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Phenotypic and genotypic characterization of peripheral B cell reconstitution following Rese-cel (Resecabtagene Autoleucel) infusion and B cell depletion across the RESET-Myositis, RESET-SSc, and RESET-SLE trials

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Key Takeaway

Rese-cel demonstrates similar PK and PD profiles across diseases with reconstituting B cells exhibiting a transitional naïve phenotype and decreased rates of somatic hypermutation, suggesting B cell reset. Initial PK/PD data in lupus at lowest dose of PC-free rese-cel demonstrate clear activity and support further dose optimization.

Background

- Pathogenic B cells can drive disease in autoimmune diseases (ADs) through the production of autoantibodies or through their function as antigen presenting cells.
- Autologous CD19-CAR T cell therapy in patients with AD has been shown to have the ability to deeply deplete B cells with an acceptable safety profile along with compelling clinical efficacy¹.
- Rese-cel (formerly CABA-201) is a fully human, autologous 4-1BBζ CD19-CAR T cell therapy designed to deeply and transiently deplete CD19+ B cells following PC with FLU/CY and a weight-based, single infusion of 1×10⁶ CAR T cells/kg, with the potential to enable an "immune system reset" with durable responses without chronic immunosuppression.
- This study aims to define pharmacokinetic (PK) and pharmacodynamic (PD) metrics that are useful when characterizing potential B cell reset across ADs. Here we present data from 50 patients treated with rese-cel and preconditioning (PC), as well as initial data from the first 2 lupus patients treated without PC (PC-free), from three open-label Phase I/II clinical trials: RESET-Myositis[®] (NCT06154252), RESET-SLE[™] (NCT06121297), and RESET-SSc[™] (NCT06328777).

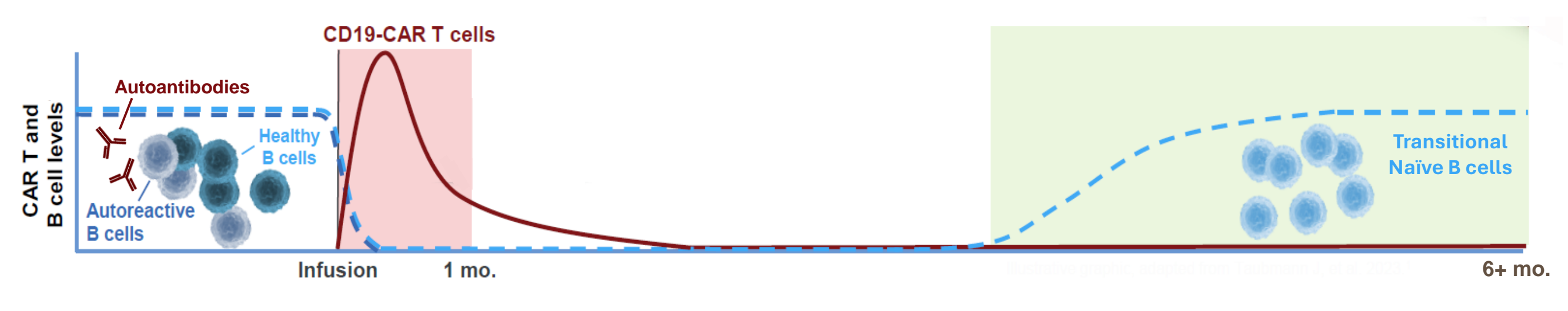


Figure 1. Proposed effect of CD19-CAR T therapy. Deep depletion of B cells in patients with rheumatological diseases may lead to cessation of disease by removing a central driver of inflammation (autoreactive B cells) and allowing the immune system to return to a tolerant state, resulting in deep and durable remissions off therapy. Some AD patients may also have antibodies derived from long-lived plasma cells, which are not targeted by CD19-CAR T therapy.

Included Patients

Table 1. Number of patients included in analyses separated by trial and cohort. PC-free patients are listed individually & not included in the figures below.

