Loncastuximab in Relapsed/Refractory WM

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Background: Chemoimmunotherapy and covalent BTK inhibitors are standard therapies for Waldenström macroglobulinemia (WM). There is no standard of care for treatment of WM after these two regimens and additional therapies are needed for relapsed WM. This prospective clinical trial was designed to evaluate the use of loncastuximab tesirine, a CD19 antibody drug conjugate, in patients with WM previously treated with at least two lines of therapy, including rituximab and a BTK inhibitor.

Methods: This multicenter, phase II trial is enrolling previously treated symptomatic patients with WM. Loncastuximab is given once every 4 weeks for 6 doses. Loncastuximab is administered in cycles 1-2 at 150 µg/kg and cycles 3-6 at 75 µg/kg. The primary outcome measure is overall response rate (ORR). Secondary outcomes include depth of response, median progression free survival, effect of bone marrow disease burden on disease response, impact of MYD88 and CXCR4 on disease response, safety of loncastuximab in WM, rate of IgM flare, rate of tumor lysis, and patient quality of life during treatment. Assumptions include H0 ≤35%, H1 ≥65%, 2-sided alpha 0.035, and power 0.85. The trial is designed to enroll 36 patients. For purposes of this interim analysis, >2 of the first 7 participants would have to attain a response to study therapy to reject futility.

Results: To date 7 patients have enrolled and initiated treatment. Baseline characteristics include median age 70 years (range 53-77); number of prior therapies 4 (range 2-5); serum IgM 2,230 mg/dL (range 723-5,955); hemoglobin 9.4 g/dL (range 8.9-12.6); bone marrow involvement 60% (range 40-90). One patient each had lymphadenopathy or splenomegaly. *MYD88* mutation was detected in 100% of cases, CXCR4 in 6/7 (86%) and TP53 in 4/7 (57%). To date there is no evidence of IgM flare or tumor lysis. Four patients have completed 6 cycles, 1 had progressive disease (PD) after Cycle 1, and 2 patients are receiving ongoing therapy. ORR is 86% (6/7). Three patients (43%) achieved a very good partial response (VGPR), 3 (43%) achieved a partial response (PR), and 1 had PD. One patient that achieved a VGPR later developed Bing-Neel syndrome. Median time to minor response was 14 days (range, 7-77), median time to ≥PR was 60 days (range, 21-105). At best response, median

IgM decreased to 252 mg/dL and hemoglobin improved to 13.4 g/dL. Median post-treatment marrow involvement (4 patients evaluable) was 5%. Notable toxicities include skin toxicity/rash in all patients (grade 1-2), 5 (71%) with edema (4=grade 1-2; 1=grade 3), 6 (86%) with cytopenias (all grade 3-4), and 5 (71%) with asymptomatic GGT elevation (3=grade 2; 2=grade 3). Although skin toxicities and GGT elevation have persisted in some patients post-treatment, cytopenias have been transient.

Conclusion: Data from the first 7 patients in this trial demonstrate an ORR of 86%. This compares favorably to other third line agents in WM and offers a fixed duration treatment option. Loncastuximab has a manageable side effect profile with skin toxicity, mild edema, asymptomatic GGT elevation, and transient cytopenias. Accrual will continue to enroll 36 total patients.