ZANUBRUTINIB IN BING NEEL SYNDROME: EFFICACY AND TOLERABILITY

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Background
Bing-Neel syndrome (BNS) is a rare complication of Waldenström's macroglobulinemia (WM), in which malignant lymphoplasmacytic lymphoma (LPL) cells invade the central nervous system (CNS). There are no prospective trials on BNS treatment. Bruton's tyrosine kinase inhibitors (BTKi) are an effective and safe treatment for WM and are known to penetrate the blood-brain barrier. Ibrutinib, a first generation BTKi, was reported to yield rapid clinical and radiological improvement in the majority of BNS patients; however, off-target activity results in frequent adverse events (AEs). Zanubrutinib, a next-generation covalent BTKi, demonstrated a trend towards faster and deeper responses, with a more favorable toxicity profile compared to ibrutinib in a comparative trial in WM.

Aims
We aimed to assess the efficacy of zanubrutinib treatment on neurological symptoms, radiological abnormalities, and cerebrospinal fluid (CSF) involvement, as well as its safety and tolerability, in patients with BNS.

Methods
In this retrospective study, participating centers were asked to report all consecutive BNS patients treated with at least one dose of zanubrutinib. Patients receiving concurrent chemotherapy were excluded. After written informed consent, data from electronic health records on clinical, radiological and CSF examinations were collected. AEs were graded according to the CTCAE, v5.0.

Results
Thus far, 24 BNS patients were included. In 19 cases (79%), BNS was identified in patients with a prior diagnosis of LPL and in 5 (21%) as new-onset LPL. Eleven patients (46%) had received BNS treatment prior to zanubrutinib, of whom 2 with ibrutinib. Median age at start of zanubrutinib was 67 years (IQR 62-74). All patients received 320mg zanubrutinib daily.
At initiation of zanubrutinib, 21 patients (88%) had various neurological symptoms, including sensory and/or motor deficits (n=10), lower limb ataxia (n=6), memory loss (n=6), seizures (n=6), behavioral changes (n=4), and cranial nerve deficits (n=4). There was radiological evidence of CNS involvement in 16 patients (67%). Cytologic assessment and/or flow cytometry of CSF was positive for clonal B cells in 17/21 (81%) cases tested at start. Molecular analysis of CSF was positive for MYD88L265P in 14/14 (100%) and for CXCR4 mutations in 0/2 tested cases at BNS diagnosis and/or start of zanubrutinib.
Median follow-up was 9 months (IQR 4-16) (**Figure 1**). Of 21 patients with neurological symptoms at baseline, 17 (81%) experienced clinical improvement up until last follow-up, with complete resolution in 7 (33%). In 8/9 patients (89%) with repeated MRI, radiological abnormalities improved. Out of 13 patients with repeated CSF analysis, 6 demonstrated persistent detectable clonal LPL cells. Only two (8%) AEs grade ≥3 were observed; grade 4 febrile neutropenia requiring temporary zanubrutinib dose reduction and grade 3 cryptococcal infection. One patient (4%) passed away due to recurrent neurological symptoms while on zanubrutinib. All other patients were alive and still on zanubrutinib at end of follow-up.

Conclusion
Treatment with zanubrutinib led to a durable clinical response in 81% of BNS patients and was well-tolerated. Negative CSF was not a requirement for clinical improvement. Our findings suggest that zanubrutinib is an effective and safe treatment modality for BNS.

Figure 1. Swimmer plot displaying follow-up duration as well as zanubrutinib treatment effect