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ORAL ABSTRACTS

654.MGUS, AMYLOIDOSIS AND OTHER NON-MYELOMA PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL

Prospective Study of Acalabrutinib with Rituximab in Patients with 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 up to 50% of these patients have an anti-myelin associated glycoprotein (MAG) antibody which is frequently associated with sensory ataxia and distal limb weakness negatively affecting function and quality of life. While rituximab is active, its activity is limited as a monotherapy and often associated with an IgM flare that can potentiate PN. BTK-inhibitors can block rituximab-associated IgM flare and are proven to markedly reduce serum IgM in Waldenström's Macroglobulinemia (WM). We therefore initiated this trial to evaluate a novel treatment for anti-MAG PN.

Methods: We initiateda prospective, single-arm phase II study of acalabrutinib and rituximab (NCT05065554). Patients with an anti-MAG antibody with 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 are eligible. Treatment consists of continuous oral acalabrutinib (100 mg twice daily) with rituximab weekly in cycles 1 and 4. Each cycle is 28 days. The primary endpoint is to evaluate the hematologic response rate. The key secondary endpoint is to evaluate the proportion of patients that achieve improvement or stability in PN based on the Inflammatory Rasch-built Overall Disability Scale (I-RODS) patient-reported disability scale. Additional secondary neurologic endpoints include the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, MRC distal sum score, INCAT sensory sum score, and a neuropathy-specific quality of life scale (IN-QOL). We hypothesize that 75% of participants (H1) will have a hematologic response versus a null (H0) of 50% or lower. With 33 evaluable patients, there will be 82% power to detect a significant difference with an alpha (2-sided) of 0.04.

Results: Eight patients, including 4 females, have enrolled as of July 1, 2023. The median age is 70 years (range 65-76), and median ECOG is 1. Median I-RODS score at baseline was 41 (range 23-48; 48 = no disability). All patients have an IgM kappa paraprotein with median baseline serum IgM of 975 mg/dL (range 226-2137), kappa free light chain of 28 mg/L (range 16-47), and M-spike of 0.6 g/dL (range 0.17-1.1). 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 clonal plasma cell population in 1 patient, and lymphoplasmacytic infiltrate in 3 patients. No adenopathy or splenomegaly were detected on baseline CT scans. Six patients (75%) are MYD88 mutated and none CXCR4 mutated. Five patients had prior rituximab therapy and two received 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%. Categorical responses include 2 very good partial responses (≥90% decrease in IgM, or normalization of IgM with persistent IgM monoclonal protein); 1 partial response (≥50% but <90% decrease in IgM); 3 minor responses (≥25% but <50% decrease in IgM) and 1 stable disease. Four of 7 patients (57%) had improvement in the I-RODS score. Median improvement was 0.5 points (range -4 to 11). One patient was removed from the trial after 28 days due to grade 3 elevation in ALT. Two other reversible grade 3 adverse events occurred including rituximab related infusion reaction and syncope unrelated to treatment.

Conclusions: The combination of acalabrutinib and rituximab has demonstrated activity in this first prospective study that is evaluating BTK-inhibition with CD20 directed therapy in patients with IgM related anti-MAG PN. Hematologic responses occurred in 86% of patients and 57% had an improvement in the I-RODS score. Treatment is well tolerated. Additional data from more detailed neurologic assessments are forthcoming. The trial continues to enroll patients. Our findings provide a framework to develop novel, more effective treatment options for anti-MAG PN.

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OffLabel Disclosure: Acalabrutinib and Rituximab are FDA approved for treatment of B-cell lymphoma, but not for MGUS or WM

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