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Università di Brescia

Dipartimento di Scienze Cliniche e Sperimentali

Dottorato di Ricerca in
«Intelligenza Artificiale in Medicina e Innovazione nella Ricerca clinica e metodologica»

Coordinatore: Prof. Domenico Russo

Biology, efficacy and safety of CD19 CAR-T Cell therapy in systemic autoimmune diseases

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XL ciclo

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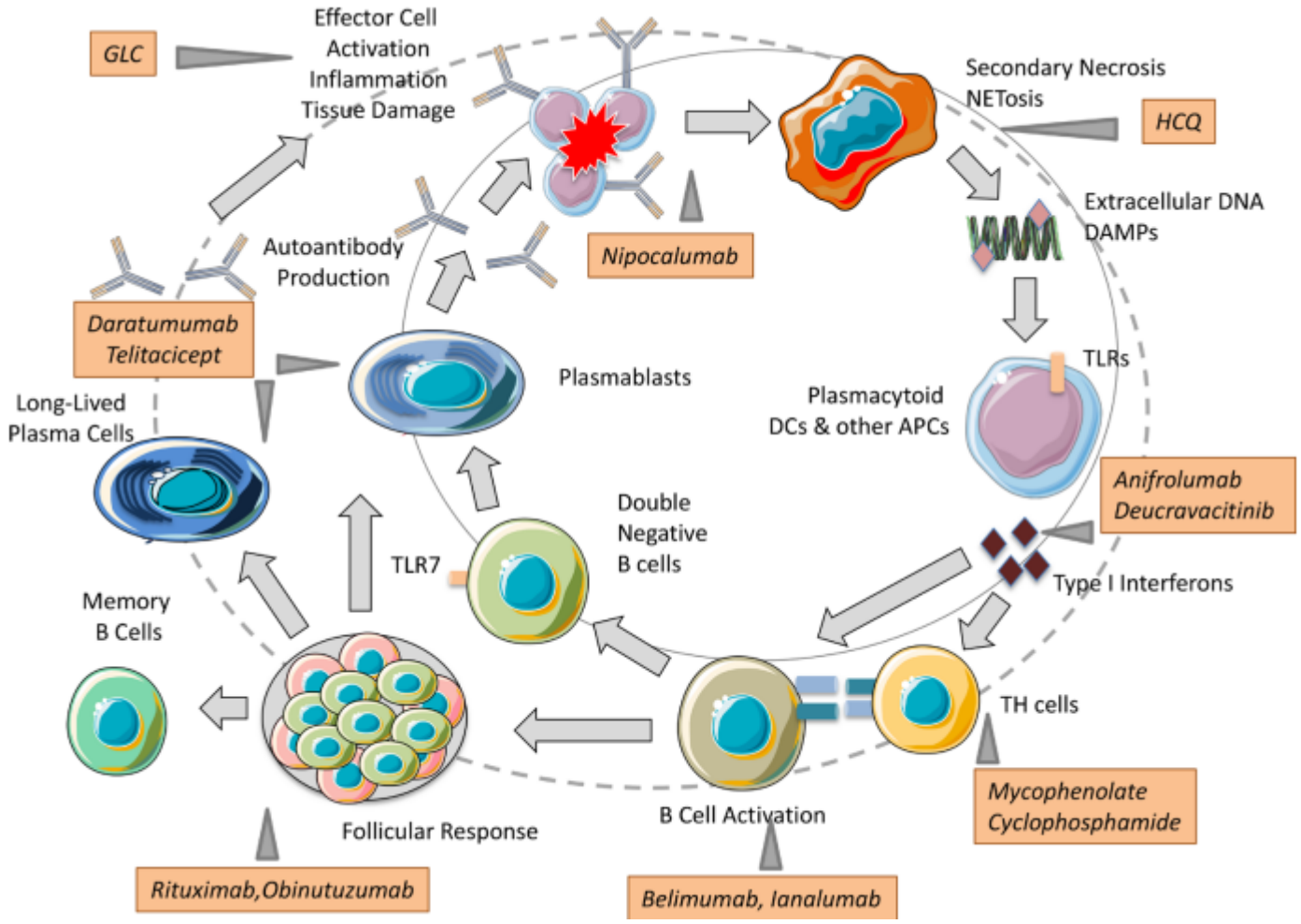
B-Cell depleting therapies in SARD

B cells are crucial orchestrator in developing of systemic autoimmune diseases:

