31st

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DESIGNING THE FUTURE OF DERMATOLOGY AND VENEREOLOGY

A Phase 1 trial of DSG3-CAART cells in mucosal-dominant pemphigus vulgaris patients: preliminary data

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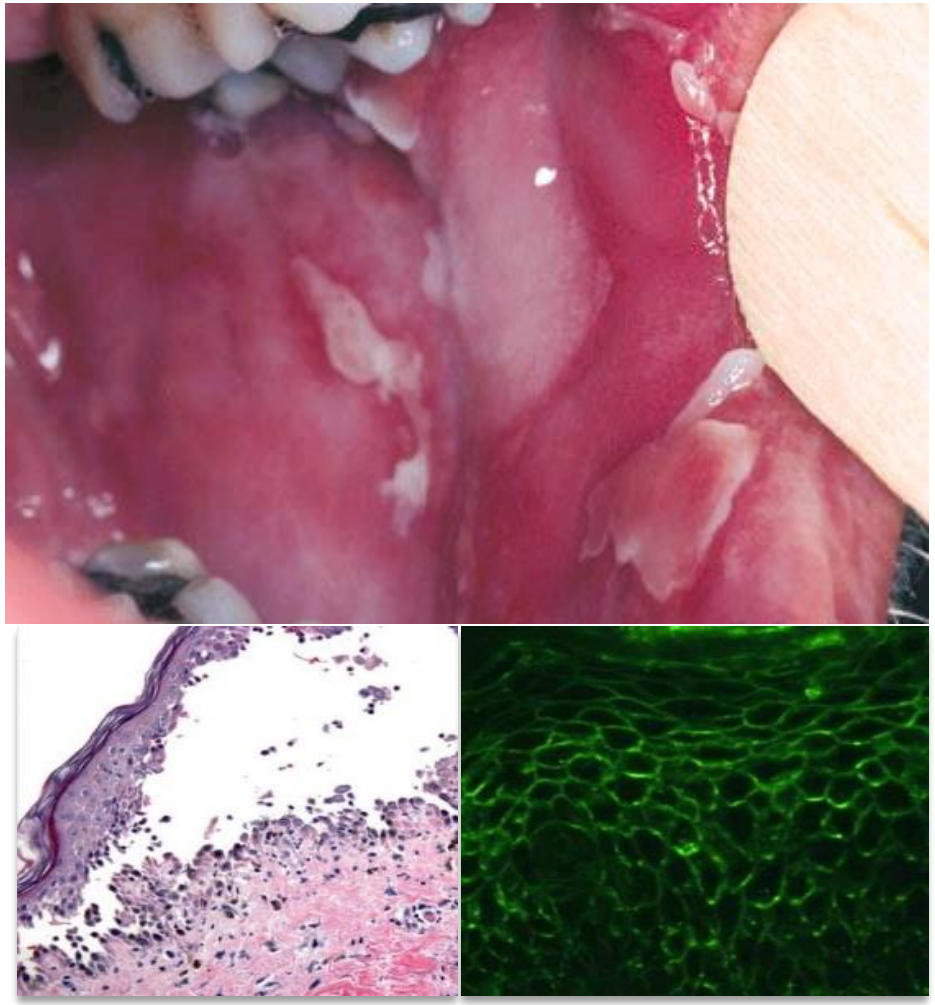
Disclosure

David J. Chang is an employee of Cabaletta Bio, Inc. and a stockholder.

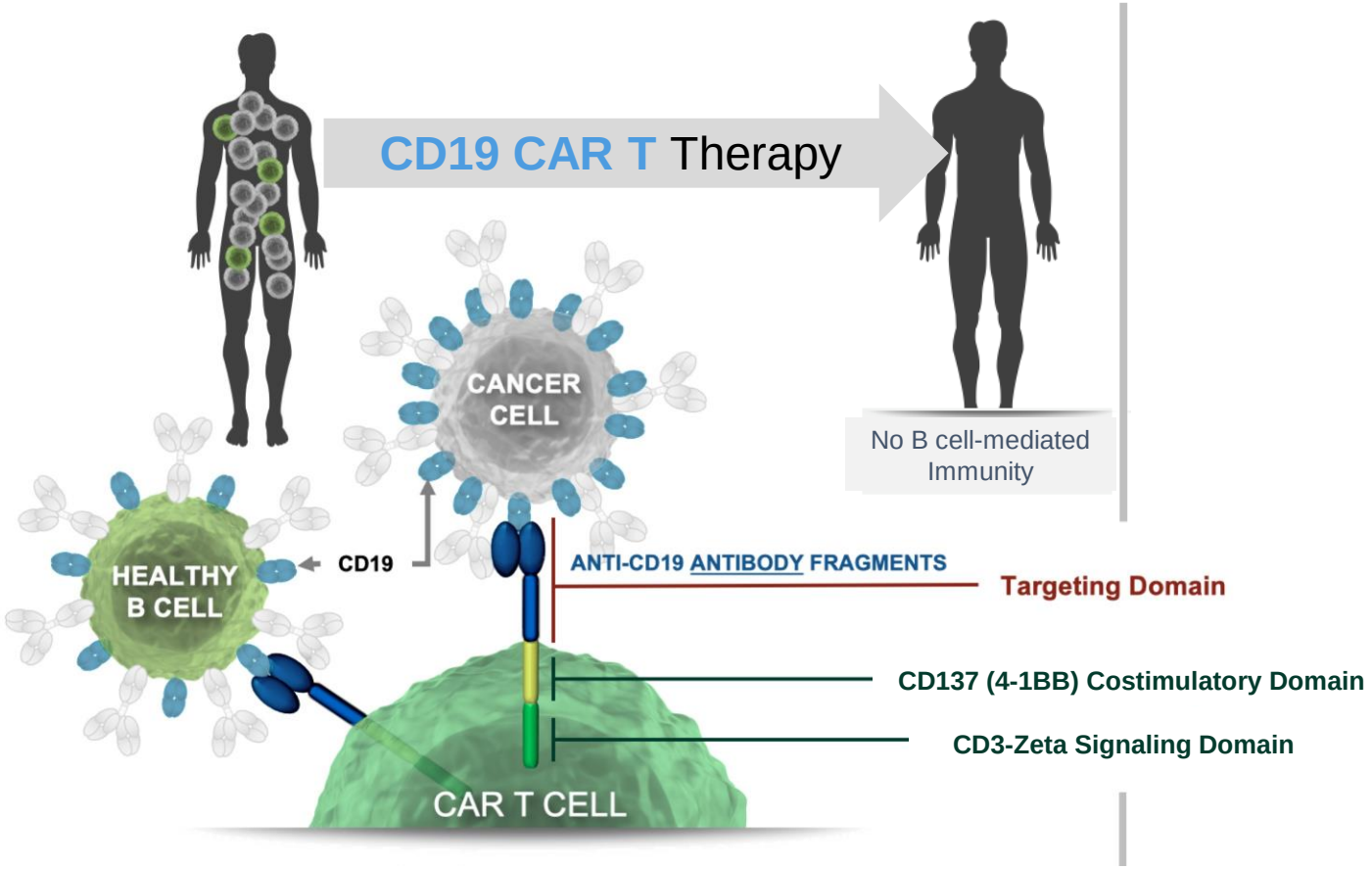
Mucosal-Dominant Pemphigus Vulgaris (mPV)



