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Preclinical Activity of Allogeneic CS1-Specific CAR T-Cells (UCARTCS1) in Multiple Myeloma

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Background

- Multiple myeloma (MM) is a hematological malignancy characterized by clonal proliferation of plasma cells within the bone marrow (BM).
- Promising clinical results have been shown with autologous BCMA CAR T-cell therapy in MM patients. However, availability and timely generation of these cells and frequent BCMA^{low} relapses illustrate the need for alternatives.
- UCARTCS1 cells are “off the shelf” allogeneic CAR T-cells derived from healthy donors targeting CS1 (SLAMF7). The genes coding for TCRα chain and CS1 are disrupted using TALEN® gene editing technology.

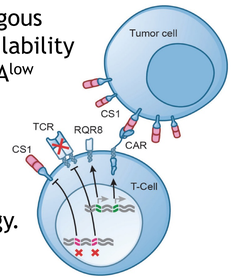


Figure 1 *UCARTCS1 CAR T-Cell*

Aim

- To evaluate activity of UCARTCS1 against MM cell lines, BM samples from MM patients and in a MM mouse model.
- To evaluate the potential impact of UCARTCS1 on non-malignant hematopoietic cells.

Method

UCARTCS1 activity was assessed by using a 24h BLI-based cytotoxicity assay for MM cell lines and a 24h flow cytometry-based cytotoxicity assay for BM samples from MM patients. BM samples were obtained from newly diagnosed (n=10; NDMM), daratumumab-naïve relapsed/refractory patients (n=10; RRMM) and from daratumumab-refractory patients (n=10; DRMM).

Results

1. Activity of UCARTCS1 in MM cell lines

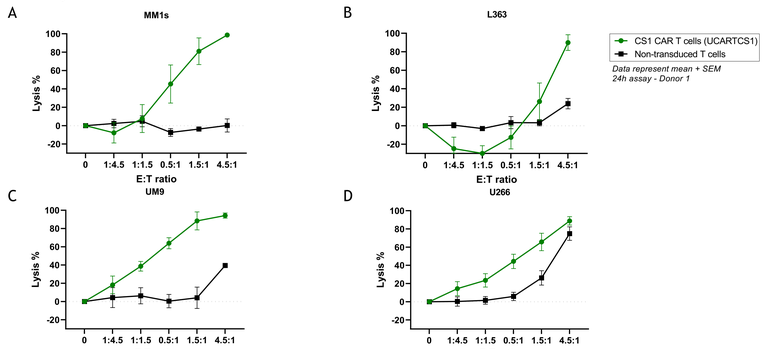


Figure 2 *(A-D) UCARTCS1 mediated lysis in four MM cell lines. Non-transduced T-cells are KO for TRAC and CS1 genes.*

2. UCARTCS1 induces dose-dependent lysis of primary MM cells

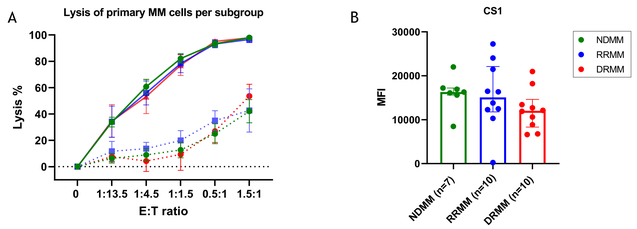


Figure 3 *(A) UCARTCS1-mediated lysis in 30 BM samples from MM patients. Solid lines represents UCARTCS1 and dotted lines non-transduced T cells. Data represents mean + SEM. (B) CSI expression level on MM cells from NDMM, RRMM and DRMM patients.*