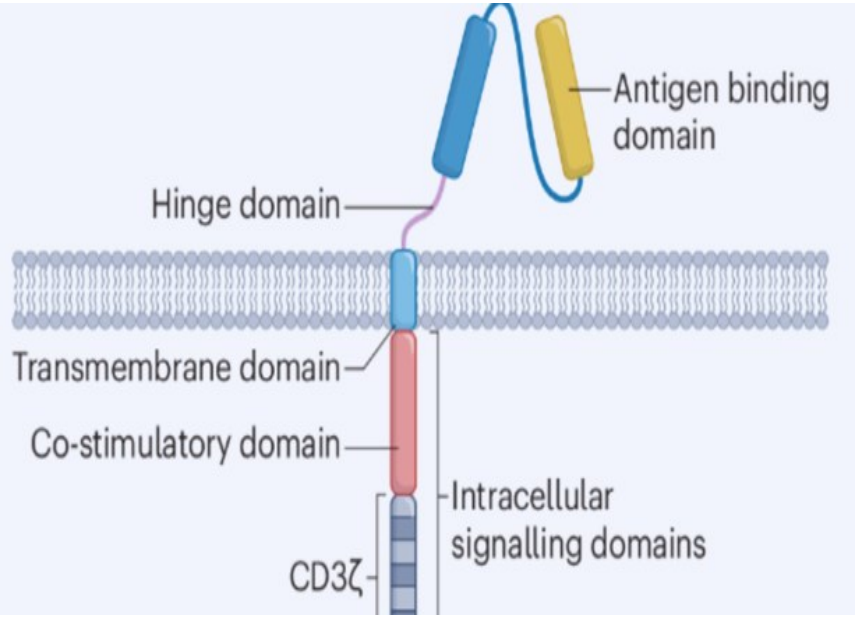
- Production of autoantibodies
- Chemokines and pro-inflammatory cytokine secretion
- Antigens presentation

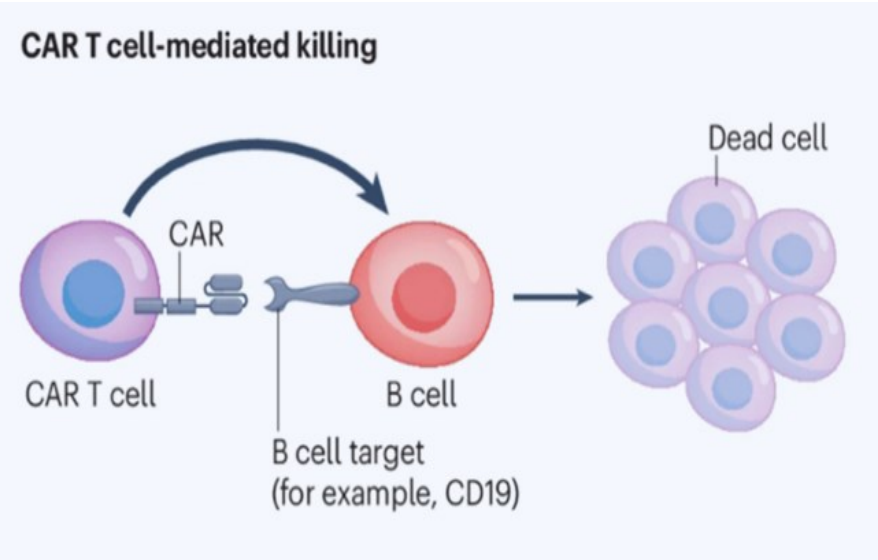
Structures resembling germinal centre are found in non-lymphoid organs that are affected by SARD



