CAR-T therapy without preconditioning in pemphigus vulgaris: Early clinical and translational data with resecabtagene autoleucel, an autologous 4-1BB CD19-CAR T

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Key Takeaway

Early data indicate that preconditioning lymphodepletion may be dispensable for the activity of humanized autologous CD19-CAR T therapy in refractory AD subjects which may lead to a safer clinical profile and greater patient access. Exploration of higher CAR T cell doses may further improve the consistency of deep B cell depletion and durability of autoantibody reduction and clinical response in PV.

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Background: Pemphigus Vulgaris & CAR T therapy in ADs

- Pemphigus Vulgaris (PV) is a painful blistering autoimmune disease (AD) mediated by anti-desmoglein (anti-DSG) autoantibodies produced by autoreactive B cells and plasma cells. The current standard of care for PV provides inadequate clinical responses without requiring chronic immunomodulatory (IM) therapies. Although IM therapies demonstrated clinical benefit, relapse is common due to incomplete tissue penetrance[1,2].
- CD19-targeting chimeric antigen receptor (CAR) T cells have demonstrated depletion of peripheral and tissue B cells in subjects with AD, including pathogenic autoreactive B cells, reducing circulating titers of autoantibodies.
- Lymphodepleting preconditioning (LD) chemotherapy is routinely administered prior to CAR T cell therapy in hematologic malignancies to enhance CAR T expansion, but it is unclear if higher doses of CAR T without LD can provide durable efficacy in ADs[8].
- Rese-cel (resecabtagene autoleucel, formerly CABA-201) is a fully human, autologous 4-1BB CD19-CAR T cell therapy, designed to deeply and transiently deplete CD19 positive B cells following a one-time weight-based infusion of $1x10^6$ CAR T cells/kg.
- Rese-cel is being evaluated in adults with active pemphigus vulgaris (PV) in the absence of pre-infusion LD in an ongoing Phase 1/2 dose finding trial (RESET-PV®, NCT04422912). Here, we report on the early clinical and translational data from the first 4 PV subjects dosed with the lowest dose of rese-cel ($1x10^6$ CAR T cells/kg) without LD and compare the results with other non-PV AD subjects treated with LD.

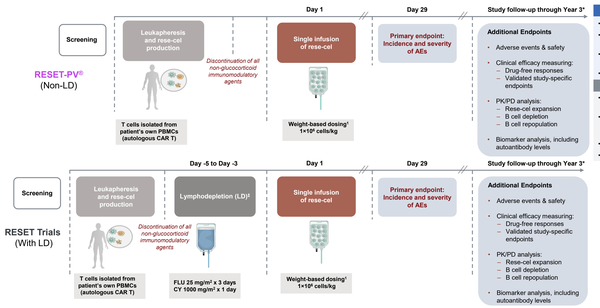

Figure 1. Differences in RESET study design for subjects with lymphodepletion versus RESET-PV

*Follow up period encompasses 15 years in total, aligned to regulatory guidance for CAR T cell therapies. Initial weight-based dose level.

