| Journal: | *American Journal of Hematology* |
| --- | --- |
| | Word count: 1,420 words (maximum ≤ 1,500 words; excludes title and graphs/figures) |

**Keywords:** Peripheral Neuropathy, sensory symptoms, pain, myeloma, progression free survival

**Data Availability Statement:** For original data, please contact hleong@karyopharm.com.

**Funding Statement:** This study was funded by Karyopharm Therapeutics, Inc.

**Acknowledgements:**

Jamie Mertoian and Emily Calderbank, medical writers supported by funding from Karyopharm Therapeutics, Inc., provided drafts and editorial assistance to the authors during preparation of this manuscript. Additional clinical support was also provided by Dra Maria Victoria Mateos, Maria Gavriatopoulo, Halyna Pylypenko, Vadim Doronin, Tuphan Kanti Dolai, Nuriet Khuazheva, Philippe Moreau, Ashraf Z. Badros, and Polina Kaplan.

**Conflict of interest statements:**

Xavier Leleu reports honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Carsgen Therapeutics Ltd, Celgene, Gilead Sciences, Janssen-Cilag, Karyopharm Therapeutics, Merck, Mundipharma, Novartis, Oncopeptides, Pierre Fabre, Roche, Sanofi, and Takeda and non-financial support from Takeda. Jennifer L Beaumont, Hailin Yu, and Stacie Hudgens are employees of Clinical Outcomes Solutions which received funding to conduct the analytic planning and execution activities associated with this research. Holger W. Auner reports an advisory role for Takeda and Karyopharm; a grant from Amgen; and a speaker's bureau role for Janssen. Hang Quach reports grants from and an advisory board role for Amgen, Celgene, Karyopharm, GlaxoSmithKline; non-financial support and research drug supply from Sanofi; and an advisory board role for Janssen Cilag and Specialized Therapeutics. Sosana Delimpasi has received honoraria from Janssen, Takeda, Amgen, and Celgene. Ivan Špička reports personal fees from Janssen-Cilag, Takeda, Sanofi Aventis, and Novartis; personal fees and non-financial support from Colgene, BMS, and Amgen. Iryna Kriachok reports a consulting role, an advisory role, and a speaker's bureau role for Takeda, Janssen, Roche, AbbVie, and MSD; and travel support by Takeda, MSD, Roche, AbbVie, and Janssen. Roman Hájek has had a consultant or advisory relationship with Janssen, Amgen, Celgene, AbbVie, BMS, Novartis, PharmaMar, and Takeda; has received honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda; and has received research funding from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda. Christopher Venner has received honoraria from BMS/Celgene, Janssen, Sanofi, Amgen, GSK, and Takeda. Mamta Krishnan Garg reports support for attending conferences from Takeda; an advisory role for Amgen, Takeda, Jansen, Novartis, and Celgene; and a speaker's bureau role for Janssen. Sundar Jagannath reports consulting services for AbbVie, Bristol-Myers Squibb, Janssen Pharmaceuticals, and Merck and involvement in clinical trials as Principal Investigator of Karyopharm, Intas Pharmaceuticals, and Dr Reddy's Laboratories. Moshe Levy reports receiving consulting fees and lecture fees from Takeda, Celgene, Seattle Genetics, AbbVie, Jazz Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb, Amgen, Spectrum Pharmaceuticals, and Janssen. Larry D. Anderson Jr. reports honoraria from advisory board activity from the following: GSK,

Amgen, Janssen, BMS/Celgene, Karyopharm, and Oncopeptides. Nizar Jacques Bahlis reports grants and personal fees from Celgene; personal fees from Janssen, Amgen, Takeda, Abbvie, GSK and Karyopharm. Thierry Facon reports an advisory board role for Karyopharm, Amgen, Roche, and Oncopeptides; and an advisory board role and a speaker's bureau role for Janssen, Celgene/BMS, and Takeda. Yi Chai, Xiwen Ma, Shijie Tang, Hoyee Leong, and Michael Kauffman are employees of and stockholders of Karyopharm. Jatin Shah reports being employed by and owning stock in Karyopharm Therapeutics and advisory board role for GSK, Celbene/BMS, Amgen, Oncopeptides, and Karyopharm. Sharon Shacham reports being employed by and owning stock in Karyopharm Therapeutics, holding patents (8999996, 9079865, 9714226, PCT/US12/048319, and I574957) on hydrazide-containing nuclear transport modulators and uses, and holding pending patents (PCT/US12/048319, 499/2012, PI20102724, and 2012000928) on hydrazide-containing nuclear transport modulators and uses. Paul Richardson reports receiving grant support and honoraria from Oncopeptides, Celgene, and Takeda, grant support from Bristol-Myers Squibb, and honoraria from Amgen, Janssen, and Karyopharm Therapeutics. All other authors declare no competing interests.

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.