Targeting cell lymphomas with CRISPR/Cas9-generated anti-CD70 allogeneic CAR-T cells

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Abstract

T lymphoma cells account for 10-20% of non-Hodgkin lymphomas and are diverse biologically and clinically. Unlike B-lineage lymphomas, T cell lymphomas are rather resistant to conventional therapies, such as chemotherapy and radiation. The high prevalence and the diversity in the biology of T cell lymphomas suggests that a significant cancer burden exists across the T cell lymphoma subtypes. CD70 (107F12) is a candidate target antigen for T cell lymphomas and has been shown in the setting of clinical trials using an enhanced ADCD antibody (ABX-107). Using flow cytometry and immunohistochemical analysis, we have shown that CTX130, an allogeneic CAR-T cell therapy targeting CD70 is able to bind CD70-expressing tumor cells and kill tumor cells in a dose-dependent and concentration-dependent manner. Consistent with prior observations, CTX130 exhibited high potency in vitro against T cell lymphoma cell lines with a wide range of tumor antigen expression. In vivo, CTX130 has been shown to achieve a range of CD70 expression levels within cell types representing other malignancies. Consistent with these prior observations, we observed that CTX130 killed tumor cells with varying levels of CD70 expression in a dose-dependent and concentration-dependent manner. Therefore, we sought to examine the potency of our allogeneic anti-CD70 CAR-T therapy against T cell lymphoma tumors in an orthotopic xenograft tumor model of Sézary Syndrome. In vivo, CTX130 may thus be a solid therapeutic to evaluate in T lymphoma patients.

Figure 1: CTX130 Is CRISPR Therapeutics’ first oncology product in clinical phase two testing both solid and liquid tumors

Figure 2: CTX130 shows potent activity against a low-expressing CD70-positive TCL cell line

Conclusions from preclinical studies

CTX130 is an allogeneic CAR-T cell therapy targeting CD70 for the treatment of both solid tumors, such as renal cell carcinoma, and T- and B-cell hematologic malignancies.

Given that CD70 shows high (~80%) prevalence in TCL, we have successfully demonstrated in vitro and in vivo efficacy of CTX130 against a T-cell lymphoma xenograft tumor model of Sézary Syndrome. In vivo efficacy against an established HuT78 TCL xenograft model of Sézary Syndrome, with CD70low HuT78 CAR-T cells were shown to effectively eradicate tumors with low CD70 expression. Additionally, CRISPRTherapeutics has obtained orphan designation approval from the FDA for Clinical Trials for a T cell lymphoma indication.

In vitro, CTX130 demonstrated low variability in its in vivo efficacy across in vivo xenograft models, including tumors with low CD70 expression, as well as tumors with high CD70 expression. In vivo efficacy was maintained across these in vivo xenograft models, including tumors with low CD70 expression.

Table 1: CTX130 has demonstrated in vivo efficacy in tumor models of a range of CD70-expressing liquid and solid tumors

Table: CD70 expression by flow cytometry in TCL and RCC cancer cell lines. Consistent with the IHC data, TCL cell lines HuT78, HH, HuT102 and MJ (indicated by the blue line) show a range of CD70 expression from low/moderate to high. RCC cell lines MCF-7 and ACHN show high and low CD70 expression, respectively. Cells were run in triplicate and are shown as negative controls for background staining.

Figure 3: TCL cancer cell lines display varying levels of CD70 protein expression

Figure 4: CTX130 shows potent and specific cytotoxicity against a low-expressing CD70-positive TCL cell line

In vitro cytotoxicity assay to evaluate CTX130 activity against the CD70-negative HuT78 cell line and CD70-negative K562 cell line. CTX130 was co-cultured with 7,500 or 76,500 cells for 24 hours at T-cell tumor cell ratios ranging from 0.1 to 4.1. Tumor cell viability was assessed using flow cytometry. The mean ± standard error. Four of the five mice treated with CTX130 exhibited high potency in vitro against T cell lymphoma cell lines with a wide range of CD70 expression in a dose-dependent and concentration-dependent manner. CTX130 may thus be a solid therapeutic to evaluate in T lymphoma patients.

Table 2: Relative CD70 expression in TCL and RCC cancer cell lines. Consistent with the IHC data, TCL cell lines HuT78, HH, HuT102 and MJ (indicated by the blue line) show a range of CD70 expression from low/moderate to high. RCC cell lines MCF-7 and ACHN show high and low CD70 expression, respectively. Cells were run in triplicate and are shown as negative controls for background staining.

Figure 5: CTX130 shows potent activity against a low-expressing CD70-positive TCL tumor xenograft model

In vivo, CTX130 showed high (~80%) prevalence in TCL, as shown by IHC, we have the ability to detect the expected activity of CTX130 as a treatment for these cancers. CTX130 has potential for the treatment of TCL, including tumors with low CD70 expression, as demonstrated by in vitro and in vivo studies.

- CTX130 shows potent and specific activity in vitro against a low-expressing TCL line.
- CTX130 shows potent activity in vivo against a low-expressing TCL xenograft tumor model.

CTX130 has entered clinical phase and CRISPR Therapeutics expects to begin treating patients with CTX130 in the second half of 2020.