Phase II Trial of single agent panobinostat (LBH589) in Relapsed or Relapsed/Refractory Waldenstrom Macroglobulinemia

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INTRODUCTION: This study aimed to determine the safety and activity of panobinostat (LBH589) in patients with relapsed or relapsed/refractory Waldenstrom Macroglobulinemia (WM). This was based on our preclinical studies showing that panobinostat induces significant activity in cell lines and patient samples.

METHODS: Eligibility criteria include: 1) patients with relapsed or relapsed/refractory WM with any prior lines of therapy, 2) measurable disease and symptomatic disease, 3) off prior chemotherapy> 3 weeks, or biological/novel therapy for WM > 2 weeks. Patients received panobinostat at 30 mg three times a week (Mondays, Wed and Fridays). Patients were assessed after every cycle for the first 6 cycles and then every 3 months thereafter. Subjects who had response or stable disease were allowed to continue on therapy until disease progression or unacceptable toxicity. A planned restaging was performed at the end of cycle 6 including CT scans and bone marrow biopsies.

RESULTS: Twenty-seven patients have been enrolled to date. The median age is 62 years (47-80), the median lines of prior therapy is 3 (range, 1-7). All of the patients received prior rituximab. The median hemoglobin at screening is 10.3 g/dL (range 8.2-14.3), the median IgM M-spike by protein electropheresis at study entry is 1.9 g/dL (range, 0.63-5.1), and median serum IgM at baseline is 3610 mg/dL (range, 804- 10, 300). The median bone marrow involvement at enrollment was high for patients with WM, 50%, range (5-95%), with more than 10 patients having 70% or higher bone marrow involvement at baseline. The median number of cycles on therapy is 4 (range 1 - 12). 4 of the patients came off due to toxicity. Minimal response (MR) or better has been achieved in 15 (60%) of patients, with 6 (24%) PR, 9 (36%) MR. In addition, 9 (36%) patients achieved stable disease and 1 (4%) showed progression. The median decrease in IgM is 1020 mg/dL (0- 3970 decrease in IgM) with a median % decrease of 37.13%. Responses were prompt. The median time to first response was 2 cycles (range, 2-4). Bone marrow biopsies at the end of study (or at 6 months follow up) are available on 7 patients, of which 3 showed a

significant decrease in bone marrow involvement and 4 showed stable involvement. The 4 patients who had stable bone marrow disease showed 1 PR and 3 MR responses by paraprotein level. Grade 3 and 4 toxicities include 4 (15%) cases of anemia including 1 case of hemolytic anemia, 1 (3%) case of grade 4 leucopenia (but the patient had grade 3 leucopenia at baseline), 7 (26%) of neutropenia, 14 (52%) of thrombocytopenia, 1 (4%) grade 3 GI bleed due to thrombocytopenia, 1 (3%) Grade 4 hyperglycemia and 1 (3%) grade 3 syncope and 3 (27%) grade 3 fatigue. The most common grade 2 toxicities were thrombocytopenia, anemia, and fatigue. There were 5 (20%) cases of asymptomatic pulmonary infiltrates of ground glass opacity observed on routine CT scans in follow up. Of these, 3 came off study for other reasons not related to the pulmonary infiltrates, 1 received a course of corticosteroids and had improvement of infiltrates, and 1 had dose reduction of therapy. All patients except for 2 have been dose reduced due to thrombocytopenia, fatigue, diarrhea, or anemia. Dose reductions include 25 mg three times a week, 20 mg three times a week and 20 mg three times every other week. The protocol was amended to allow a starting dose of 25 mg three times a week, which is better tolerated than 30 mg in this patient population.

CONCLUSIONS: Panobinostat is an active therapeutic agent in patients with relapsed or refractory WM, with an overall response rate of 60% in patients with relapsed or refractory WM. The dose schedule of 25 mg three times a week is better tolerated in this patient population. Further studies to include this agent in combination with rituximab or bortezomib are being evaluated.