Results: Rese-cel pharmacokinetics

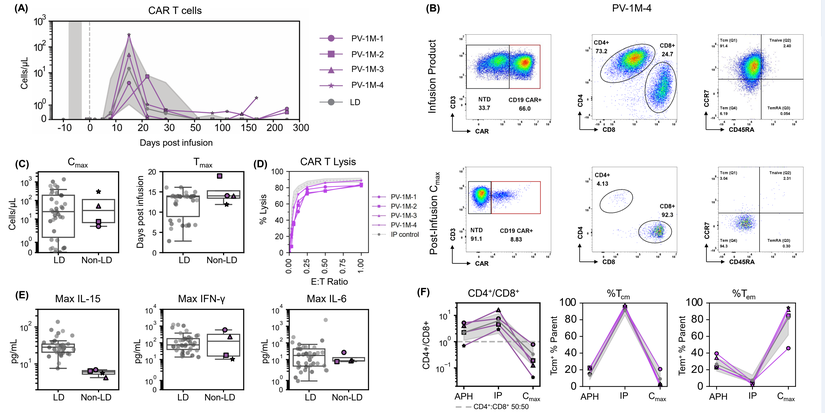

Figure 2. Rese-cel pharmacokinetic (PK) profile & CD19 CAR T cell characterization. (A) PK response of rese-cel in PV subjects represented as number of CAR T cells/µL blood from baseline through all follow-up timepoints. Note, subject PV-1M-2 did not have PBMCs isolated at Day 15. Median and 50th percentile intervals of values from LD subjects is shown in gray (LD). **(B)** Flow cytometric characterization of rese-cel infusion product (IP; top panel) and rese-cel cells at C_{max} (bottom panel) from representative subject PV-1M-4. Left column depicts CD19-CAR+ and non-transduced (NTD) T cells as a percentage of total CD3+ T cells. Middle column depicts CD4+ and CD8+ T cells as a percentage of CD19-CAR+ T cells. Right column depicts expression of memory markers, CCR7 and CD45RA; central memory (T_{cm}) (CCR7+CD45RA-), naïve (T_{naive}) (CCR7+CD45RA+), effector memory (T_{em}) (CCR7-CD45RA-), and effector memory re-expressing RA (T_{emRA}) (CCR7-CD45RA+). **(C)** Left plot; maximum CAR T cell concentration in blood (C_{max}) and (right plot) time (in days post-infusion) to maximum concentration (T_{max}). Boxplots represent median, 25th percentile interval, 75th percentile interval and range. LD subjects shown in gray (LD) and PV subjects without LD shown in magenta (Non-LD). **(D)** In vitro lysis of GFP+CD19+ NALM6 target cells by CD19-CAR T cells from subjects' iP. Area under the curve (AUC) generated for each effector to target (E:T) ratio (ranging from 0:1 to 1:1) and integrating the target cells over time curve (5 days). Percent lysis determined by the difference between each $AUC_{E:T}$ and $AUC_{0:1}$ divided by the $AUC_{0:1}$ then multiplied by 100. **(E)** Maximum (max) serum concentrations of IL-15, IFN-γ and IL-6 for one month after rese-cel infusion. **(F)** Ratio of CD4+ to CD8+ cells, T_{cm} profile as percentage of parent, and T_{em} profile as percentage of parent in patient apheresis (CD3+ parent), infusion product (CAR+ parent), and C_{max} (CAR+ parent).