- Anti-desmoglein 3 (DSG3) antibodies are **98-100% sensitive and specific** for diagnosis
  Amagai et al, BJD 1999; Schmidt et al, Exp Derm 2010
- Anti-DSG3 antibodies are **necessary and sufficient** for blister formation
  Amagai et al, JCI 1992; Amagai et al, JCI 1994; Mascaro et al, Clin Imm Immunopath 1997
- Treatment with **rituximab plus steroids (~3500 mg/yr)** leads to transient remission; **4-9% annual rate of serious infections** with repeated infusions
  Joly et al, Lancet 2017; Werth et al, NEJM 2021
- The ideal therapy would selectively eliminate pathogenic anti-DSG3-expressing B cells while sparing healthy B cells

http://www.vgrd.org/archive/cases/2004/pv/pv.htm

CD19 CAR T Therapy for B-Cell Hematologic Malignancies



53 - 81% complete remission[1]
40 - 57% long-term remission[1]

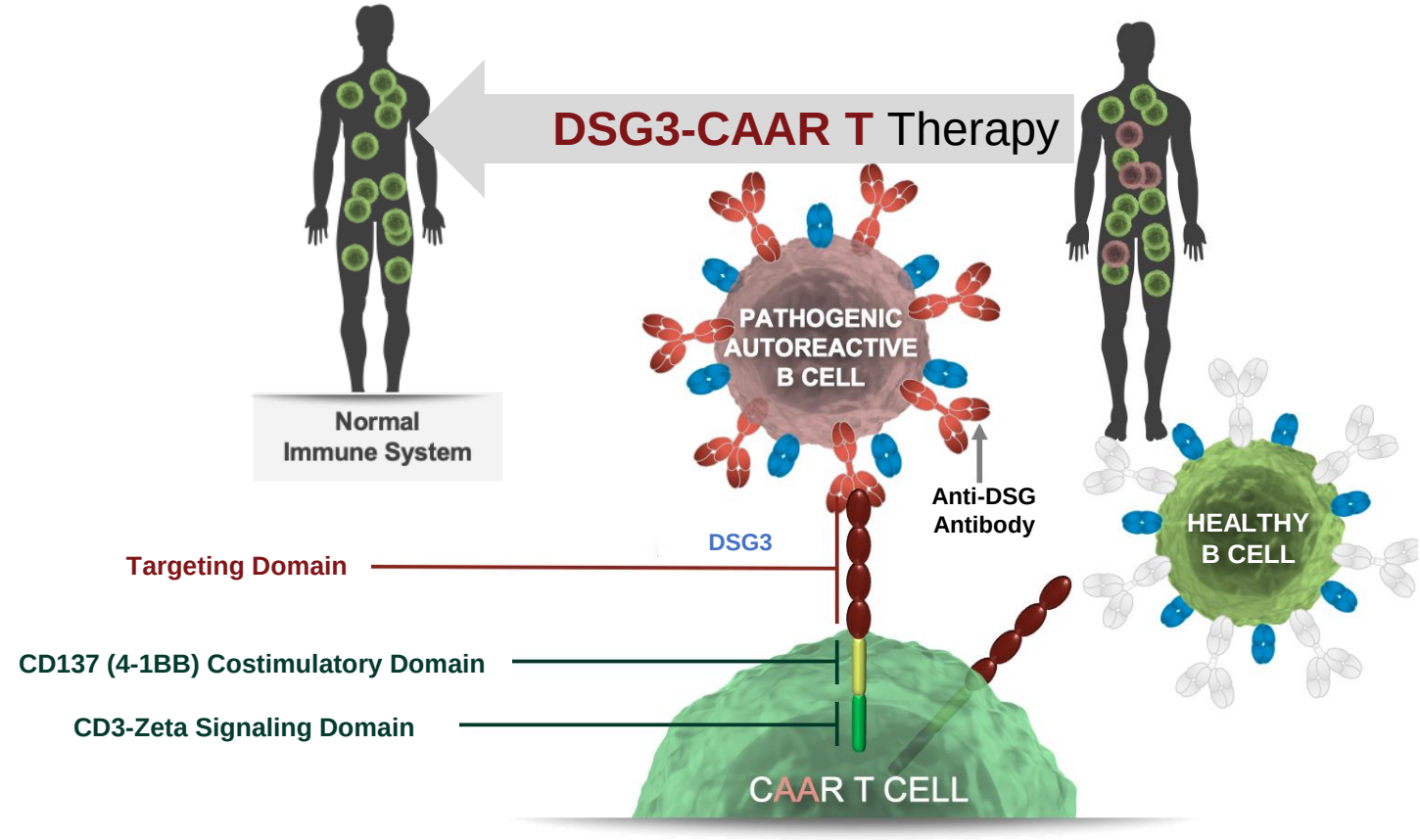
Chimeric Antigen Receptor T cell

Tisagenlecleucel (Kymriah)

1. Maude et al, NEJM 2018, Locke et al, Lancet Oncol 2018, Wang et al, NEJM 2020, Abramson et al, Lancet 2020

DSG3-CAAR T for Mucosal-Dominant Pemphigus Vulgaris

- Pathogenic B cells in mPV are defined by a surface anti-DSG3 B cell receptor
- Replacing the anti-CD19 targeting domain in the CAAR T cell with the DSG3 autoantigen may direct antigen-specific rather than total B cell depletion



Chimeric **A**uto**A**ntibody **R**eceptor **T** cell

DSG3-CAAR T

Study Objective and Endpoints

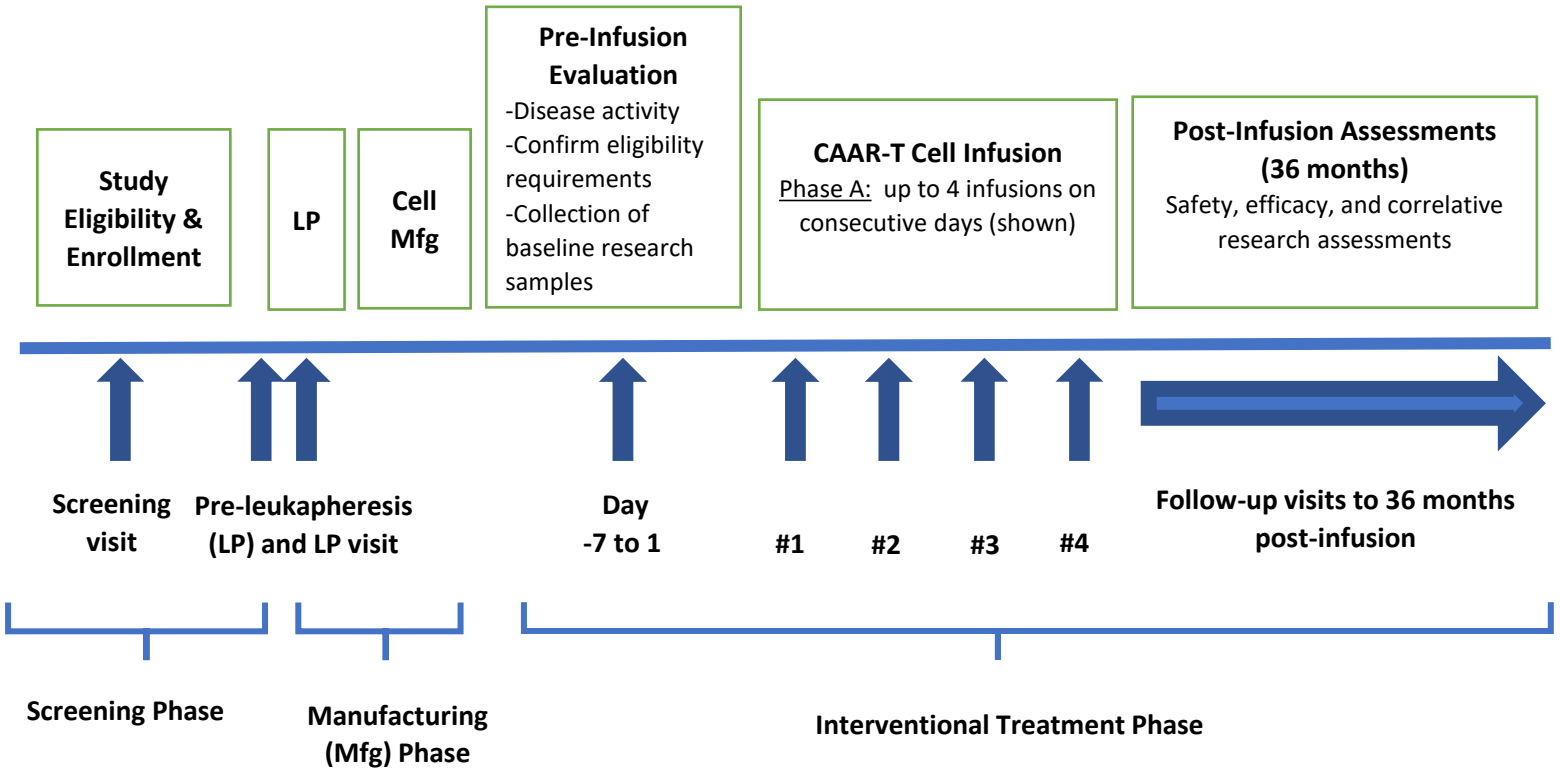
- **Primary objective**: to determine the maximum tolerated dose of DSG3-CAART in adult subjects with active mPV

