Sustained Depletion of B-Cells by a Humanized, Fc-Engineered Anti-CD20 Antibody, AME-133v, in Patients with Relapsed Follicular Lymphoma

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Introduction

AME-133v is a humanized anti-CD20 monoclonal antibody that has a 13 to 20-fold increase in binding affinity and approximately 6-fold more potent effector function in antibody-dependent cell-mediated cytotoxicity (ADCC) compared to rituximab. Phase I/II clinical trials of AME-133v in patients with relapsed follicular lymphoma have demonstrated an overall response rate of greater than 30% with a complete response rate of 16%. The extent and duration of depletion of CD19+ B-cells in peripheral blood was used as a surrogate of therapeutic levels of AME-133v. Analysis from the Phase I/II clinical trials is presented in this report.

Methods

CD-19 positive B-cells in peripheral blood were measured in 77 patients with relapsed follicular lymphoma enrolled in two phase I/II clinical trials of AME-133v. These studies assessed five different doses of AME-133v (from 2 mg/m^2 to 375 mg/m^2). AME-133v was administered intravenously four times at weekly intervals in both trials. Blood samples were taken at multiple time points throughout the trial and a central lab measured levels of circulating CD19+ B-cells using fluorescence-activated cell sorting (FACS).

Results

Excluding the four patients enrolled in the 2 mg/m^2 dose cohort, depletion of peripheral B-cells occurred in all patients and was sustained over time (Table 1). Baseline levels of B-cell counts ranged from 4 x 10^3 to 1,187 x 10^3 cells/μL, with an average of 102 x 10^3 cells/μL and a median of 60 x 10^3 cells/μL. Within 24 hours of the first infusion, all patients had depletion of circulating B-cells; ninety-six percent of patients had less than 10 x 10^3 cells/μL and two patients had less than 20 x 10^3 cells/μL. Interestingly, AME-133v was effective at depleting B-cells even at doses as low as 7.5 mg/m^2.

To assess sustainability of B-cell depletion after four doses of AME-133v, CD19+ cell counts were evaluated at nine weeks after the fourth infusion and every three months thereafter. Complete depletion of CD19+ lymphocytes was sustained for nine weeks. At five months after the last infusion of AME-133v, nearly two-thirds of patients had no detectable circulating B-cells. Sustained B-cell depletion lasted for at least eight months following the last infusion in 63% of patients.

Table 1. B-cell counts for all patients in 7.5, 30, 100 and 375 mg/m^2 cohorts. Percentages are cumulative.

Time Point	**Cell Count (x 10^3 cells/μL)**					
	0	**< 1**	**2 to 10**	**11 to 30**	**31 to 50**	**< 100**

Day 1 (24 hours after last infusion)	62 %	66 %	96 %	100 %	100%	100%
Day 7 (day of infusion 2)	75%	80%	95%	97%	97%	98%
Day 28 (1 week after last infusion)	78 %	87%	95%	98%	98%	100%
Day 84 (9 weeks after last infusion)	78%	87%	91%	96%	96%	98%
Day 174 (5 months after last infusion)	60%	60%	70%	86%	93%	100%
Day 264 (8 months after last infusion)	26%	26%	41%	63%	81%	89%
Day 354 (11 months after last infusion)	0%	0%	15%	40%	55%	80%

Conclusion

The rapid and sustained effect of AME-133v on B-cell depletion, even in low-affinity FcγRIIIa patients, indicates a potentially relevant biological activity of the antibody in treating B-cell non-Hodgkin lymphoma. Notably, this depletion occurred even at very low doses of drug administration and persisted over time. This may be related to its higher affinity for CD20, increased ADCC, or both. The sustained B-cell depletion may result in prolonged clinical response and might mitigate the need for maintenance therapy. A randomized trial is being planned to compare efficacy of AME-133v vs. rituximab.