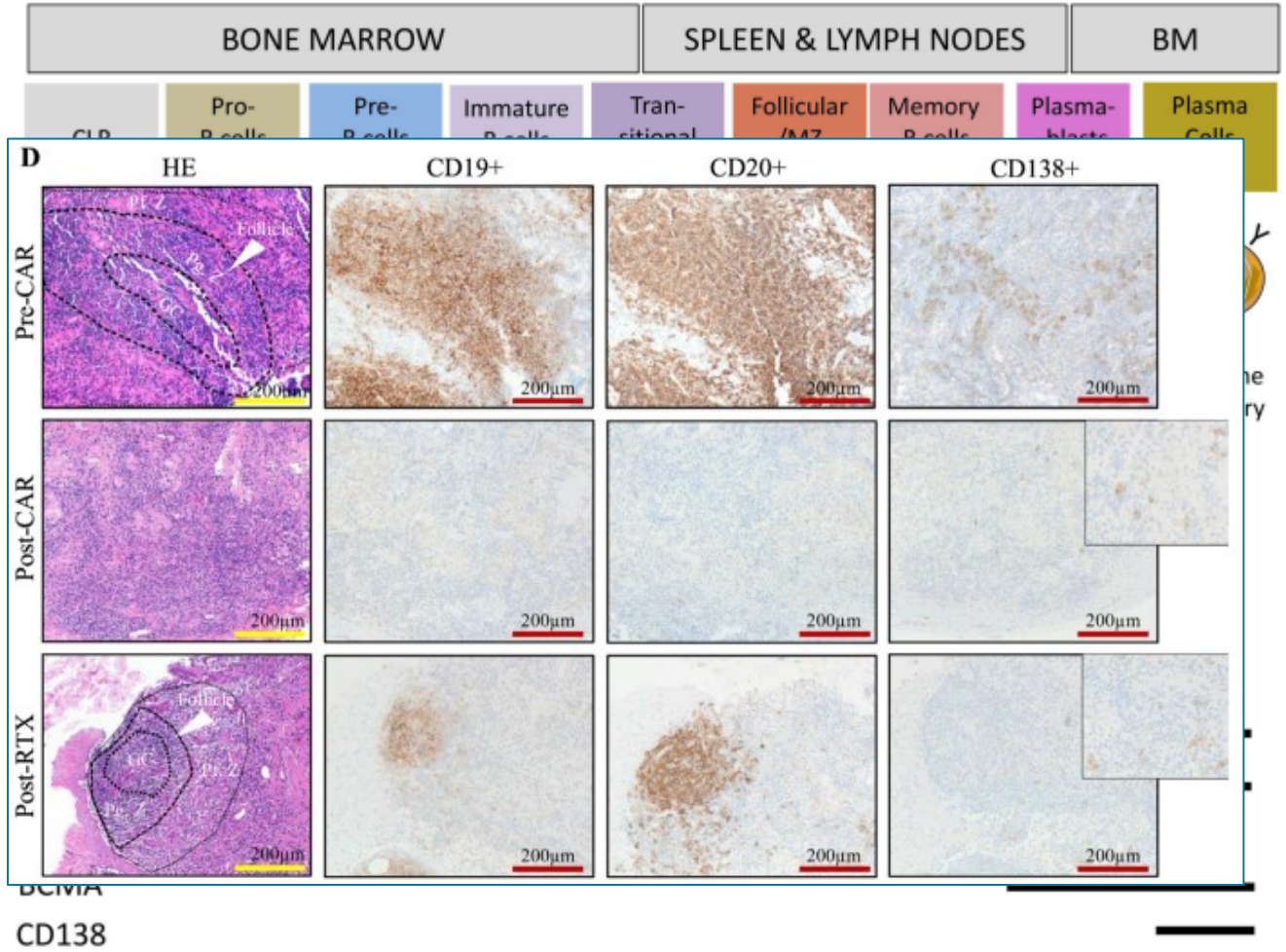
Schett G et al,, ARD, 2024

What is a CAR-T cell





Why targeting CD19



Schett G. et al., Nat. Rev. Rheumatol., 2024;
Tur C. et al., Ann Rheum Dis. 2025

CAR-T cell therapy side effects – Focus on CRS grading

Cytokine Release Syndrome (CRS)

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Localized Inflammatory Cytokine-associated Toxicity Syndrome (LICATS)

Immune effector cell-associated HLH-like syndrome

ASTCT CRS Consensus Grading

CRS Parameter[5]	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1,2]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension[1]	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/ or[3]		
Hypoxia[1]	None	Requiring low-flow nasal cannula[4] or blow-by	Requiring high-flow nasal cannula[4], facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

1) Not attributable to any other cause
2) In subjects who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity
3) CRS grade is determined by the more severe event
4) Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min
5) Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

Lee D et al, Biology of Blood and Marrow Transplantation, 2018

Aim of the study

Aim of the study is to evaluate the biology, safety and efficacy of CD19 CAR-T cell therapy in systemic autoimmune diseases

Materials and methods

Patients:

Inclusion criteria

- ✓ Diagnosis of SSc, IIM or SLE
- ✓ Severe and refractory disease: failure of glucocorticoids + at least 2 immunosuppressive treatments (alone or in combination) for at least three months

Exclusion criteria

- x Long disease duration (>7 years)
- x Severe organ damage due to disease or comorbidities

Methods:

- ***CD19 CAR-T cell therapy efficacy on disease activity and damage accrual***

a) ***SLE:*** SLEDAI-2K, CLASI, SJC and TJC, SLICC-DI, LLDAS, DORIS remission criteria, proteinuria 24h, complement C3 and C4, anti-dsDNA, ANA and anti-ENA, aPLs.

b) ***IIM:*** MMT-8, CDASI, extra-muscular disease activity, PhGA, MDI, CPK, LDH, NT-pro-BNP, TnT, CRP, ferritin, MSA and MAA

c) ***SSc:*** mRSS, DUCAS, SCTC-DI, NT-pro-BNP, CRP, ANA and anti-ENA (extended panel for SSc specific and related autoantibodies