Clinical course and efficacy outcomes

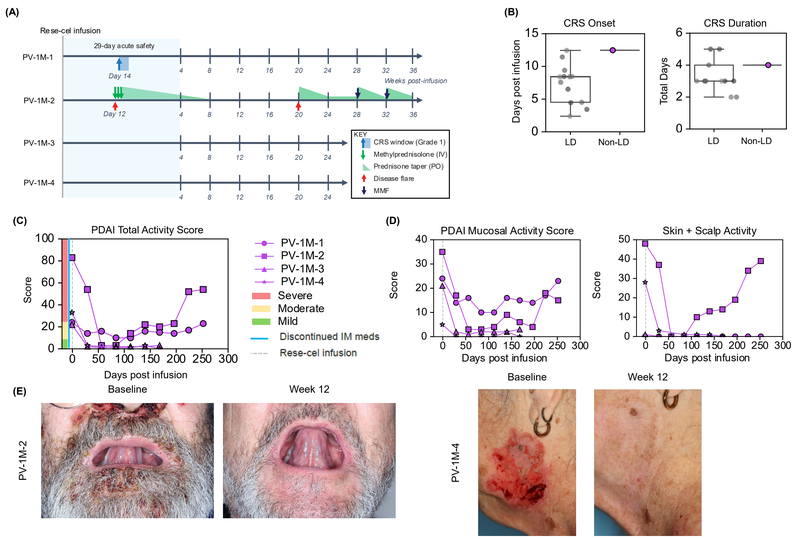

Figure 4. Clinical course and efficacy outcomes. (A) Post-infusion clinical courses for each subject inclusive of the 29-day acute safety window and respective follow-up. PV-1M-1 exhibited an isolated episode of CRS (Grade 1) 14 days after rese-cel infusion. PV-1M-2 required a burst-taper of methylprednisolone followed by prednisone for ongoing severe symptoms starting day 12. At week 20 post-infusion, PV-1M-2 required a second burst-taper of prednisone and began MMF at week 28. Timelines are not to scale; prednisone depicted if over protocol-allowable dose. **(B)** CRS onset and duration for PV subjects (Non-LD, magenta) compared to LD subjects shown in gray. **(C)** PDAI Total Activity Scores (mucosal, skin, and scalp) over time with color scale referring to severe (red), moderate (yellow), and mild (green) activity[6]. Teal line denotes cessation of immunomodulatory medications and gray dashed line denotes day of infusion. **(D)** PDAI Mucosal (left) and PDAI Skin (right) Activity Scores over time. **(E)** Medical photography in subjects PV-1M-2 and PV-1M-4 depicting active skin lesions at baseline that are resolved at week 12 post-infusion. Data cutoffs as follows: 36 weeks for PV-1M-1 and for PV-1M-2, 24 weeks for PV-1M-3 and PV-1M-4.

Methods

Rese-cel cell pharmacokinetic (PK) profiles were assessed by dPCR for transgene in PBMC samples. PK was reported as cells per µL of blood and was estimated by including the patient's white blood cell count per visit and the vector copy number for each patient's manufactured product using the following equation:

$$\frac{CAR\ T\ cells}{\mu L\ blood} = \frac{CAR\ copies}{\mu g\ DNA} * \frac{1\mu g\ DNA}{1e5\ cells} * \frac{PBMC}{\mu L\ blood} * \frac{1}{VCN}$$

where an estimation of 1 µg DNA per $1x10^5$ cells was used[3] and the patient's PBMC count was determined using combined lymphocyte and monocyte counts[4]. Serum cytokines were measured via a multiplexed V-plex or U-plex mesoscale discovery (MSD) immunoassay. Flow cytometric analyses were performed on cell samples from apheresis, infusion product (IP), and post-infusion PBMC samples to assess CAR expression in T cells, memory (via CD45RA and CCR7), and CD4/CD8 expression in CD3+ and CAR+ T cells. B cell numbers were also quantified using flow cytometry (via dual CD19 and CD20 expression) and evaluated to assess maturity (via CD24 and CD38). All flow cytometry was performed using custom multi-color antibody panels. Samples and controls were read on the Novocyte Quanteon flow cytometer (Agilent), and data were analyzed using FlowJo Software. Rese-cel cytotoxicity assays were performed *in vitro* using the IncuCyte® platform. Serum antibody panels were used to measure select PV and vaccine-associated antibodies in patient sera utilizing the Luminex FlexMap instrument. Serum antibody levels were reported as net median fluorescence intensity (MFI). The LD group consisted of 38 rese-cel treated AD subjects that were evaluated across four distinct phase I/II, multi-center, open-label studies: RESET-Myositis®, RESET-SLE™, RESET-SSc™, and RESET-MG™ (NCT06154252, NCT06121297, NCT06328777, and NCT06359041, respectively).

