Ex-vivo exposure-response characterization of antitumor activity of anti CD123 X CD3 DuoBody in primary acute myeloid leukemia (AML) bone marrow samples

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Objective and Introduction: To characterize ex-vivo exposure-response in AML patients. Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled clonal expansion of hematopoietic progenitor cells and is the second most common form of leukemia. CD123 (IL-3 receptor alpha) is over-expressed on AML leukemic stem cells (LSCs) and blasts compared with normal hematopoietic progenitor cells, and represents a promising target of antibody therapies for AML. CNTO 9958 is a bispecific duobody that can induce T-cell mediated cell killing by simultaneously binding to the T cell receptor (TCR) co-receptor CD3e that is expressed on T cells and to CD123 on malignant AML cells.

Methods: Relapsed/refractory (r/r) AML patients typically have gone through several prior treatments and it is anticipated that target cell killing in such patients’ blood and bone marrow may vary based on the effectiveness of their immune system at the time of treatment. To explore this difference ex-vivo, 20 AML patients’ fresh bone marrow samples were collected and treated with CNTO 9958 at varying CNTO 9958 concentrations and incubation times. The ex-vivo exposure-response relationship was established by applying Sigmoid Emax model.

Results: Ex-vivo tumor cell killing was also accompanied with T-cell activation and proliferation. Incubation time dependent Target blast cell killing and T-cell activation increased with increase in CNTO 9958 concentrations. Based on patient blast reductions ex-vivo, profiles were hypothesized to be ex-vivo responders and non-responders. Model identified initial slope of blast depletion as potential surrogate of response ex-vivo. In general, patients with higher baseline effector/target ratio and CD3+ T-cells showed better ex-vivo target cell killing compared to the results from other patients.

Conclusion: Such ex-vivo exposure-response analysis and emergent correlations may further be explored in clinic to support patient stratification strategy, clinical response enrichment and identify patients’ baseline characteristics that may potentially be early predictors of clinical response.