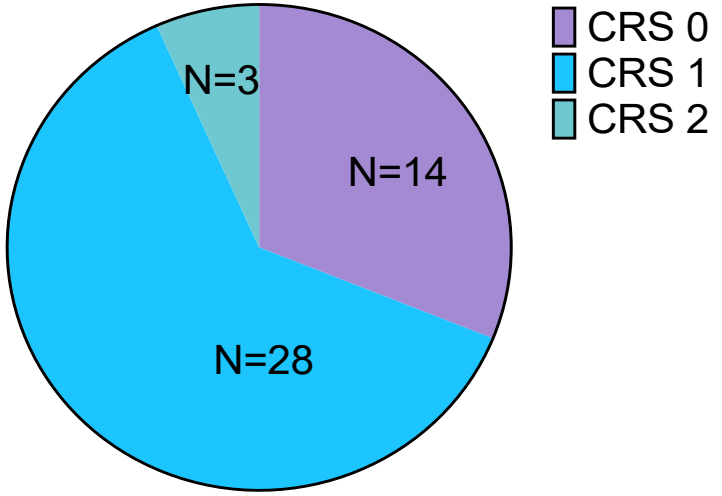
N.B Patients affected by IIM and SSc evaluated for lung function with scheduled PFT and HRCT

- ***Monitoring for CD19 CAR-T potential side effects (CRS, ICANS, HLH-like, LICATS)***
- ***Evaluation of peripheral T and B cells subpopulations at baseline and their depletion and repopulation after CD19 CAR-T cell therapy together with CD19 CAR-T expansion and persistence in blood flow***
- ***Monitoring for preservation of prior immunization, development of secondary immunodeficiencies or cytopenia and development of secondary lymphoproliferative disorders***

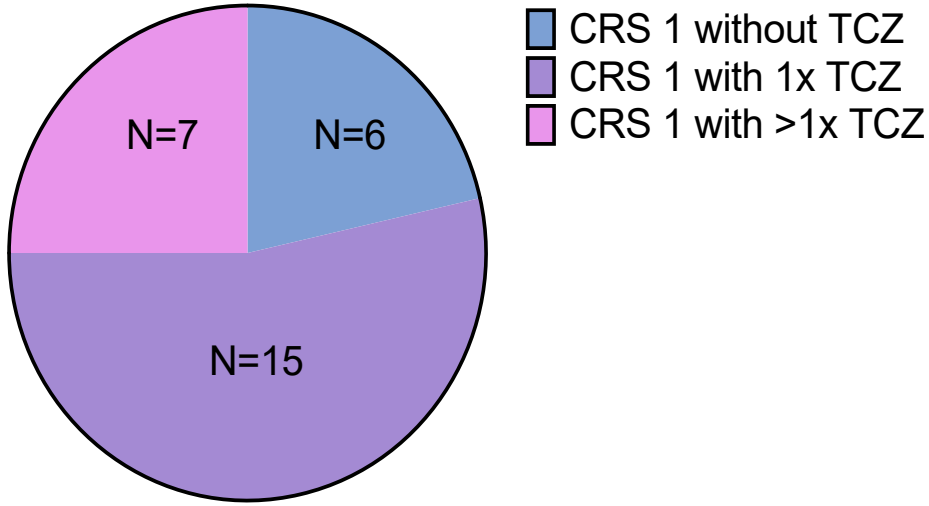
Results - 1

45 autoimmune patients (24 SLE, 13 SSc, 8 IIM) treated with CAR T cell therapy at the Department of Internal Medicine 3, **Friedrich Alexander Universität Erlangen-Nürnberg** were enrolled.

	N=45
DEMOGRAPHIC FEATURES	
Sex (female), N (%)	30 [66.7]
Age (years)	35 [23 - 43]
Body weight (kg)	68.5 [61 - 77]
Disease duration (years)	3 [1 - 6]
Number of prior treatments	5 [4 - 7]
CRS CLINICAL FEATURES	
CRS grade 0, N (%)	14 [31.1]
CRS grade 1, N (%)	28 [62.2]
CRS grade 2, N (%)	3 [6.7]
CRS onset day	1 [1 - 5]
CRS duration days	2.2 [1- 4]