Trial	Cohort (n = number of patients)		
RESET-Myositis	DM + ASyS (n=10)	IMNM (n=6)	JiIM (n=1)
RESET-SLE	SLE (n=12)	LN (n=6)	-
RESET-SSc	SSc-Skin (n=6)	SSc-Organ (n=9)	-

Rese-cel Expansion*

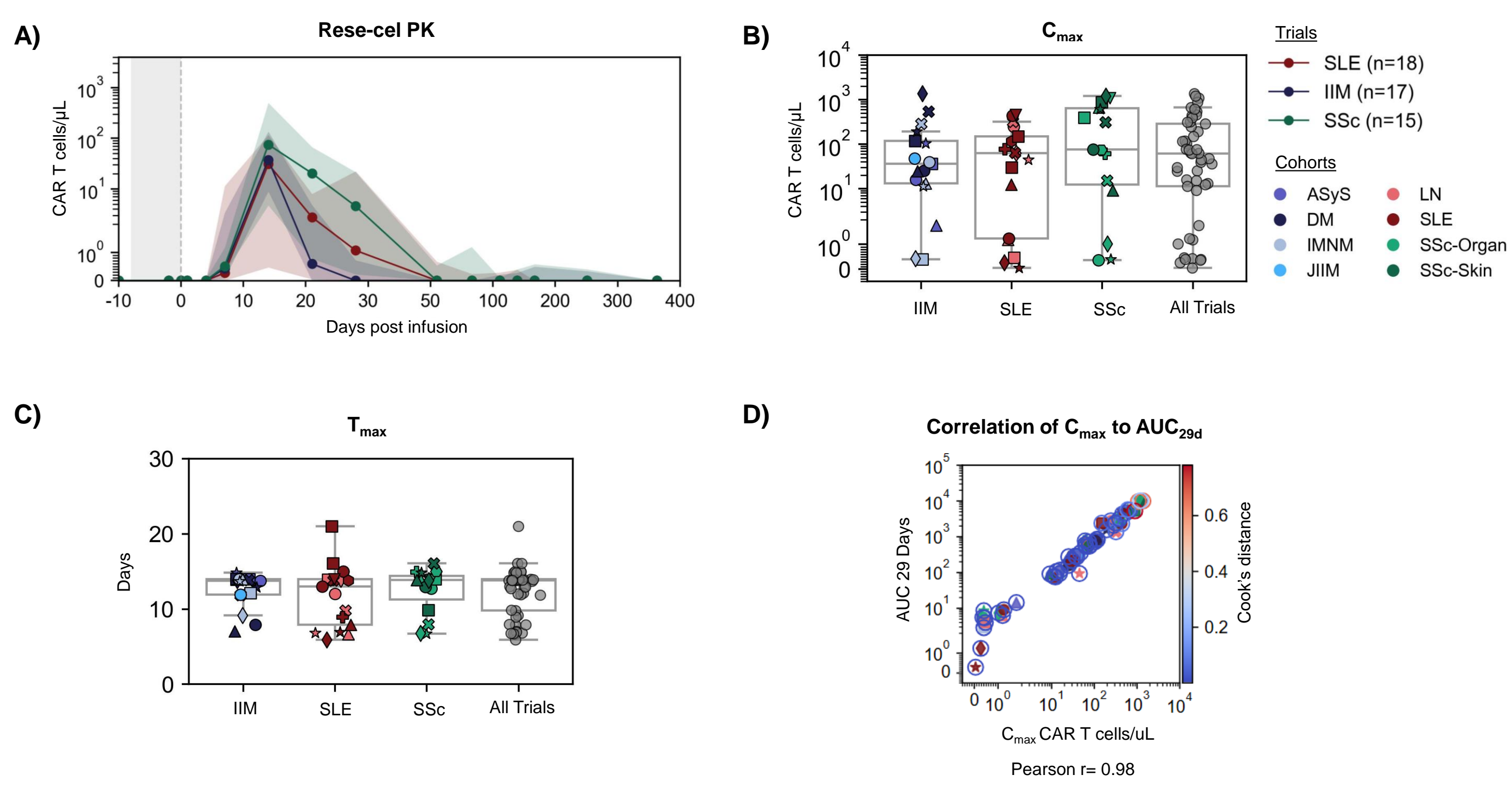


Figure 2. Rese-cel PK profile in patients treated with PC. (A) PK of rese-cel in number of CAR T cells/μL blood from baseline through post-infusion follow-up measured by dPCR. Lines represent the median and shaded regions indicate the interquartile range (IQR, 25th-75th percentile). Rese-cel infusion shown as vertical gray dotted line and PC window across all patients represented as vertical gray shading. (B) Maximum concentration of rese-cel in blood (C_{max}) in number of CAR T cells/μL blood across 3 individual trials with "All Trials" including all patients with PC with IIM, SLE, and SSc (shown in gray). All boxplots depict the median, IQR, maximum, and minimum. (C) T_{max} across individual and all trials. (D) Correlation between CAR T cell C_{max} and AUC_{29d} (Day 0-29) across all patients. Points represent individual patients; circle color/size indicate Cook's distance (influence). Pearson correlation coefficient shown.