- **Primary endpoint**: adverse events (AEs) related to DSG3-CAART within 3 months of infusion, including dose-limiting toxicities (DLTs), such as cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

- **Secondary endpoints** include:
  - DSG3-CAART persistence (qPCR)
  - Anti-DSG3 Antibody levels (ELISA)
  - Disease activity (Pemphigus Disease Area Index (PDAI) Mucous Membrane score)

Study Design

Ongoing open-label, dose-escalation Phase 1 trial (NCT04422912)



Study Design – DSG3-CAART Cell Manufacturing

Ongoing open-label, dose-escalation Phase 1 trial (NCT04422912)

Study Eligibility & Enrollment

LP

Cell Mfg

Pre-Infusion Evaluation
-Disease activity
-Confirm eligibility requirements
-Collection of baseline research samples

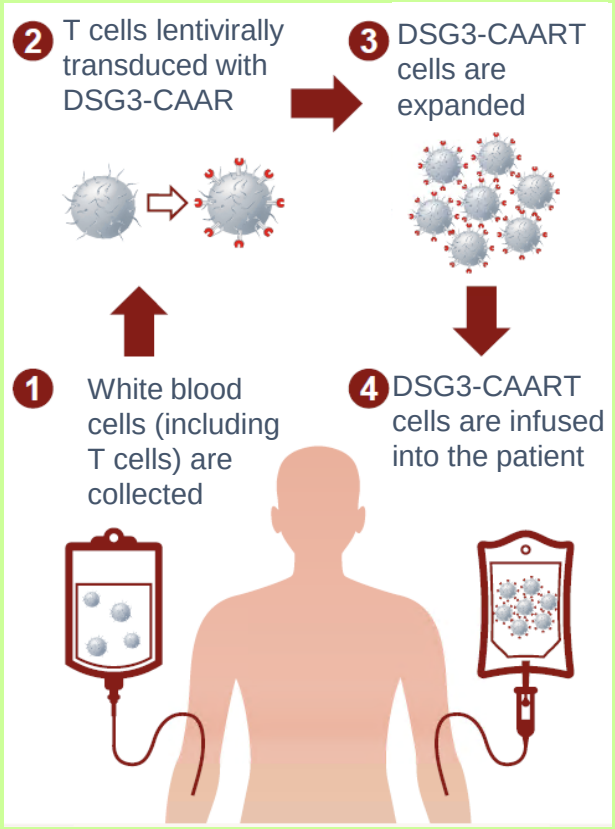
CAAR-T Cell Infusion
Phase A: up to 4 infusions on consecutive days (shown)

Post-Infusion Assessments (36 months)
Safety, efficacy, and correlative research assessments

Screening visit | **Pre-leukapheresis (LP) and LP visit** | **Day -7 to 1** | **#1** | **#2** | **#3** | **#4** | **Follow-up visits to 36 months post-infusion**

Screening Phase | **Manufacturing (Mfg) Phase** | **Interventional Treatment Phase**

DSG3-CAART Cell Manufacturing



(~4-5 weeks vein-to-vein)

Study Design – Inclusion and Exclusion Criteria

- Major inclusion criteria
  - Age ≥18 years
  - Biopsy-confirmed diagnosis of mPV
  - Inadequately managed by ≥1 standard immunosuppressive therapies
  - Active disease
  - Anti-DSG3 antibody positive
- Major exclusion criteria
  - Recent rituximab
  - Prednisone > 0.25 mg/kg/day
  - Other autoimmune disorder requiring immunosuppressive therapies
  - Recent investigational treatment
  - Absolute lymphocyte count < 1,000/µL at screening

Study Design – Dosing Regimen and Cohorts

- Systemic immunosuppressants are stopped and prednisone tapered to low dose prior to infusions
- Subjects within a cohort are administered DSG3-CAART infusions sequentially
- Dose is escalated only after current cohort has tolerated the dose through 28 days post-infusion

Cohort	Total DSG3-CAART Cell Dose	Fold Increase in Dose	Subjects per Cohort
A1	$2x10^7$	1x	3
A2	$1x10^8$	5x	3
A3	$5x10^8$	25x	3 [+1 A1-1 re-treated at the A3 dose]
A4	$2.5x10^9$	125x	3
A5	$5\text{-}7.5x10^9$	250 to 375x	4[a]
P4[b]	$2.5x10^9$ + cyclophosphamide and IVIg	125x	3
A6m[b]	$1\text{-}1.5x10^{10}$	500 to 750x	3

planned

[a] A 4th subject was dosed in Cohort A5 to generate additional data

[b] Cohort P4 and A6m will be enrolled concurrently.

Subject Screening Characteristics

	Cohort A1 $2x10^7$ (n=3)	Cohort A2 $1x10^8$ (n=3)	Cohort A3 $5x10^8$ (n=3)	Cohort A4 $2.5x10^9$ (n=3)	Cohort A5 $5\text{-}7.5x10^9$ (n=4)[a]	Overall (n=16)
Age, years, median (range)	39 (32-57)	53 (50-54)	60 (47-70)	60 (56-70)	48 (34-57)	54 (32-70)
Female (%)	67%	67%	67%	67%	0%	50%
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)	1.6 (0.2-5.3)	3.4 (0.1-15.0)
Anti-DSG3 Ab Level, U/mL, median (range)	92 (51-104)	147 (86-168)	147 (63-169)	147 (114-162)	144 (124-169)	144 (51-169)
Pemphigus Disease Area Index, median (range)	17 (5-20)	6 (6-14)	12 (2-18)	3 (1-4)	5 (4-18)	6 (1-20)
Prior use of corticosteroids (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (75%)	15 (94%)
Prior use of mycophenolate (%)	2 (67%)	3 (100%)	1 (33%)	2 (67%)	2 (50%)	10 (63%)
Prior use of rituximab (%)	3 (100%)	3 (100%)	0 (0%)	2 (67%)	1 (25%)	9 (56%)