Results: Baseline Demographics

	RESET-PV®			
Patient	**PV-1M-1**	**PV-1M-2**	**PV-1M-3**	**PV-1M-4**
Age, sex	48, M	64, M	53, F	70, F
PV type	Mucosal	Mucocutaneous	Mucosal with minor skin involvement	Mucocutaneous
Disease duration (approx. years)	7	3	8	11
Autoantibodies	DSG3	DSG3, DSG1	DSG3, DSG1	DSG3,DSG1
Baseline¥ PDAI Total Activity Score⊕	**24**	**83**	**22**	**33**
Baseline¥ PDAI Skin Activity	0	44	1	26
Baseline¥ PDAI Scalp Activity	0	4	0	2
Baseline¥ PDAI Mucous Membrane Activity	24	35	21	5
GC dose at baseline (mg/day)	0	20	10	13
Prior therapies	**RTX€**, MMF, MTX, GC	GC, IVIg, **RTX€**, MMF	**RTX€**, MMF, IVIg	**RTX€**,MTX,GC,AZA

Table 1. Baseline Demographics.

¥- Baseline disease scores at pre-infusion visit; **€** - RTX last received ~13 months (PV-1M-1), ~29 months (PV-1M-2), >6 years (PV-1M-3) and > 10 years (PV-1M-4) prior to infusion. **Φ**- Defined PDAI values for mild, moderate and severe disease are ≤ 8, 9-24 and ≥25[5]

Rese-cel pharmacodynamics

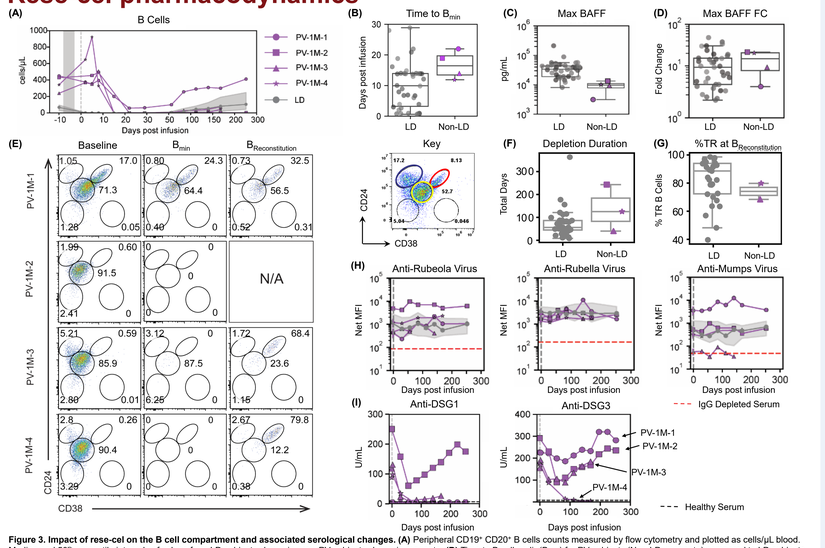

Figure 3. Impact of rese-cel on the B cell compartment and associated serological changes. (A) Peripheral CD19+ CD20+ B cells counts measured by flow cytometry and plotted as cells/µL blood. Median and 50th percentile intervals of values from LD subjects shown in gray. PV subjects shown in magenta. **(B)** Time to B cell nadir (B_{min}) for PV subjects (Non-LD, magenta) compared to LD subjects shown in gray (LD). Boxplots depict the median, 25th percentile interval, and range. **(C)** Maximum (max) serum BAFF concentration and **(D)** fold change (FC) for max BAFF for LD and non-LD subjects **(E)** Maturation status of CD19+ CD20+ B cells as determined by CD24 and CD38 expression before and after CAR-T cell infusion as determined by flow cytometry at baseline, time at which B cells reach nadir (B_{min}), and time of B cell reconstitution, where B cells have returned to sufficient levels to support phenotypic analysis (subject PV-1M-1 Day 29, subject PV-1M-2 did not return, subject PV-1M-3 Week 12, subject PV-1M-4 Week 24). Dot plot on the left indicates key gates of interest: transitional naïve (T1 and T2/T3) B cells (CD24++ CD38++) (red), mature naïve B cells (CD24+CD38+) (yellow), activated naïve or memory B cells (CD24+CD38-) (blue). **(F)** Duration of time elapsed from B cell depletion through the return of B cells. **(G)** the percent of the reconstituted B cells that are transitional (TR) at the earliest time when B cells have returned to sufficient levels to support phenotypic analysis. **(H)** Serum antibodies against vaccines over time represented at mean fluorescence intensity with a serum dilution of 1:10,000. **(I)** Serum levels of anti-DSG1 and anti-DSG3 autoantibodies over time represented as U/mL.

