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A Phase 1 Trial Of Targeted DSG3-CAART Cell Therapy In Mucosal-Dominant Pemphigus Vulgaris (mPV) Patients: Early Cohort Data

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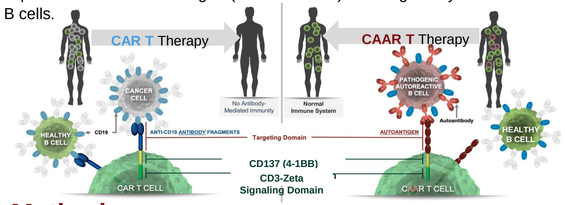
Background

Mucosal-dominant pemphigus vulgaris (mPV) is a painful blistering mucosal disease mediated by anti-desmoglein 3 (DSG3) autoantibodies (Abs). Standard of care, including rituximab, steroids and other immunosuppressive agents, is not curative, requires chronic administration, and is associated with serious infections due to persistent immunosuppression. The ideal therapy would selectively eliminate pathogenic anti-DSG3-expressing B cells while sparing healthy B cells. Based on the long-lasting remission of B cell cancers with chimeric antigen receptor T (CART) cells, we developed chimeric autoantibody receptor T (CAART) cells to target B cell-mediated autoimmune diseases, using the same construct but switching the targeting domain to the autoantigen. For mPV patients, autologous T cells have been genetically modified to express the DSG3 autoantigen (DSG3-CAART) and target only the anti-DSG3 B cells.



Methods

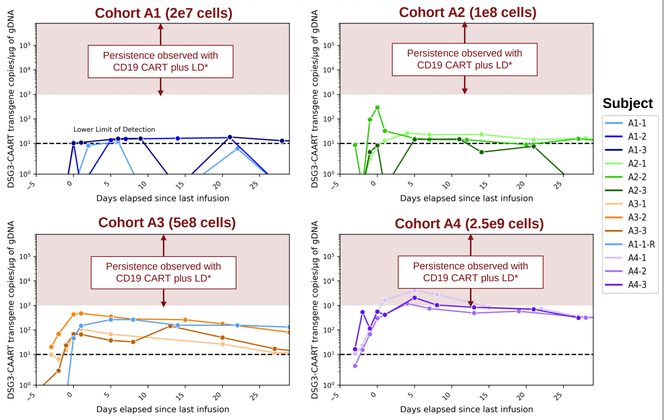
The objective of this ongoing Phase 1 open-label trial (NCT04422912) is to determine the maximum tolerated dose of DSG3-CAART in adult subjects with active, anti-DSG3 Ab positive, biopsy confirmed mPV inadequately managed by ≥1 standard therapy. The primary endpoint is incidence of adverse events (AEs), including dose-limiting toxicities (DLTs), such as cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), related to DSG3-CAART within 3 months of infusion. Secondary endpoints include CAART persistence (qPCR), anti-DSG3 Ab levels (ELISA) and disease activity (Pemphigus Disease Area Index (PDAI) Mucous Membrane score). After discontinuing or tapering immunosuppressives, subjects in cohorts 1-4 received 2e7, 1e8, 5e8 and 2.5e9 DSG3-CAAR-transduced cells as fractionated infusions and without lymphodepletion. Retreatment at a higher dose was permitted for subjects who did not achieve remission within 6 months of therapy or flared after remission.

Overview of Dose Escalation

Cohort	Total Cell Dose	Fold increase in dose	Subjects per cohort
A1	2e7	1x	3
A2	1e8	5x	3
A3	5e8	25x	3 [+1 A1-1 re-treated at the A3 dose]
A4	2.5e9	125x	3
A5	5 - 7.5e9	250 to 375x	3 (+3) [ongoing]
A5e*	5 - 7.5e9	250 to 375x	3 (+3) [planned]
A6m**	1 - 1.5e10	500 to 750x	3 (+3) [planned]

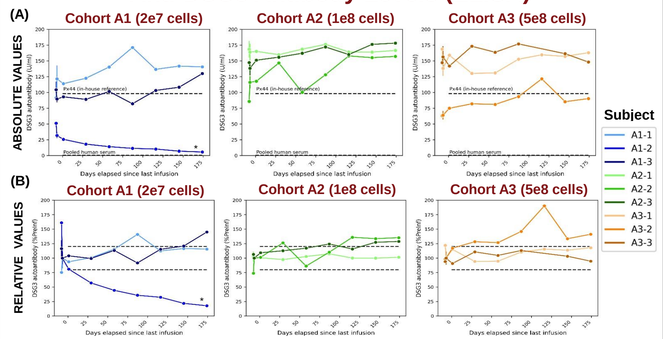
*A5e represents an enhanced manufacturing process **A6m represents multiple infusions ≥1 week apart

Persistence of DSG3-CAART (qPCR)



There was a dose dependent increase in DSG3-CAART persistence with cohort A4 approaching the lower end of range observed with CD19 CART therapy (AUC_{d29} Pearson correlation coefficient = 0.96). Subject A1-1 was retreated with the A3 dose (5e8 cells), represented as A1-1R, and resulted in similar persistence as other subjects in cohort A3.
*The shaded area indicates levels of persistence typically observed in adult patients who have B-cell malignancies treated with CD19 CART cells plus lymphodepletion (LD) (at a median dose of tisagenlecleucel of 3e8).