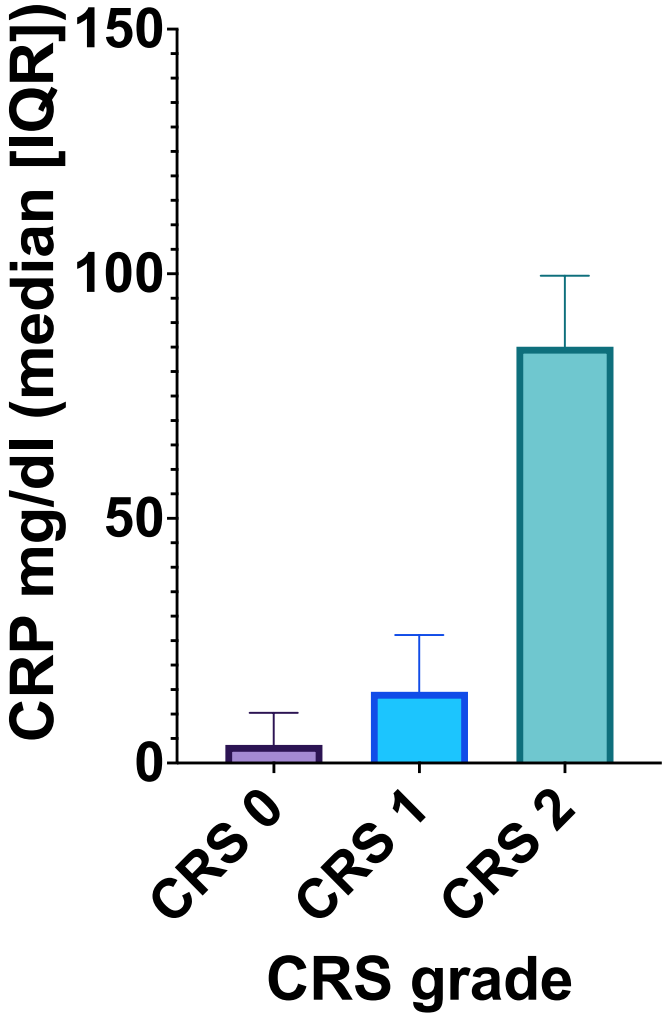
Total=45

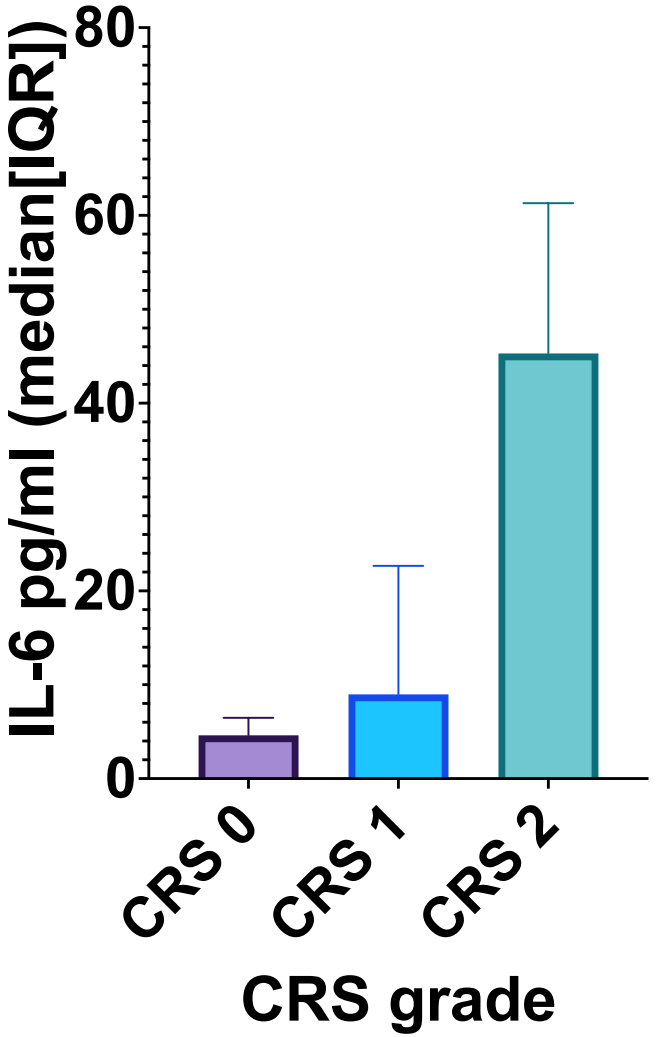


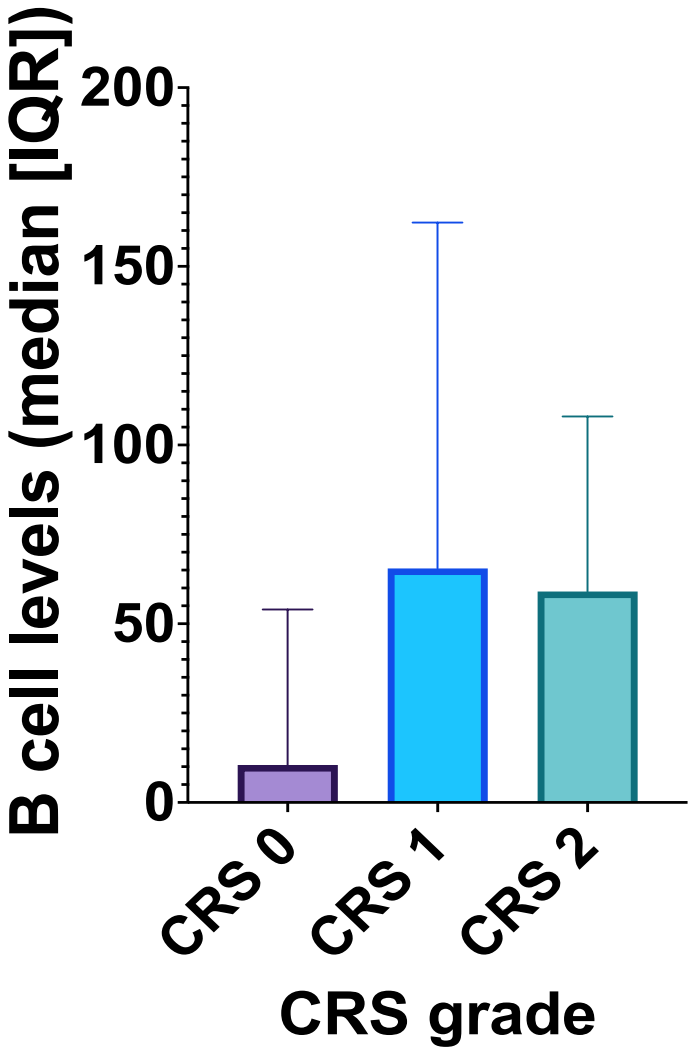
Total=28

Results - 2

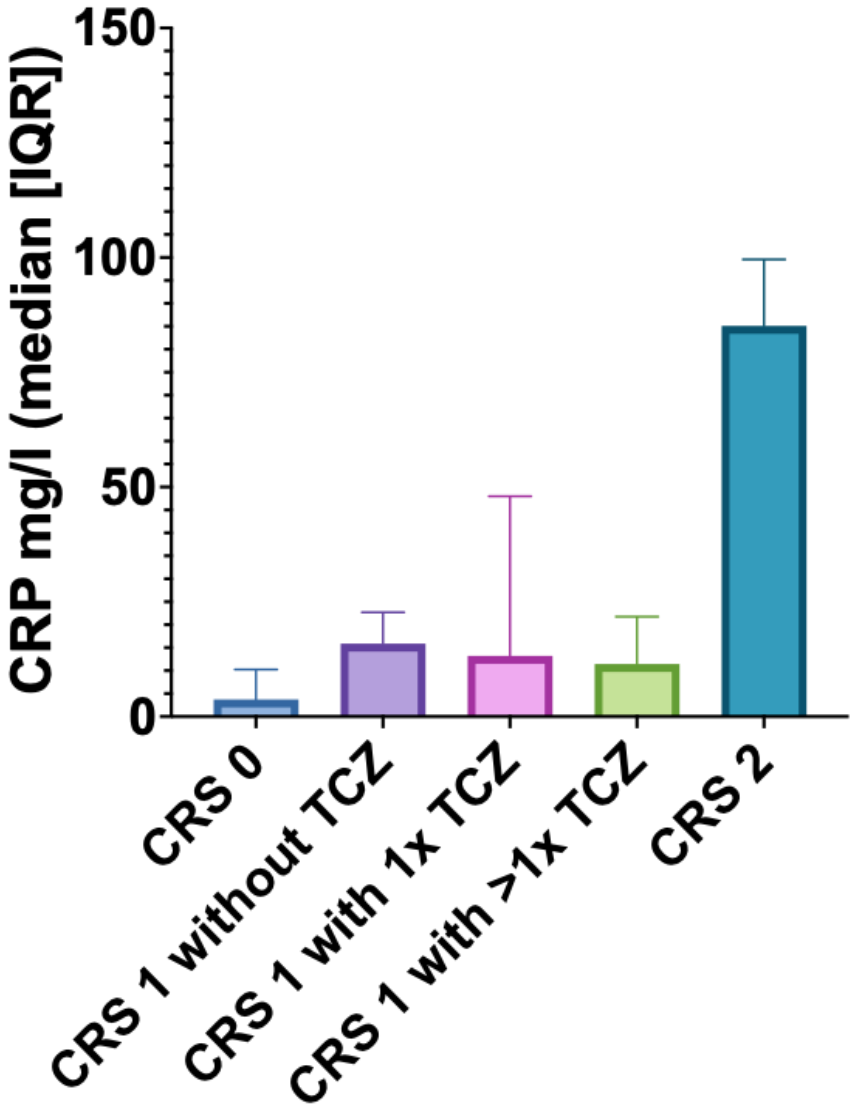
Characteristic	Overall [N = 45]	CRS 0 [N = 14]	CRS 1 [N = 28]	CRS 2 [N = 3]	p-value
Age at application (years)	35 [23 – 43]	31 [20 – 47]	36 [24 – 43]	42 [24 - 55]	0.6
Sex					0.9
- Female, N (%)	30 [67]	10 [71]	18 [64]	2 [67]	
- Male, N (%)	15 [33]	4 [29]	10 [36]	1 [33]	
Body weight (kg)	69 [61 - 77]	65 [61 - 70]	71 [60 - 81]	70 [70 - 96]	0.3
Disease duration (years)	3.0 [1.0 - 6.0]	3.5 [1.0 - 5.0]	3.0 [1.0 - 7.5]	2.0 [1.0 - 3.5]	0.7
No. of prior treatments	5 [4 - 7]	5 [3 - 6]	5 [4 - 7]	5 [5 - 7]	0.5
Diagnosis					0.7
- IIM, N (%)	8 [18]	2 [14]	5 [18]	1 [33]	
- SLE, N (%)	24 [53]	7 [50]	16 [57]	1 [33]	
- SSc, N (%)	13 [29]	5 [36]	7 [25]	1 [33]	
CRP (mg/l)	9 [3 - 20]	4 [1 - 9]	15 [4 - 25]	85 [39 - 100]	0.003
IL-6 (pg/ml)	7 [4 - 21]	5 [3 - 6]	9 [4 - 22]	45 [23 - 61]	0.003
Ferritin (ng/ml)	151 [84 - 242]	117 [54 - 390]	159 [105 - 240]	214 [148 - 407]	0.6
B cells prior LD (cells/µl)	31 [0 - 108]	9 [0 - 23]	66 [14 - 158]	61 [59 - 108]	0.047