[a] A 4th subject was dosed in Cohort A5 to generate additional data

Safety Data within 3 Months Post-Infusion (28 Days for Cohort A5)

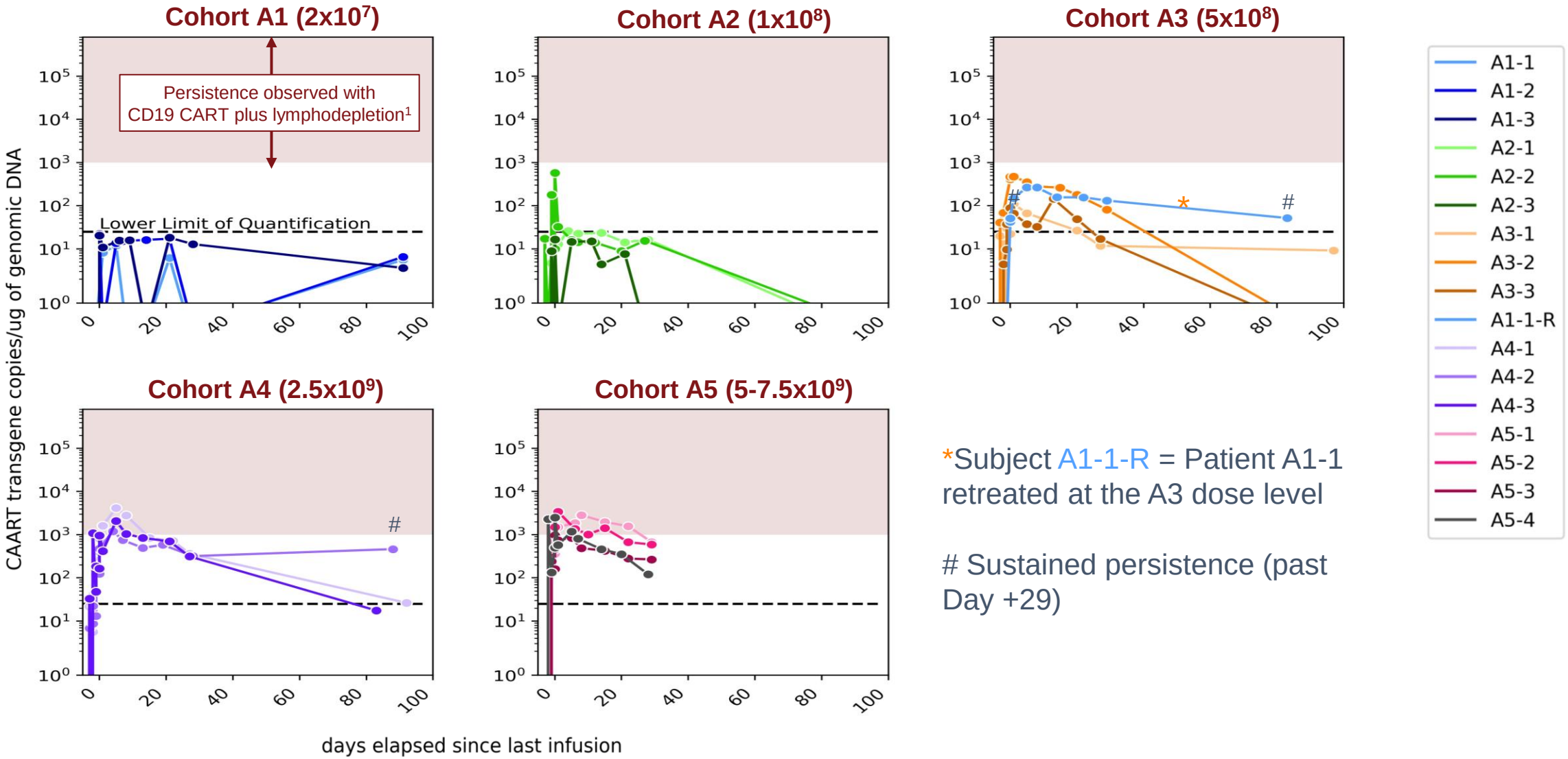
	Cohort A1 $2x10^7$ (n=3)	Cohort A2 $1x10^8$ (n=3)	Cohort A3 $5x10^8$ (n=3)	Cohort A4 $2.5x10^9$ (n=3)	Cohort A5 $5\text{-}7.5x10^9$ (n=4)[a]	Overall (n=16)
# Subjects with ≥1 AEs (%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	4 (100%)	16 (100%)
# Subjects with ≥1 Related AEs (%)	0 (0%)	1 (33%)	1 (33%)	1 (33%)	1 (25%)	4 (25%)
# Subjects with ≥1 SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1[b] (25%)	1 (6%)
# Subjects with ≥1 Related SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1[b] (25%)	1 (6%)
# Subjects with Cytokine Release Syndrome (CRS) (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1[b] (25%)	1 (6%)
# Subjects with Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (%)	0 (0%)	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%)	0 (0%)

[a] A 4th subject was dosed in Cohort A5 to generate additional data; safety data for Cohort A5 only through 28 days post-infusion.

[b] Subject A5-4 developed Grade 1 CRS several hours after each of the 2 infusions that resolved within 2 days (related SAEs due to hospitalization). The events were not considered to be DLTs and did not delay study progression.

DSG3-CAART Persistence (qPCR) after Infusion

Cohorts A4 and A5 approached the lower end of range that was observed with CD19 CART therapy plus lymphodepletion for B-cell malignancies



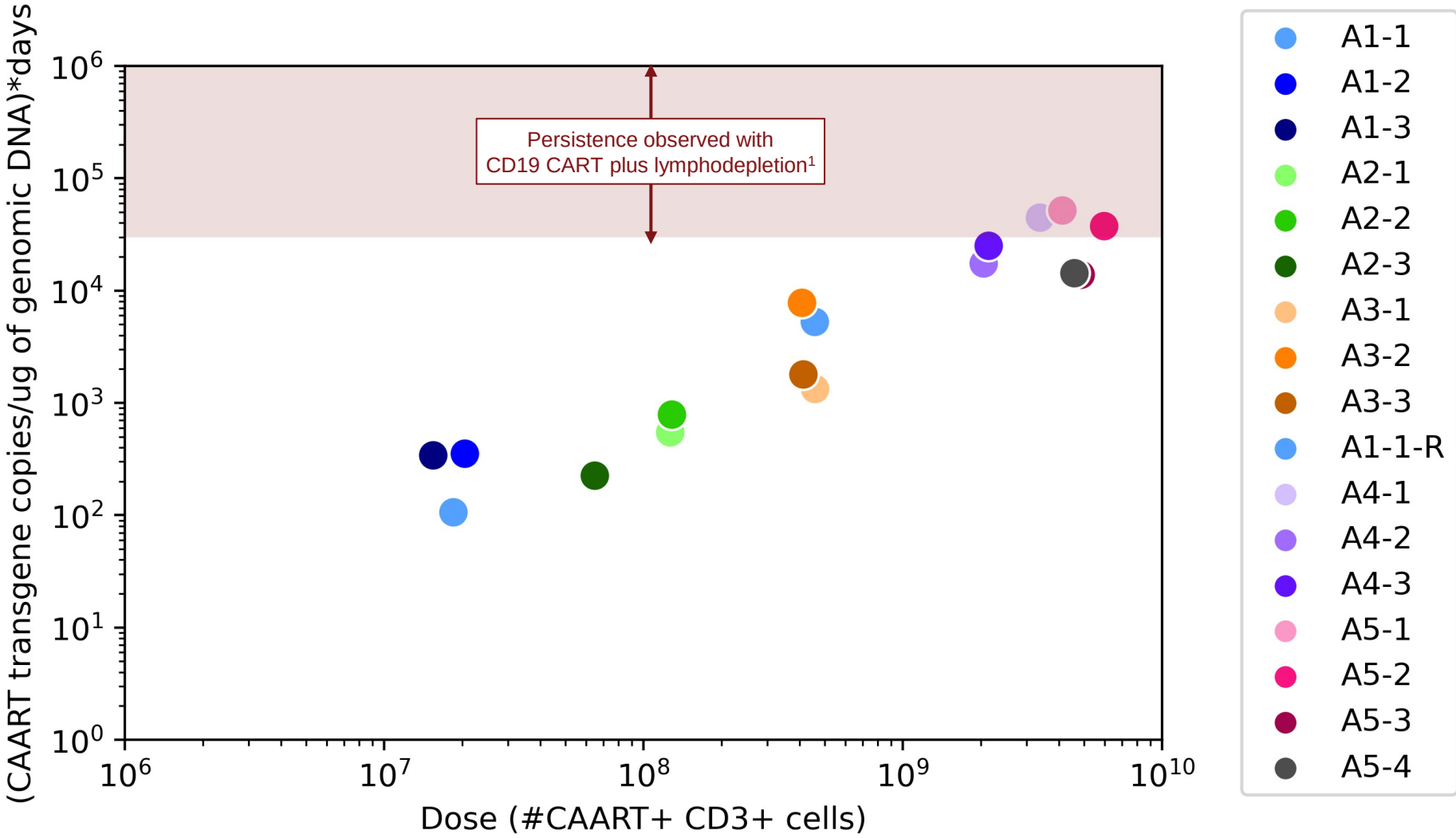
*Subject A1-1-R = Patient A1-1 retreated at the A3 dose level

