

## **Abstract: S289**

### **Title: INTERIM ANALYSIS OF THE PHASE I SAFETY RUN IN COHORT OF THE MONOCENTRIC "CD19.CAR-T CELLS IN SYSTEMIC B CELL-MEDIATED AUTOIMMUNE DISEASE" (CASTLE) STUDY**

**Abstract Type: Oral Presentation**

**Session Title: Gene therapy, cellular immunotherapy and vaccination - Clinical**

#### **Background:**

Systemic autoimmune diseases that have pathognomonic auto-antibodies are based on an aberrant activation of B cells. Autologous CD19 chimeric antigen receptor (CAR) T cells allow deep depletion of B cells in humans and represent a new possibility to treat autoimmune disease. Previous observations suggested that a single infusion of CD19-CAR-T cells is not only well tolerated in patients with SLE and other autoimmune diseases but also induces sustained drug-free remission (Müller et al, 2024 NEJM). However, safety and efficacy of CD19-CAR-T cell therapy in autoimmune disease has to be demonstrated in controlled clinical studies.

#### **Aims:**

To assess the safety and preliminary efficacy of CD19-CAR-T therapy in autoimmune diseases in a controlled clinical study

#### **Methods:**

CASTLE (CAR-T cells in systemic B cell-mediated autoimmune disease) is a phase I/II basket study that assesses the safety (primary endpoint) and preliminary efficacy (secondary endpoint) of CD19-CAR-T therapy in systemic lupus erythematosus (SLE), idiopathic inflammatory myositis (IIM) and systemic sclerosis (SSc). It consists of a phase I safety part with 8 patients which after safety review followed by a phase II extension cohort of 16 patients. Lymphodepletion is done using cyclophosphamide/fludarabine followed a single infusion of MB-CART19.1 at a dose of one million CD19-CAR-T cells/kg body weight. To be included, patients had to have a diagnosis of SLE, IIM or SSc, (ii) active disease with organ involvement and (iii) failed treatment with a least two immunosuppressive drugs before inclusion. Next to standard CTC AE collection, AEs of special interest were recorded including cytokine-release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), bone marrow toxicity, disease flairs, and infections. Preliminary efficacy was assessed by assessing B cell depletion, CAR-T cell expansion and clinical responses.

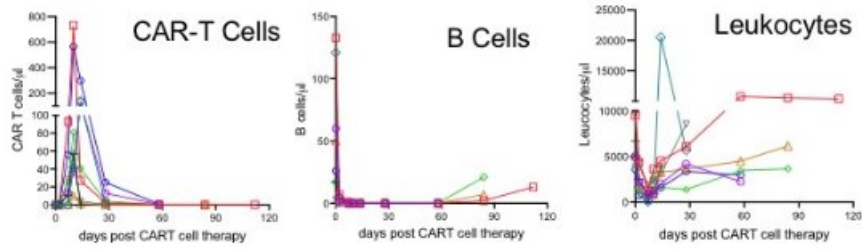
#### **Results:**

This report describes part I of the CASTLE study comprising 8 patients (5 SLE, 2 SSc, 1 IIM). 6 patients were females, 2 were males. Median age was 33.5 years (range 20-81 years), median disease duration 3 years [range: 1-9 years) and median follow up time 2.4 months (range: 1-5 months). Patients failed on a median number of 4 (range N=3-6) immunosuppressive treatments. From all 8 patients, safety data and B cell/CAR-T cell efficacy data were available, while clinical efficacy data were available from 5/8 patients with sufficiently long follow-up ( $\geq 6$  weeks). No higher grade CRS (grade 3 or 4) was observed (grade 0: N=3; grade 1: N=4; grade 2: N=1). No ICANS and no prolonged bone marrow toxicity (grade III/IV neutropenia/leucocytopenia  $> 28$  days) were observed. AESI were two late-stage neutropenias that resolved with G-CSF treatment, one flare of SLE before CAR-T cell therapy that required glucocorticoids and two cases of pneumonia (SARS-CoV-2 and CMV) that resolved upon treatment. B cells were completely depleted in all patients within 10 days (Figure 1). CAR-T cells expanded in all patients. Among the 5 patients (3 SLE, 1 SSc, 1 IIM) that had sufficiently long follow-up ( $\geq 6$  weeks), three achieved DORIS remission (SLE), one achieved ACR Moderate/Major response (IIM) and one achieved no worsening of lung function (SSc). Furthermore, all patients could successfully stop glucocorticoids and immunosuppressive drugs after CAR-T cell infusion.

#### **Summary/Conclusion:**

These data underline the safety of CD19-CAR-T therapy in autoimmune disease. No higher grades of CRS, ICANS or BM toxicity was observed. Attention has to be given to late-stage neutropenia, exacerbation of the underlying diseases, and infections.

Summary of safety of CD19 CAR T cell therapy in the first part of the CASTLE study								
Patient #	1	2	3	4	5	6	7	8
Disease	SLE	SSc	HIM	SLE	SLE	SSc	SLE	SLE
CRS (grade 0-4)	0	2	0	1	1	0	1	1
ICANS (grade 0-4)	0	0	0	0	0	0	0	0
Bone marrow toxicity	0	0	0	0	0	0	0	0
Severe Infections (Pneumonia)	0	0	1	0	0	0	1	0
Late-stage neutropenia	0	0	0	1	1	0	0	0
Disease Flare	0	0	0	0	0	0	1	0



**Keywords:** Clinical trial, Autoimmune disease, CD19, CAR-T