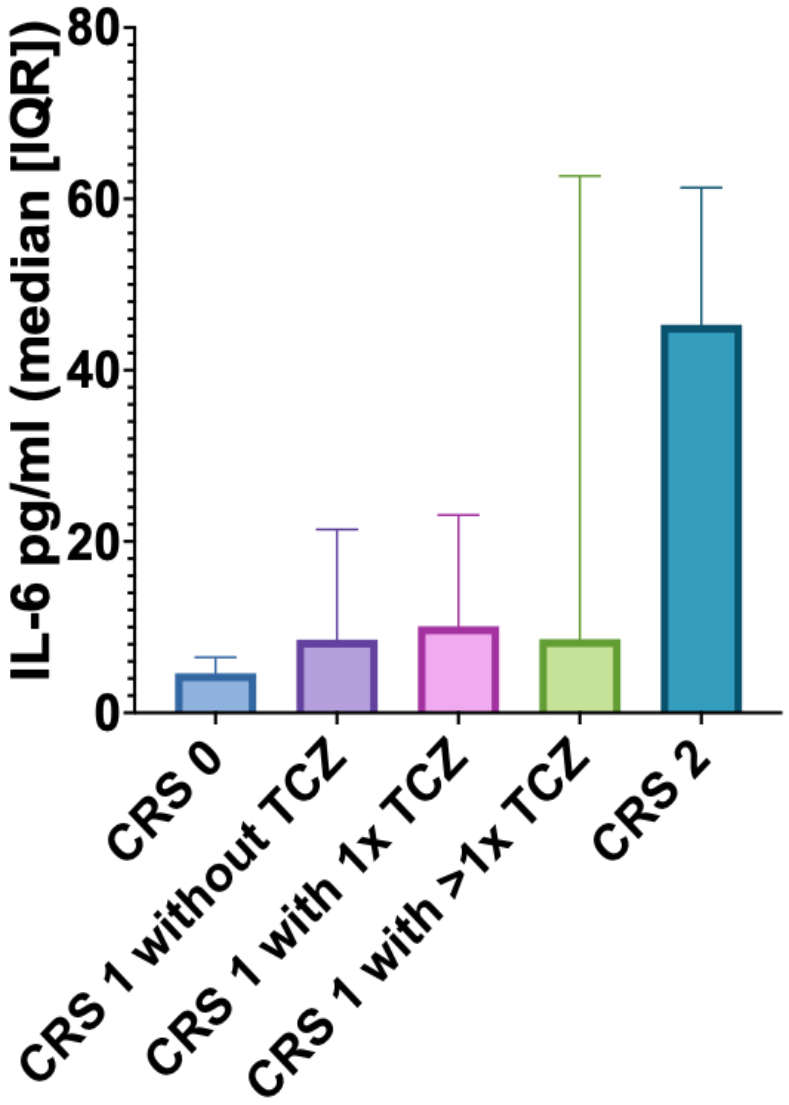

CRP mg/dl (median [IQR])
150
100
50
0
CRS 0
CRS 1
CRS 2
CRS grade

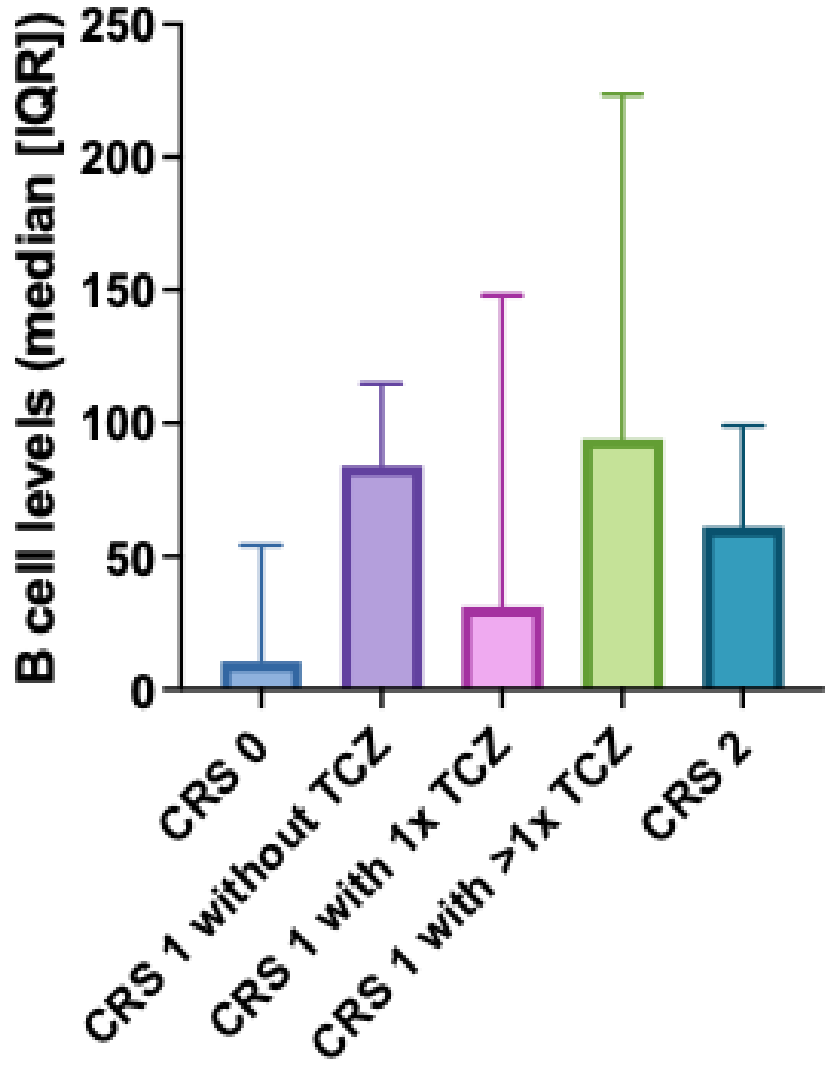

IL-6 pg/ml (median[IQR])
80
60
40
20
0
CRS 0
CRS 1
CRS 2
CRS grade


B cell levels (median [IQR])
200
150
100
50
0
CRS 0
CRS 1
CRS 2
CRS grade

Results - 3


CRP mg/l (median [IQR])
150
100
50
0
CRS 0
CRS 1 without TCZ
CRS 1 with 1x TCZ
CRS 1 with >1x TCZ
CRS 2


IL-6 pg/ml (median [IQR])
80
60
40
20
0
CRS 0
CRS 1 without TCZ
CRS 1 with 1x TCZ
CRS 1 with >1x TCZ
CRS 2


B cell levels (median [IQR])
250
200
150
100
50
0
CRS 0
CRS 1 without TCZ
CRS 1 with 1x TCZ
CRS 1 with >1x TCZ
CRS 2

Conclusions

- **Higher baseline CD19⁺ B cell counts before lymphodepletion** were predictive of **CRS development and severity** and were accompanied by elevated inflammatory markers (IL-6, CRP).
- Baseline immune profiling—combining **B cell counts and inflammatory biomarkers**—may help **predict CRS risk** more accurately.
- **Reducing B cell burden prior to CAR T infusion** (e.g., with B cell–depleting agents or optimized lymphodepletion chemioterapy) may help **mitigate CRS incidence and severity.**
- However **prolonged B-cell aplasia** and **reduced levels of immunoglobulins** are reported in those undergoing anti-CD20 therapy before CD19⁺ CAR-T cell therapy

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GRAZIE PER L'ATTENZIONE!

FAU
Friedrich-Alexander-Universität
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