Anti-DSG3 Antibody Levels (ELISA)



(A) Absolute values of anti-DSG3 Ab levels over time. Dashed line depicts Ab control for assay. (B) Relative anti-DSG3 Ab levels over time normalized to the Pre-Infusion timepoint. Dashed lines represent ± 20% from the Pre-Infusion timepoint, which is considered relevant. Cohort A4 data not yet mature.
*Subject A1-2 was treated with rituximab within 12 months of infusion (rituximab excluded within 12 months of screening unless disease worsening).

Safety Data within 3 Months Post-Infusion

	Cohort A1 2e7 (n=3)	Cohort A2 1e8 (n=3)	Cohort A3 5e8 (n=3)	Cohort A4 2.5e9 (n=3)	Overall (n=12)
# Subjects with ≥1 AEs (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	12 (100%)
# Subjects with ≥1 Related AEs* (%)	0 (0%)	1 (33%)	1 (33%)	1 (33%)	3 (25%)
# Subjects with ≥1 SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Subjects with ≥1 Related SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Subjects with Cytokine Release Syndrome (CRS) (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Subjects with Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Subjects with Dose-Limiting Toxicity (DLT) (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

The DSMB did not consider the overall safety profile in these cohorts to be clinically relevant to change the study design or pause the study.
*Excludes dysgeusia associated with DMSO in the infusion; A2-1: mild fatigue; A3-2: mild nausea and moderate insomnia; A4-3: mild fever, palpitations, noncardiac chest pain, headache, elevated CRP, elevated LDH, and moderate sinus tachycardia.

Disease Activity
(PDAI Mucous Membrane Score)

Cohort (Dose)	Subject	Prior RTX or IVIg*	Meds stopped or tapered prior to inf.	Screen	Pre-Inf.	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo. 5	Mo. 6
A1 (2e7)	A1-1	RTX 10m	PRD	20	10	13	33	PRD 70	IVIg 27	26	MMF 30
A1 (2e7)	A1-2	RTX 6.5m IVIg 3m		5	2	1	1	1	0	1	0
A1 (2e7)	A1-3	RTX 9m	MMF	17	4	3	1	2	6	2	13
A2 (1e8)	A2-1	IVIg 4m		6	5	2	1	2	3	PRD 2	5
A2 (1e8)	A2-2			14	3	3	0	1	4	PRD 4	11
A2 (1e8)	A2-3	IVIg 4m		6	1	3	PRD 4	7	4	RTX 1	5
A3 (5e8)	A3-1			2	2	0	0	PRD 0	0	0	PRD 24
A3 (5e8)	A3-2		PRD, MMF	12	10	10	22	20	20	10	21
A3 (5e8)	A3-3			18	14	8	14	17	16	PRD 6	7
# Subjects with PDAI=0 or 1 (Clear/Almost Clear)				0	1	2	5	3	2	3	1

RTX=rituximab; IVIg=intravenous immunoglobulin, MMF=mycophenolate, PRD=prednisone. Systemic PV therapy changes were more permissive after month 3; new PV therapy or PRD dose increases shown in red and PRD taper starts shown in green at the time the therapy change occurred. Cohort A4 data not yet mature.
*RTX or IVIg within12 months prior to infusion. RTX permitted within 12 months prior to screening if disease worsening; IVIg permitted >2 weeks prior to screening.

Baseline Characteristics

	Cohort A1 2e7 (n=3)	Cohort A2 1e8 (n=3)	Cohort A3 5e8 (n=3)	Cohort A4 2.5e9 (n=3)	Overall (n=12)
Age, years, median (range)	39 (32-57)	53 (50-54)	60 (47-70)	60 (56-70)	55 (32-70)
Female (%)	67%	67%	67%	67%	67%
Disease Duration, years, median (range)	3.4 (0.5-4.3)	4.3 (3.9-13.0)	0.7 (0.3-15.0)	3.5 (0.1-12.4)	3.7 (0.1-15.0)
Anti-DSG3 Ab Level, U/mL, median (range)	92 (51-104)	147 (86-168)	147 (63-169)	147 (114-162)	130 (51-169)
Pemphigus Disease Area Index, median (range)	17 (5-20)	6 (6-14)	12 (2-18)	3 (1-4)	6 (1-20)
Prior use of corticosteroids (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	12 (100%)
Prior use of mycophenolate (%)	2 (67%)	3 (100%)	1 (33%)	2 (67%)	8 (67%)
Prior use of rituximab (%)	3 (100%)	3 (100%)	0 (0%)	2 (67%)	8 (67%)

Conclusions

- Early cohort data from the first-in-human trial of DSG3-CAART, a novel investigational precision cell therapy for the autoimmune disease mPV, demonstrate that doses up to 2.5e9 DSG3-CAART cells were generally well-tolerated with no CRS, ICANS, or related SAEs
- There was a clear dose dependent increase in DSG3-CAART persistence
- The persistence in cohort A4 is approaching the lower end of range that was observed with CD19 CART therapy plus lymphodepletion for B-cell malignancies
- Retreatment of one subject demonstrated similar persistence as other subjects in the dose cohort, suggesting a lack of immune-mediated rejection
- To date, no clear pattern was observed in changes in anti-DSG3 Ab levels or disease activity in the low dose cohorts where the A3 dose (5e8) represents 6.7 -10% of the ongoing A5 cohort dose (5-7.5e9)
- These early cohort data warrant further exploration of:
  - Higher doses to increase in vivo presence of DSG3-CAART
  - Manufacturing enhancement designed to increase product potency and trafficking to tissue where the target B cells reside

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