901 A Phase I/II Trial of Fludarabine, Bendamustine, and Rituximab (FBR) Chemoimmunotherapy for Previously Treated Patients with CLL

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Chemoimmunotherapy (such as fludarabine, cyclophosphamide, and rituximab) has been the most significant advance in treatment for patients with CLL, achieving the highest complete remission rates, longest progression-free and overall survival compared to chemotherapy combinations or monotherapy. Bendamustine (B) is a well-tolerated, alkylating agent that induces a DNA damage and repair response. In vitro data in 30 CLL patient (pt) samples suggested an increased DNA damage response (measured as H2AX phosphorylation), activation of p53 protein and PUMA, and cell death when fludarabine was combined with bendamustine (El-Mabhouh, A, unpublished). To translate this observation to the clinic, we are conducting a phase I/II trial of escalating doses of bendamustine at 20, 30, 40, or 50 mg/m^2 on D1,2,3 with fludarabine 20 mg/m^2 administered prior to bendamustine on D2&3. Rituximab 375-500 mg/m^2 was given on D3. Courses were repeated each 28 days to assess the safety and tolerability, clinical efficacy, and pharmacodynamics (PD) in previously treated pts with CLL. Responses were assessed after 3 courses and end of treatment. We report results of the phase I portion of this study. For phase I, dose-limiting toxicities (DLT) were assessed in course 1 and were Grade (G) ≥3 treatment-related, non-hematologic adverse event (AE), and hematologic toxicity G≥3 that lasted beyond D42 of course 1. MTD was defined as the cohort with ≤1 DLT in 6 treated pts. All pts (n=19) had active CLL and were previously treated; median number of prior treatments was 2 (1-6). Pts had high-risk features, median β-2 microglobulin was 4 (2.4-8.7); Rai stage III-IV was 10/19; 13/15 were ZAP70$^+$; 12/15 had unmutated IGHV; and FISH identified 2 with del17p and 7 with del11q. 19 patients were evaluable for course 1 toxicities and DLT. Course 1 toxicities were predominantly G1-2 and most common were nausea, fatigue, and hyperglycemia. One of 6 pts experienced DLT (G3 nausea/vomiting/dehydration) in the B-20 cohort; 0 of 3 pts experienced DLT in the B-30 cohort; 1 of 6 pts experienced DLT (G4 sepsis) in the B-40 cohort; and 1 of 4 pts experienced DLT (G3 neutropenia) in

the B-50 cohort. Pts continued on treatment, 5 with dose reduction, (Table) for up to 6 courses. The B-50 cohort continues enrollment and treatment, all other cohorts completed treatment. Among 14 pts evaluable for response, there were 5 complete responders (3 MRD negative by 4-color flow cytometry) and 8 partial responders (2 PRs were CRi by IWCLL 2008 criteria); only 1 pt was a non-responder (Table). Considering all courses given, the most common G3-4 AEs that occurred in more than 10% of courses (n=56) were: neutropenia (30%) and thrombocytopenia (13%). All other AEs were G1-2 and resolved. There were no treatment-related deaths. More frequent AEs with higher doses of bendamustine supports selection of the 30 mg/m^2 dose level to move forward in phase II. To test fludarabine triphosphate-mediated mitigation of DNA repair response induced by bendamustine, on D1, bendamustine was infused alone and on D2, the fludarabine dose was given 2 hours prior to bendamustine infusion. Circulating CLL cells from 7 pts (3 B-20 and 3 B-40, and 1 B-50) were evaluated for PD endpoints. Median intracellular fludarabine triphosphate level at the start of bendamustine infusion was 12 μM (range 5-21 μM). This was sufficient to increase by 3-5-fold the H2AX phosphorylation response. Molecular markers of DNA damage response and cell death (ATM, p53, PUMA, Mcl-1) are being evaluated.

In conclusion, the FBR regimen was tolerated up to the highest bendamustine dose evaluated, with significant efficacy in previously treated patients with CLL. We are extending the clinical and PD investigations in a phase II study with B-30 dose.

Table

Cohort*	n	Median courses	Total courses	Total AEs per Cohort (C1)		Eval for Response	Percent Responders	
				G1-2	G3-4	n	CR	OR
B-20	6	3(2-6)	22	22	4	6	50	83
B-30	3	4(3-5)	12	18	1	3	0	100
B-40	6	2.5(1-4)	16	45	14	5	40	100
B-50	4	1.5(1-2)**	6**	31	8	-	-	-

*Bendamustine dose mg/m^2 daily x 3; **Treatment continues

AEs, adverse events; G, grade; n, number; CR, complete remission; OR, overall response

Disclosures: No relevant conflicts of interest to declare