Sustained persistence (past Day +29)

1. The range of persistence observed with CD19 CART therapy in oncology has not been confirmed to be necessary or sufficient for clinical responses in patients with mPV.

DSG3-CAART Persistence (qPCR) AUC

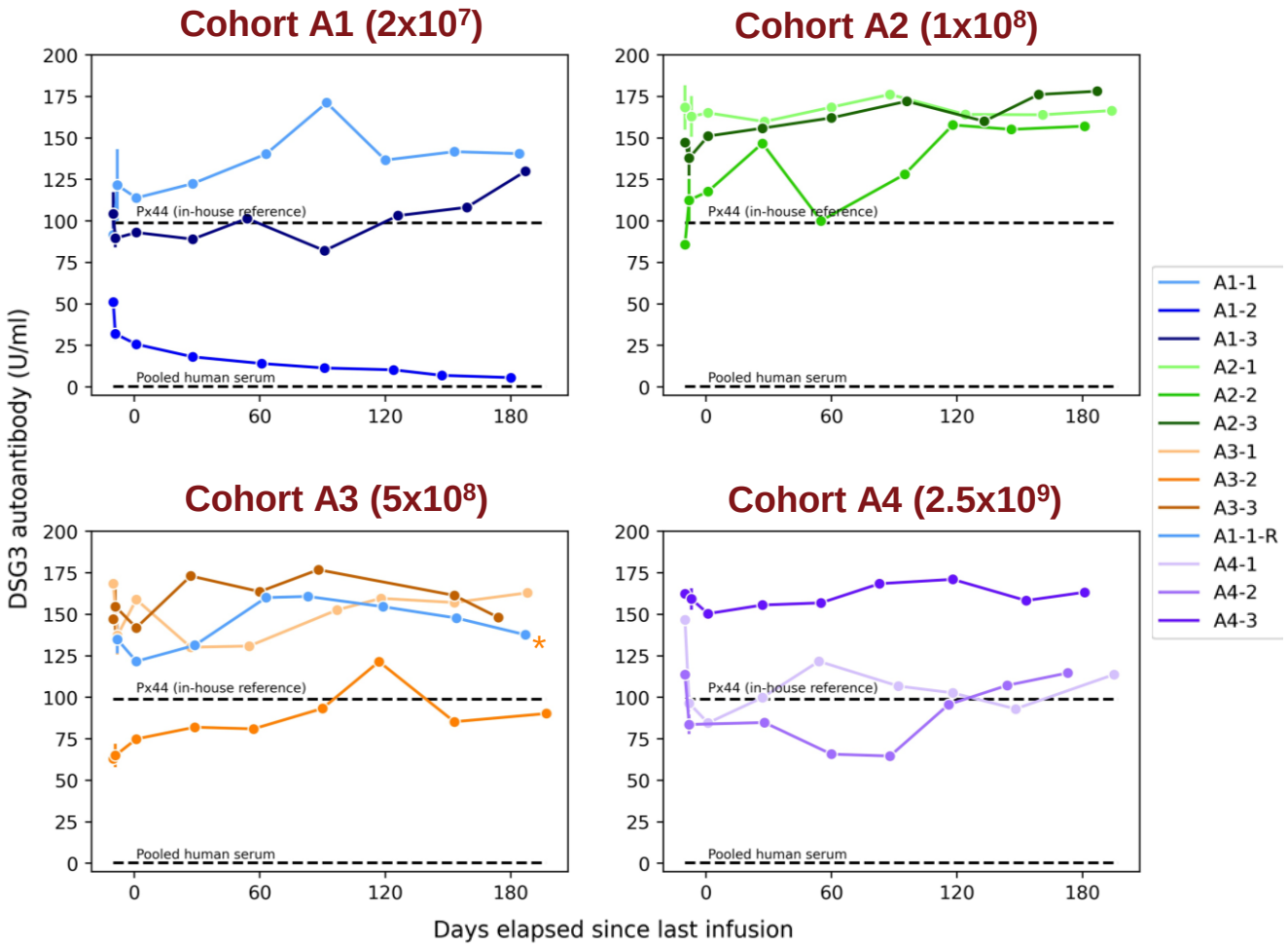
Linear relationship through Cohort A4, but leveling off with Cohort A5



1. The range of persistence observed with CD19 CART therapy in oncology has not been confirmed to be necessary or sufficient for clinical responses in patients with mPV.