3. CS1 expression levels on non-malignant hematopoietic cells

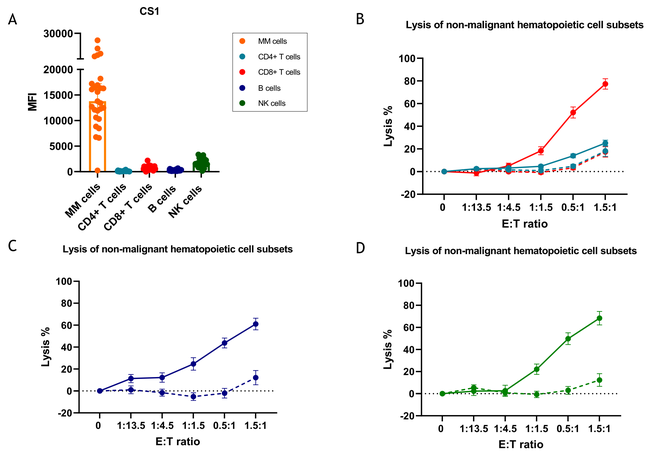
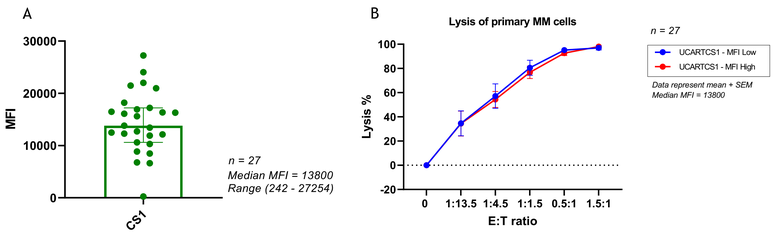


Figure 4 *(A) CS1 expression level on MM cells and normal hematopoietic cells. (B-D) Lysis of non-malignant hematopoietic cells in 30 BM samples. Solid lines represent UCARTCS1 and dotted lines non-transduced T cells. Data represent mean + SEM.*

4. Impact of patient and tumor characteristics



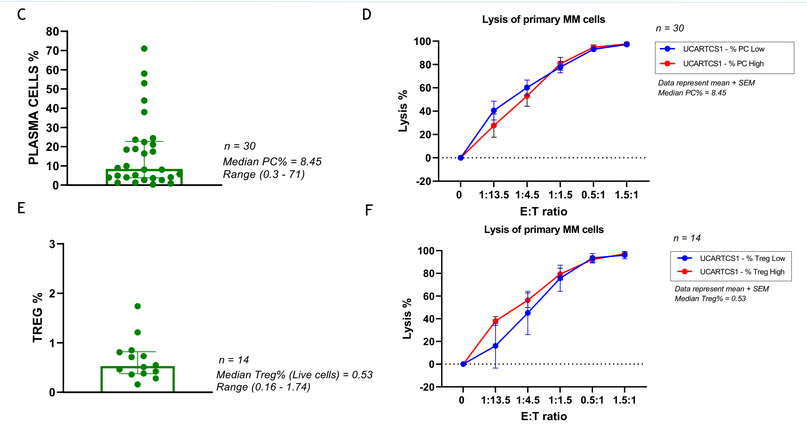


Figure 5 *(A-B) CS1 expression level on tumor cells and impact on lysis. Patients were divided into 2 groups (low vs high) according to whether CS1 expression levels were above or below the median value. (C-D) Percentage of tumor cells and impact on lysis. (E-F) Percentage of Tregs and impact on lysis.*

5. UCARTCS1 effectively kills MM cells in vivo

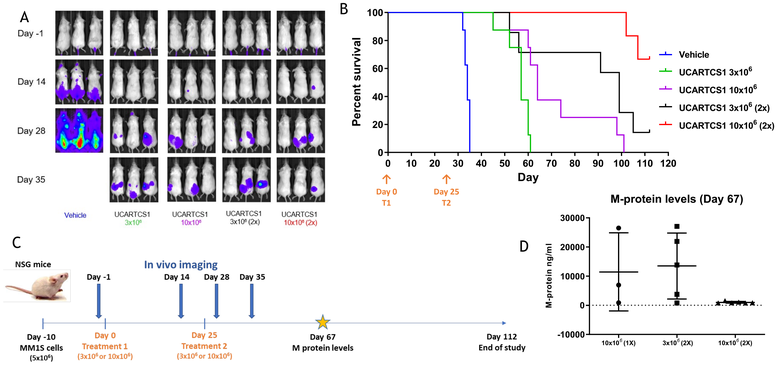


Figure 6 *(A-D) NSG mice injected with MM1s (iv) on day -10 and treated with one or two doses of 3M cells, or with one or two doses of 10M cells. Treatment days were on day 0 and day 25. BLI readout at day -1, day 14, day 28 and day 35. M-protein levels were assessed at day 67.*

Conclusion

- UCARTCS1 has potent anti-MM activity against MM cell lines and primary MM cells, as well as in a MM xenograft model. There was no difference in ex vivo activity in between heavily pretreated and newly diagnosed patients.
- These data support the ongoing phase 1 clinical trial with UCARTCS1 in heavily pretreated MM patients (NCT04142619)