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Peripheral Neuropathy in Phase 3 ASPEN Study of Bruton Tyrosine Kinase Inhibitors for Waldenström Macroglobulinemia

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Abstract *(499 of 500-word limit)*:

Background: Peripheral neuropathy (PN) is a significant cause of morbidity in patients with Waldenström macroglobulinemia (WM). Zanubrutinib and ibrutinib are covalent Bruton tyrosine kinase (BTK) inhibitors indicated for the treatment of WM, but data on their efficacy for WM-associated neuropathy specifically are limited. The phase 3, open-label ASPEN study (NCT03053440) compared the efficacy and safety of zanubrutinib with ibrutinib in patients with WM.

Aims: This ad hoc analysis examined the impact of zanubrutinib or ibrutinib treatment on PN symptoms in patients enrolled in the ASPEN trial.

Methods: Patients with relapsed/refractory WM or treatment-naive WM unsuitable for chemoimmunotherapy were eligible for the ASPEN study. Patients with mutated myeloid differentiation primary response 88 (*MYD88*) (cohort 1) were randomized 1:1 to zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily in 28-day cycles. Patients with wild-type or undetermined *MYD88* (cohort 2) received zanubrutinib 160 mg twice daily. All enrolled patients with symptomatic PN were included in this analysis. Association between PN and WM was not formally assessed by a neurologist. Logistic regression was performed between PN symptom resolution and several different predictors. Health-related quality of life (HRQOL) was assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30).

Results: At screening, PN was present as a symptom of WM in 49 patients (21.4% of the study population; n=27 zanubrutinib; n=22 ibrutinib). Of these, 35 patients (71.4%) experienced resolution of PN symptoms, with a median time to resolution of 10.1 months (range, 1-46.8). In cohort 1, 78% (14/18) and 84% (16/19) of patients who achieved major response had resolution of PN symptoms in the zanubrutinib and ibrutinib arms, respectively. The median time to PN symptom resolution was 4.6 months (range, 1.1-46.8) for patients receiving zanubrutinib in cohort 1 and 14.1 months (range, 1-44) for patients receiving ibrutinib. Logistic regression modeling demonstrated a strong relationship between major response and PN symptom resolution (coefficient, 1.99; HR, 7.32; P=.0287). Normalization of IgM levels (cutoff: minimum IgM ≤ upper limit of normal) and maximum IgM percent reduction from pretreatment baseline were associated with increased likelihood of PN symptom resolution, although neither was statistically significant (P=.0526 and P=.0546, respectively). Patients who had PN symptom resolution had greater improvement in HRQOL compared with those without PN symptom

resolution, according to median change from baseline to final score in EORTC-QLQ-C30 global health status (66.7 to 75.0 vs 50.0 to 54.2). Median physical functioning score improved from 80.0 to 86.7 in patients with PN symptom resolution and was unchanged in patients without PN symptom resolution (both 66.7).

Conclusions: In this phase 3 international study, PN symptom resolution with BTK inhibitors correlated with the depth of disease response, with faster PN symptom resolution with zanubrutinib than ibrutinib. These PN improvements may be in response to reduction in IgM levels. While further investigation of BTK inhibitors in PN-specific studies incorporating detailed neurophysiological investigations is required, this analysis supports the potential use of BTK inhibitors as treatment for PN symptoms in patients with WM.