Anti-DSG3 Antibody Levels (ELISA) Across Cohorts A1-A4

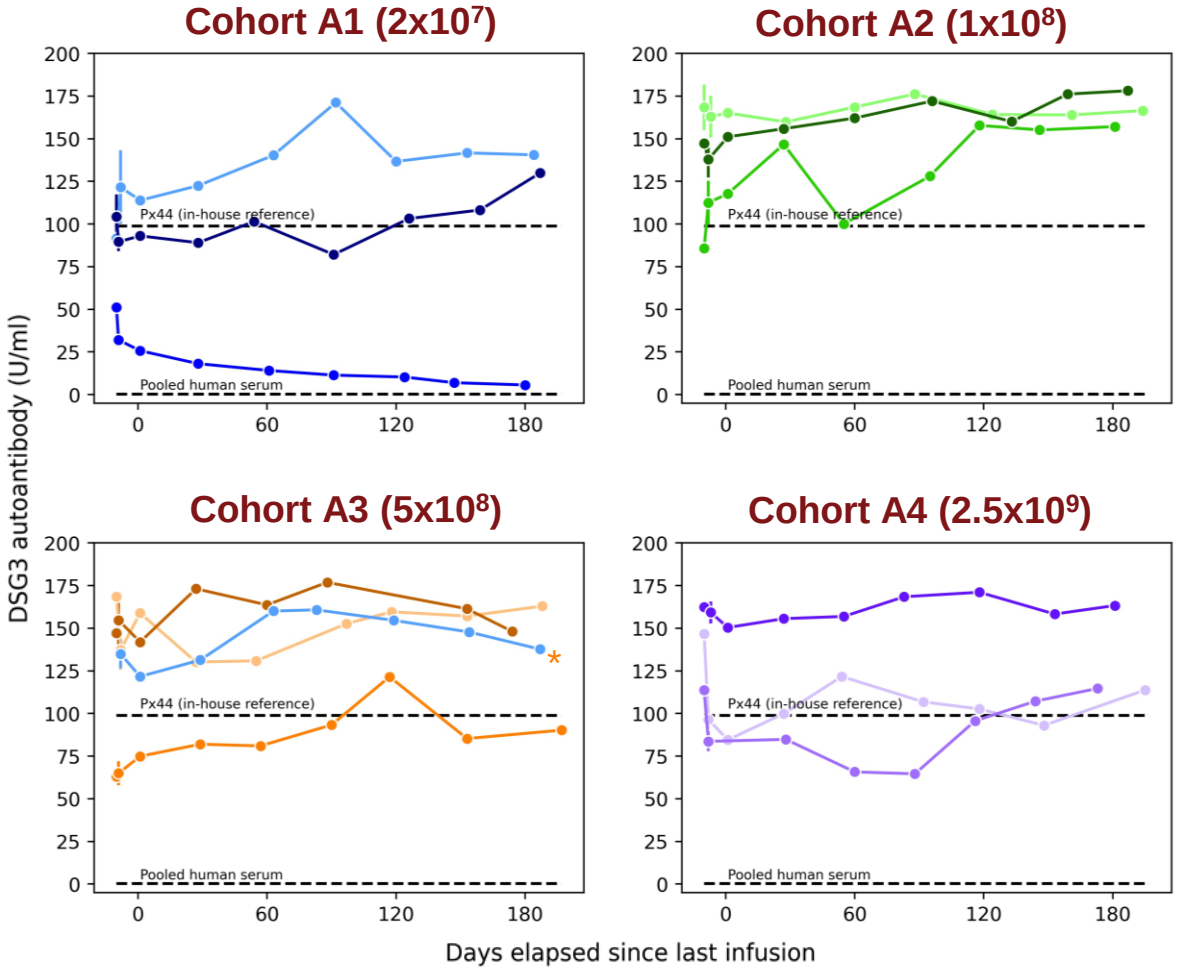
ABSOLUTE VALUES



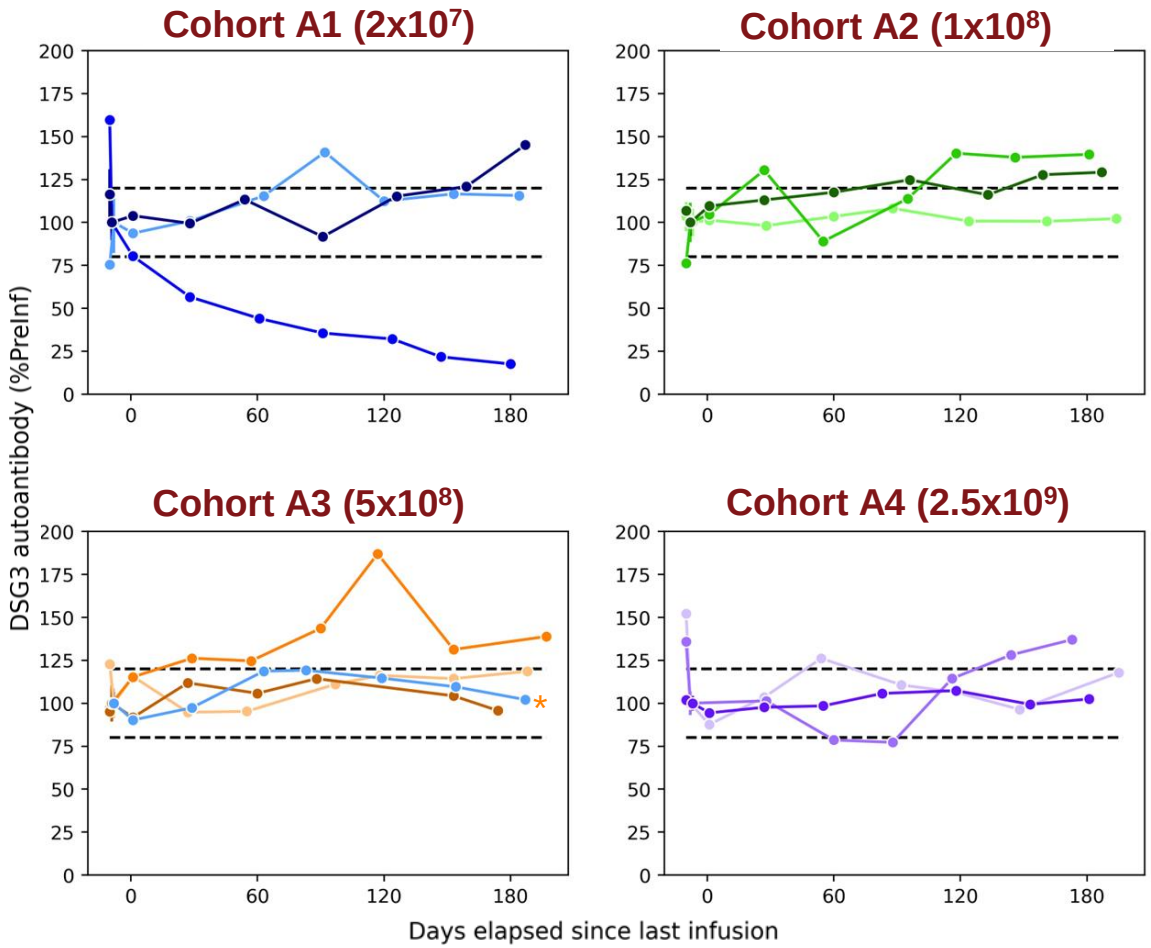
*Subject A1-1-R = Patient A1-1 retreated at the A3 dose level

Anti-DSG3 Antibody Levels (ELISA) Across Cohorts A1-A4

ABSOLUTE VALUES



NORMALIZED VALUES



*Subject A1-1-R = Patient A1-1 retreated at the A3 dose level

Dashed lines represent ± 20% from the Pre-Infusion timepoint

Disease Activity (PDAI Mucous Membrane Score)

Cohort (Dose)	Subject	Prior RTX or IVIg*	Meds stopped or tapered prior to inf.	Screen	Pre-Infusion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
A1 ($2x10^7$)	**A1-1**	RTX 10m	PRD								
A1 ($2x10^7$)	**A1-2**	RTX 6.5m IVIg 3m									
A1 ($2x10^7$)	**A1-3**	RTX 9m	MMF								
A2 ($1x10^8$)	**A2-1**	IVIg 4m									
A2 ($1x10^8$)	**A2-2**										
A2 ($1x10^8$)	**A2-3**	IVIg 4m									
A3 ($5x10^8$)	**A3-1**										
A3 ($5x10^8$)	**A3-2**		PRD, MMF								
A3 ($5x10^8$)	**A3-3**										
A4 ($2.5x10^9$)	**A4-1**		PRD, MMF								
A4 ($2.5x10^9$)	**A4-2**										
A4 ($2.5x10^9$)	**A4-3**										

RTX=rituximab; IVIg=intravenous immunoglobulin; MMF=mycophenolate; PRD=prednisone
*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.

