Prospective Study of Acalabrutinib and Rituximab in Symptomatic Anti-MAG mediated IgM Peripheral Neuropathy

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Background: Peripheral neuropathy (PN) occurs in 20-25% of patients with an IgM paraprotein and is typically related to an anti-myelin associated glycoprotein (MAG) antibody which is frequently associated with sensory ataxia and distal limb weakness. PN progression negatively affects functional abilities and quality of life. While rituximab is active, its activity as a single agent is limited and often associated with an IgM flare that can potentiate PN. BTK-inhibitors can block rituximab-associated IgM flare and are proven to reduce serum IgM in Waldenström's Macroglobulinemia (WM). We therefore initiated this trial to evaluate a novel treatment for anti-MAG PN.

Methods: This is a prospective, single-arm phase II trial of acalabrutinib and rituximab (NCT05065554) in patients with an anti-MAG antibody and an IgM monoclonal gammopathy or WM; and a predominantly sensory demyelinating PN with a modified Rankin score of ≥1 with progressive symptoms or a score of ≥2. Treatment is continuous oral acalabrutinib (100 mg twice daily) with rituximab weekly in cycles 1 and 4. Each cycle is 28 days. The primary endpoint is hematologic response rate. The key secondary endpoint is the proportion of patients that achieve improvement or stability in PN based on the Inflammatory Rasch-built Overall Disability Scale (I-RODS). Additional secondary neurologic endpoints include the INCAT disability score, MRC distal sum score, INCAT sensory sum score, and a neuropathy-specific quality of life scale. Assumptions include H0 ≤50%, H1 ≥75%, 2-sided alpha 0.04, and power 82% with 33 evaluable patients.

Results: At the time of this data collection 8 patients, including 4 females, have enrolled. The median age is 70 years (range 65-76). Median I-RODS score at baseline was 41 (range 23-48; 48 = no disability). All patients have an IgM kappa paraprotein with median serum IgM of 975 mg/dL (range 226-2137). Anti-MAG antibody titer range is 1:70,000 to 1:819,200 IU/L. Bone marrow biopsy showed no disease in 4 patients, a plasma cell clone in 1, and lymphoplasmacytic infiltrate in 3. No adenopathy or splenomegaly were detected on baseline scans. Six patients (75%) have an MYD88 mutation with no CXCR4 mutations. Five patients had prior rituximab and two prior IVIG.

With a median time on treatment of 175 days (range 28-510), the overall response rate among 7 evaluable patients using IWWM-11 criteria was 86% including 2 very good partial responses, 1 partial response, 3 minor responses, and 1 stable disease. Four of 7 patients (57%) had improvement in the I-RODS score; median improvement 0.5 (range -4 to 11). One patient was removed from the trial due to grade 3 elevation in ALT. Two other reversible grade 3 adverse events occurred including rituximab infusion reaction and syncope unrelated to treatment.

Conclusions: The combination of acalabrutinib and rituximab has demonstrated activity in this first prospective study evaluating BTK-inhibition with rituximab in patients with IgM related anti-MAG PN. Hematologic responses occurred in 86% of patients and 57% had an improvement in I-RODS score. The trial continues to enroll and our findings provide a framework to develop novel, effective treatment options for anti-MAG PN.