Summary

- These preliminary, hypothesis-generating data indicate that even with a low dose of rese-cel without LD, some autoimmune patients demonstrate durable activity of humanized autologous CD19 directed CAR T therapy for at least 6 months.
- Following infusion, CAR T cell peak expansion was similar between non-LD PV subjects and LD treated subjects.
  - CAR T cells at C_{max} shifted to a $CD8^+$ and effector memory phenotype, consistent with other AD subjects treated with rese-cel[7,8].
- Circulating B cells rapidly depleted in all 4 subjects, and completely depleted in 3 of the 4 with kinetics of B cell depletion similar across subjects irrespective of LD.
  - Median maximum post-infusion BAFF levels in PV subjects was 10,597 pg/mL (range: 3,120-13,322) compared with 36,391 pg/mL (IQR: 19,014-44,930) in LD-treated subjects.
  - Maximum fold change in BAFF was comparable across both LD and non-LD subjects.
  - Also consistent with LD-treated AD subjects, reconstituting B cells in fully depleted subjects were transitional naïve with PV-1M-4 exhibiting the highest percentage at reconstitution.
- In the RESET-PV trial, rese-cel was well-tolerated with a single cytokine release syndrome (CRS; gr 1) and no dose-limiting toxicity, no grade ≥3 cytopenias, or immune effector cell-associated neurotoxicity syndrome (ICANS).
- Reductions in PDAI total activity scores were noted in all subjects off IM therapies and 2/4 on no or minimal GC.
  - Two subjects (PV-1M-3 and PV-1M-4) demonstrated improvement in PDAI scores that was maintained through Week 24, although PV-1M-3 exhibited rising levels of serum anti-DSG3 after an initial drop.
  - One subject (PV-1M-2) demonstrated initial improvement but started rescue medications at Week 20 for increasing symptoms; another subject (PV-1M-1) demonstrated a partial response on PDAI.
  - Anti-DSG3 and anti-DSG1 antibodies reduced in parallel with improvement in PDAI total activity scores.
- Consistent with the hypothesis that higher doses of rese-cel might allow for the elimination of LD, dose escalation of rese-cel is warranted and may further improve the consistency of deep B cell depletion and durability of autoantibody reduction and clinical response.
- As CAR T therapies are increasingly being utilized in the treatment of refractory ADs, the potential to infuse cell products without LD is attractive and may lead to a safer clinical profile and greater patient access.

RESET-PV Data Cut: 02APR2026; Other non-PV RESET trial Data Cut: 30Oct2025.

Abbreviations: AD, autoimmune disease; AZA, Azathioprine; BAFF, B cell activating factor; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CY, cyclophosphamide, DLT, Dose-limiting toxicities; DSG1 & 3, desmoglein 1 & 3;FLU, fludarabine; GC, glucocorticoid; ICANS, immune effector cell-associated neurotoxicity syndrome; IM, immunomodulatory medication; IP, infusion product; IQR, interquartile range; IV, intravenous; IVIg, intravenous immunoglobulin; LD, Lymphodepleting preconditioning; mAb, monoclonal antibody; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mRNA, messenger ribonucleic acid; MTX, methotrexate N/A, not applicable; PD, pharmacodynamic; PDAI, pemphigus disease area index; PK, pharmacokinetic; PV, pemphigus vulgaris; RESET, REstoring SElf-Tolerance; rese-cel, resecabtagene autoleucel; SAE, serious adverse event; TOC, tocilizumab;

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