B cell Depletion & Repopulation Kinetics*, †

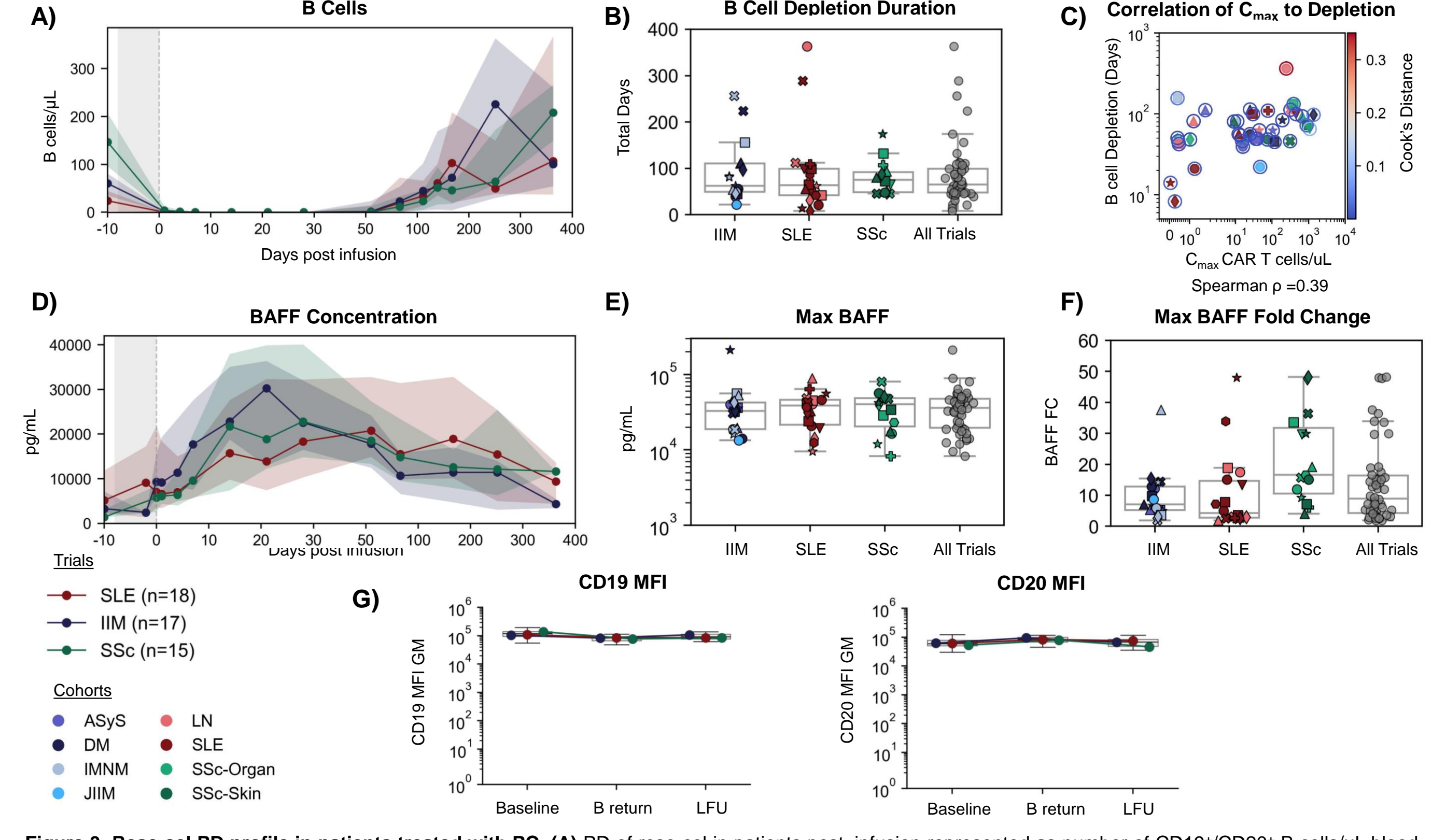


Figure 3. Rese-cel PD profile in patients treated with PC. (A) PD of rese-cel in patients post-infusion represented as number of CD19⁺/CD20⁺ B cells/μL blood from baseline through post-infusion follow up measured via flow cytometry. Lines represent the median, and shaded regions indicate the interquartile range (25th-75th percentile). Rese-cel infusion shown as vertical gray dotted line and PC window across all patients related to infusion represented as vertical gray shading. B cell count data excluded from any patient after receiving B cell-depleting rescue therapy. (B) B cell depletion duration across 3 separate trials with "All Trials" including all patients with PC: IIM, SLE, and SSc (shown in gray). All boxplots depict the group median, interquartile range, maximum, and minimum. (C) Correlation of B cell depletion duration to C_{max} in cells/μL. Spearman correlation coefficient shown. (D) BAFF concentration in pg/mL. Line represents the median, and shaded regions indicate the interquartile range (25th-75th percentile). (E) Maximum (max) BAFF concentration post-infusion within and across trial(s). (F) BAFF fold change (FC) at max from baseline within and across trial(s). (G) CD19 and CD20 mean fluorescence intensity (MFI) at baseline, B cell return, and latest follow-up (LFU) measured by flow cytometry represented as geometric mean across within and across trial(s).

