CLN-978, A NOVEL CD19/CD3/HSA T CELL ENGAGER WITH EXTENDED SERUM HALF-LIFE, IS EFFECTIVE AGAINST LYMPHOMA CELLS EXPRESSING VERY LOW LEVELS OF CD19

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**Background** T cell therapies targeting the B cell antigen CD19 have profoundly changed the way we treat various B cell malignancies. Both the CD19/CD3-bispecific T cell-engaging bispecific antibody construct blinatumomab and various autologous CD19-specific CAR-T cell therapies have exhibited robust clinical activity in relapsed/refractory acute lymphocytic leukemia (ALL) and non-Hodgkin lymphoma (NHL). However, both therapies fail in patients where tumor cells have low levels of target expression and thereby escape elimination under selective pressure by downregulation of the CD19 antigen. CLN-978 is a single-chain fusion protein consisting of two tandemly arranged humanized single chain Fv domains with specificities for CD19 and CD3, and one humanized VHH domain with specificity for human serum albumin. It was designed for high-affinity binding to CD19, to enable killing of low-CD19 expressing blasts, and for long serum half-life.

**Methods** To determine the minimal copy number of CD19 on target cells necessary for redirected lysis by CLN-978, a chemically inducible system was used to tune the level of expression of a human CD19 (hCD19) transgene in CHO cells. Target expression was confirmed by quantitative flow cytometry, which revealed a broad range of CD19 surface expression levels ranging from 78 to more than 185,000 CD19 copies per cell. The findings with inducible hCD19-expressing CHO cells were corroborated with mouse A20 lymphoma cell lines stably transfected with hCD19, ranging from 325 to 17,000 CD19 copies per cell.

**Results** CLN-978 induced potent redirected lysis, T cell activation, and corresponding cytokine release when hCD19-expressing A20 or hCD19-expressing CHO cell lines were co-cultured with purified T cells from healthy donors. Potent target cell lysis was detected at pM concentrations of CLN-978 in all cell lines regardless of CD19 copy number. Importantly, complete maximal killing was observed at all expression levels, indicating that CLN-978 was capable of redirecting T cells even against target cells expressing very low levels of hCD19. Redirected lysis was specific because parental A20 or CHO cells, which do not express hCD19, were spared.

**Conclusions** CLN-978 elicited potent efficacy against B cell lymphoma cells expressing very low levels of hCD19, which frequently arise as a mechanism of resistance following treatment with CD19-directed therapies. The characteristics of CLN-978 may translate into high response rates and longer response duration in NHL patients expressing normal and very low levels of CD19 on malignant B cells. CLN-978 is currently in Phase 1 clinical development (NCT05879744).

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