Disease Activity (PDAI Mucous Membrane Score)

Cohort (Dose)	Subject	Prior RTX or IVIg*	Meds stopped or tapered prior to inf.	Screen	Pre-Infusion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
A1 ($2x10^7$)	**A1-1**	RTX 10m	PRD					PRD	IVIg		MMF
A1 ($2x10^7$)	**A1-2**	RTX 6.5m IVIg 3m									
A1 ($2x10^7$)	**A1-3**	RTX 9m	MMF								
A2 ($1x10^8$)	**A2-1**	IVIg 4m							PRD		
A2 ($1x10^8$)	**A2-2**								PRD		
A2 ($1x10^8$)	**A2-3**	IVIg 4m				PRD			RTX		
A3 ($5x10^8$)	**A3-1**							PRD			PRD
A3 ($5x10^8$)	**A3-2**		PRD, MMF								
A3 ($5x10^8$)	**A3-3**								PRD		
A4 ($2.5x10^9$)	**A4-1**		PRD, MMF					IVIg			
A4 ($2.5x10^9$)	**A4-2**					PRD			PRD		
A4 ($2.5x10^9$)	**A4-3**							PRD			

RTX=rituximab; IVIg=intravenous immunoglobulin; MMF=mycophenolate; PRD=prednisone
*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.
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.

Disease Activity (PDAI Mucous Membrane Score)

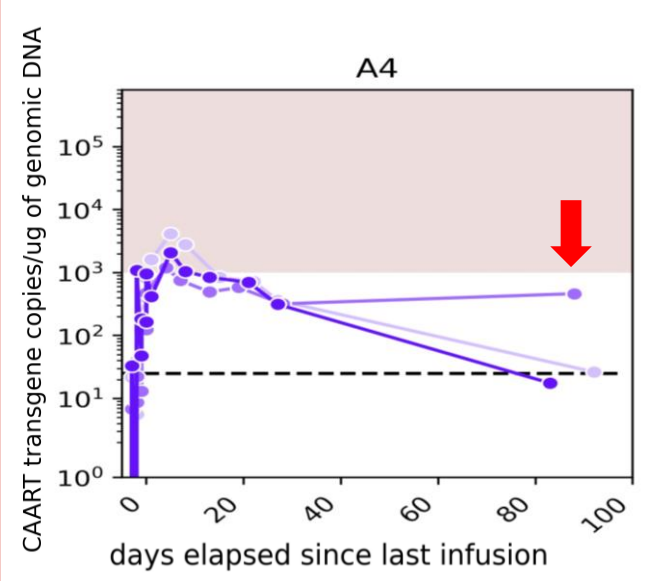
Cohort (Dose)	Subject	Prior RTX or IVIg*	Meds stopped or tapered prior to inf.	Screen	Pre-Infusion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
A1 ($2x10^7$)	**A1-1**	RTX 10m	PRD	20	10	13	33 PRD	70 IVIg	27	26 MMF	30
A1 ($2x10^7$)	**A1-2**	RTX 6.5m IVIg 3m		5	2	1	1	1	0	1	0
A1 ($2x10^7$)	**A1-3**	RTX 9m	MMF	17	4	3	1	2	6	2	13
A2 ($1x10^8$)	**A2-1**	IVIg 4m		6	5	2	1	2	3 PRD	2	5
A2 ($1x10^8$)	**A2-2**			14	3	3	0	1	4 PRD	4	11
A2 ($1x10^8$)	**A2-3**	IVIg 4m		6	1	3 PRD	4	7	4 RTX	1	5
A3 ($5x10^8$)	**A3-1**			2	2	0	0 PRD	0	0	0 PRD	24
A3 ($5x10^8$)	**A3-2**		PRD, MMF	12	10	10	22	20	20	10	21
A3 ($5x10^8$)	**A3-3**			18	14	8	14	17	16 PRD	6	7
A4 ($2.5x10^9$)	**A4-1**		PRD, MMF	3	5	3	6 IVIg	4	2	12	7
A4 ($2.5x10^9$)	**A4-2**			1	1 PRD	1	1	0	0 PRD	8	0
A4 ($2.5x10^9$)	**A4-3**			4	5	4	5	4 PRD	5	4	8
# Subjects with PDAI=0 or 1 (Clear/Almost Clear)				**1**	**2**	**3**	**6**	**4**	**3**	**3**	**2**

RTX=rituximab; IVIg=intravenous immunoglobulin; MMF=mycophenolate; PRD=prednisone
*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.
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.

Data on Subject A4-2 ($2.5x10^9$ DSG3-CAART Dose)

Persistence of DSG3-CAART detected via qPCR

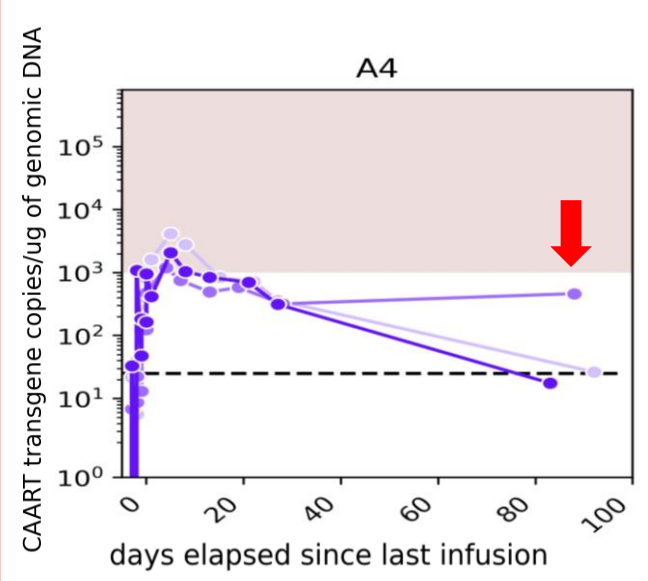
1. DSG3-CAART persistence detected at 3 months (not observed with other subjects in Cohorts A1-A4)



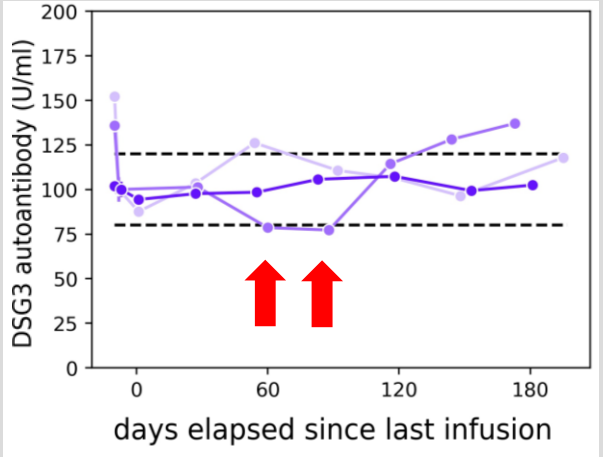
Data on Subject A4-2 (2.5x10^9 DSG3-CAART Dose)