PC-free SLE/LN PK & PD†

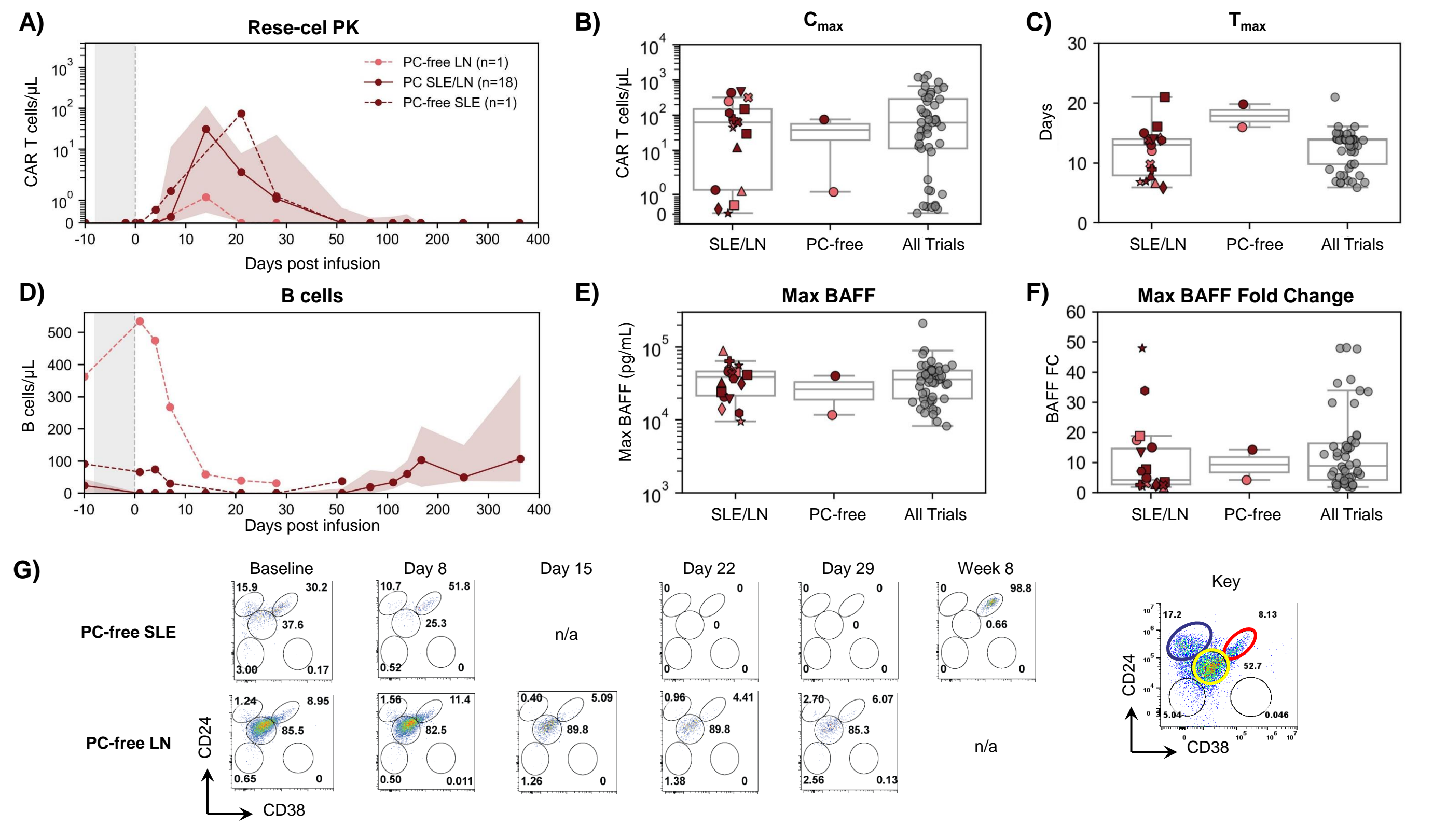


Figure 4. Rese-cel PC-free SLE/LN PK and PD. (A) Median rese-cel PK profile in PC SLE/LN patients in number of CAR T cells/μL blood from baseline through post-infusion follow-up measured by dPCR (shading indicates interquartile range, IQR). Individual dashed lines represent PC-free SLE and LN patients. Rese-cel infusion shown as vertical gray dotted line and PC window represented as vertical gray shading. (B) Maximum concentration of rese-cel (C_{max}) in CAR T cells/μL blood. All boxplots depict all PC SLE/LN patients (left lane), PC-free SLE and LN patients (middle lane), and patients with PC across all trials (right lane; gray); boxplots indicate the group median, IQR, maximum, and minimum. (C) Boxplot of time to peak rese-cel concentration (T_{max}). Individual dashed lines represent PC-free SLE and LN patients. (D) Median B cell counts in PC SLE/LN patients represented as number of CD19⁺/CD20⁺ B cells/μL blood from baseline through follow-up as measured by flow cytometry. Serum BAFF by concentration (E) and fold-change (FC) (F) at the post-infusion maximum (max). (G) Maturation status of B cells determined by CD24 / CD38 expression measured by flow cytometry from baseline through post-infusion follow-up in PC-free patients. Key indicates gates of interest: transitional naïve B cells (red), mature naïve B cells (yellow), and activated naïve or memory B cells (blue). Note, the PC-free SLE patient did not have samples collected at Day 15.

