Clinical and preclinical activity of SL-401, a targeted therapy directed to the interleukin-3 receptor on cancer stem cells and tumor bulk of hematologic malignancies, against blastic plasmacytoid dendritic cell neoplasm (BPDCN).

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Background: Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN), a rare and aggressive dendritic cell-derived hematologic malignancy that typically involves the skin and invariably progresses to a leukemic phase, has a dismal prognosis with a median survival of approximately 14 months. Since BPDCN cells express high levels of the interleukin-3 receptor (IL-3R), SL-401, a novel targeted therapy directed to IL-3R, is being developed to treat BPDCN and other IL-3R-expressing hematologic malignancies. SL-401 is a recombinant biologic comprised of IL-3 conjugated to a truncated diphtheria toxin, a potent inhibitor of protein synthesis (Frankel et al, Prot Eng 13, 575, 2000). SL-401 is cytotoxic in vitro to IL-3R-expressing leukemia blasts (Frankel et al, Leukemia 14, 576, 2000) and inhibits tumor growth in vivo (Black et al, Leukemia 17, 155, 2003). Recently, SL-401 demonstrated ultra-high anti-tumor potency against BPDCN cells in the femtomolar (10⁻¹⁵ M) range (Angelot-Delettre et al, Blood 118 Suppl 2588, 2011).

Methods: In a Phase I/II trial of SL-401 in patients with IL-3R-expressing advanced hematologic malignancies, 4 patients with heavily pretreated BPDCN received a single cycle of SL-401 as a 15-minute infusion daily for 5 days.

Results: All patients had CD4+/CD56+/CD123+ (IL-3Ralpha) expressing blasts and had failed previous combination chemotherapy regimens and allogeneic bone marrow transplantation. There were no serious adverse events. Three patients treated with SL-401 at 12.5 µg/kg/day (the planned pivotal Phase IIb trial dose) experienced complete responses (CRs). The CRs included disappearance of BPDCN in the skin, bone marrow, peripheral blood, spleen and lymph nodes. CR durations are 5, 3+, and 1+ months to date.
Conclusions: Given these robust clinical responses, as well as the mechanistic rationale for SL-401 in BPDCN, additional BPDCN patients are being evaluated in the study and a pivotal Phase IIb multi-cycle trial in this ultra-orphan indication is being planned.