Phenotypic & Genotypic Analysis of Repopulated B cells*

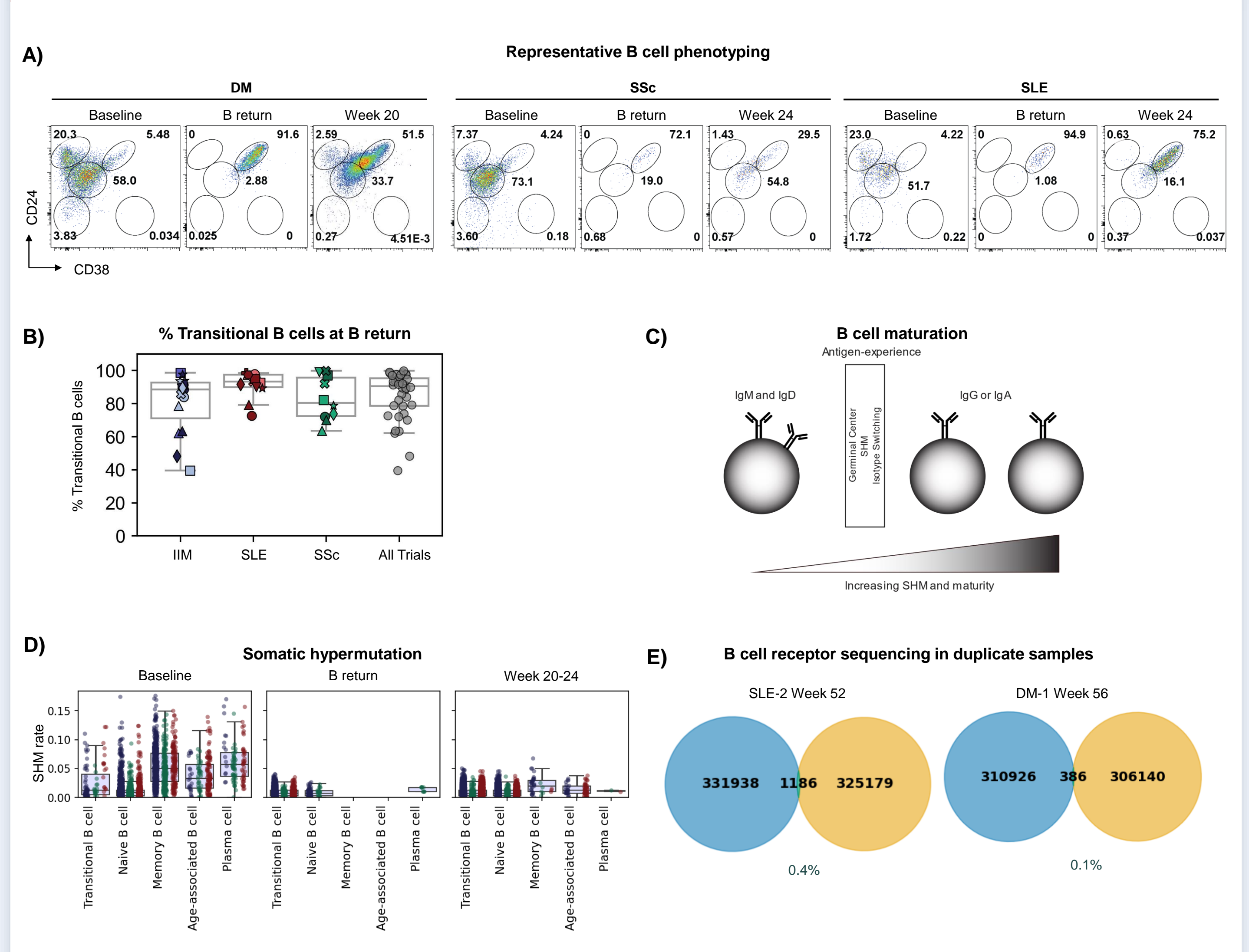


Figure 5. Effects of rese-cel treatment on B cell phenotypes and genotypes. (A) Flow cytometry phenotyping of CD24 and CD38 expression in CD19⁺/CD20⁺ lymphocytes at baseline (Aph), at first evaluable time of repopulation (B return), and at Week 20-24. Representative patient per trial shown and gates defined in Figure 4C. (B) Percent transitional naïve B cells (CD19⁺CD20⁺CD24⁺CD38^{hi}) at B return for all patients. (C) Schematic of B cell maturation process. Upon experiencing antigen, early IgM/IgD B cells (transitional naïve) enter the germinal center and undergo somatic hypermutation (SHM) and isotype switching and become mature memory B cells. A fraction of the memory cells become age-associated B cells and plasma cells. (D) Distribution of IGH VJ-region SHM rates measured by single-cell sequencing across B cells at baseline, B return, and Week 20-24 for DM-2, SSc-Skin-1, and SLE-2. Boxplots represent median and interquartile range (IQR). Points denote individual cells colored by patient. (E) BCR sequencing was performed on two independent aliquots from the same sample of the Week 52 (SLE-2) and Week 56 (DM-1) samples. The number and percentage of overlapping B cell clones between aliquots from the same sample are shown, along with total clone counts per aliquot. Percentage overlap is calculated as the number of shared clones divided by the mean clone count across replicates.

Summary

- Rese-cel rapidly expands and contracts within the first month with a high correlation between C_{max} and AUC across SLE, IIM and SSc patients in the RESET trials
- B cells are rapidly depleted within 2 weeks with a median time to repopulation of approximately 2 months
 - B cell depletion duration is weakly correlated with rese-cel exposure (C_{max})
- BAFF induction post-infusion (median maximum BAFF is 36,391 pg/mL with a median fold-change of 9) is indicative of deep B cell depletion
- At repopulation, B cells exhibit a predominantly transitional naïve phenotype and are less somatically hypermutated compared to B cells at baseline, suggesting B cell reset
 - B cell repertoires are highly diverse, limiting the use of clonal overlap from BCR sequencing in measuring B cell repertoire turnover and B cell reset
- In the initial low dose of rese-cel (1×10⁶ CAR T cells / kg) without PC, similar PK profiles were observed compared to that dose with PC. B cell depletion occurred in 1 of 2 patients with BAFF induction paralleling depletion depth. Initial PK and PD data from this lowest dose of rese-cel in the PC-free SLE/LN cohort are encouraging and further dose optimization is ongoing