Anti-DSG3 antibody levels transiently decreased >20%

1. DSG3-CAART persistence detected at 3 months (not observed with other subjects in Cohorts A1-A4)



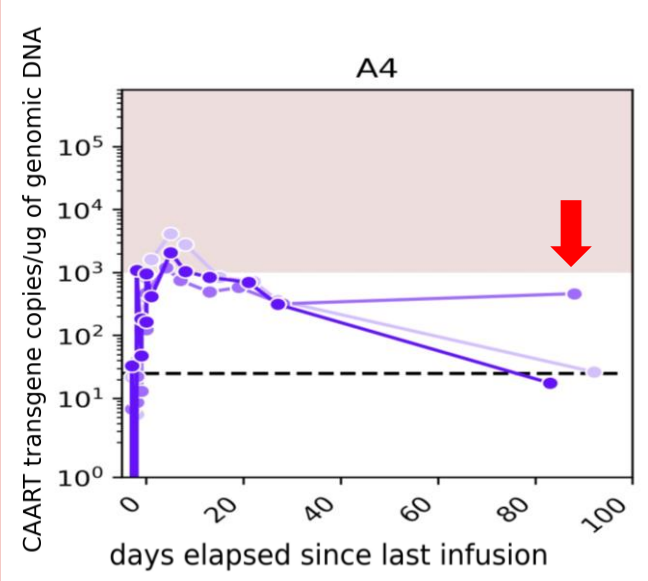
2. Anti-DSG3 Ab levels decreased >20% at 2 and 3 months post-infusion



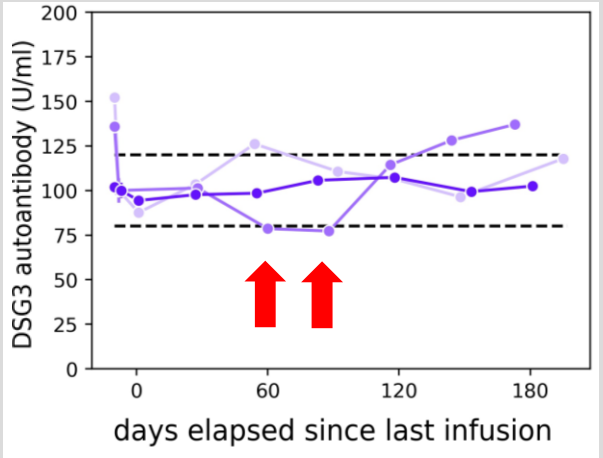
Data on Subject A4-2 ($2.5x10^9$ DSG3-CAART Dose)

Disease activity and steroid dose transiently decreased

1. DSG3-CAART persistence detected at 3 months (not observed with other subjects in Cohorts A1-A4)



2. Anti-DSG3 Ab levels decreased >20% at 2 and 3 months post-infusion



3. PDAI Mucous Membrane score decreased from 1 to 0 at 3 and 4 months post-infusion and
4. prednisone tapered from 10mg QD to 1mg QD over the 4 months after DSG3-CAART infusion

Disease Activity Measure	Screen	Pre-Infusion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
PDAI	1	1 PRD	1	1	0	0 PRD	8	0
ODSS[1]	10	5	5	6	0	0	26	1

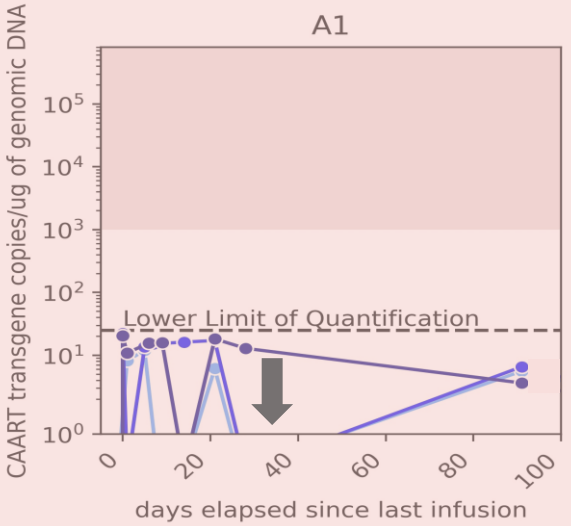
1. Oral Disease Severity Score

Cabaletta Bio®

Data on Subject A1-2 (1x10^7 DSG3-CAART Dose)

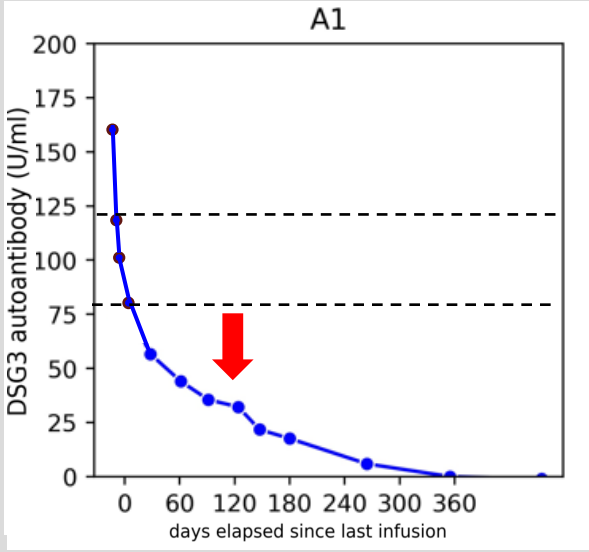
Anti-DSG3 Ab levels and disease activity decreased

DSG3-CAART persistence below lower limit of quantification



1 Anti-DSG3 Ab levels decreased >20%

- RTX 6.5 months before DSG3-CAART
- Continued disease activity and elevated anti-DSG3 ab prompted IVIg 3 months before DSG3-CAART
- Anti-DSG3 ab continued to decrease for 1 year post-DSG3-CAART infusion



2 PDAI Mucous Membrane score decreased from 2 to 0 at 4 and 6-12 months post-infusion

Disease Activity Measure	Screen	Pre-Infusion	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12
PDAI	5	2	1	1	1	0	1	0	0	0
ODSS[1]	22	9	7	5	6	0	7	0	0	0

1. Oral Disease Severity Score

Cabaletta Bio®

Rationale for Next Planned Dosing Cohorts

- Cohort P4: A4 dose ($2.5x10^9$ cells) combined with cyclophosphamide (CY) and IVIg preconditioning
  - CY to potentially reduce cells that compete for cytokines needed for DSG3-CAART activation/proliferation
  - CY to potentially reduce pathogenic B cells that secrete anti-DSG3-antibodies that may bind and block DSG3-CAART
  - IVIg to potentially reduce anti-DSG3 antibodies that may bind and block DSG3-CAART
  - Some leveling off of persistence with A5 dose
  - CY and IVIg have the potential to provide transient disease improvement, and up to 9 months may be required to assess DSG3-CAART effect

- Cohort A6m: 2x A5 dose ($1-1.5x10^{10}$ cells)
  - Two A5 infusions administered 3 weeks apart to potentially increase the duration of in vivo exposure and persistence of DSG3-CAART (increase the AUC)

Summary and Conclusion

- Data from the first-in-human trial of DSG3-CAART for mPV demonstrate that doses up to $7.5x10^9$ cells (Cohort A5) were generally well-tolerated with no DLT, including CRS or ICANS > Grade 1, through 07 Sep 2022
- There was a dose dependent increase in DSG3-CAART persistence through Cohort A4, but a leveling off with Cohort A5
- The persistence observed in Cohorts A4 and A5 approached the lower end of range that has been observed with CD19 CART therapy plus lymphodepletion for B-cell malignancies[1]
- No clear pattern was observed in changes in anti-DSG3 Ab levels or disease activity through Cohort A4; one subject in Cohort A4 demonstrated a transient improvement in several assessments of efficacy
- These data warrant further exploration of dosing regimen to potentially further increase in vivo exposure and activity of DSG3-CAART cells:
  - Combination regimen with cyclophosphamide and IVIg pretreatment (Cohort P4)
  - Higher dose with 2 doses of A5 given 3 weeks apart (Cohort A6m)

1. The range of persistence observed with CD19 CART therapy in oncology has not been confirmed to be necessary or sufficient for clinical responses in patients with mPV.

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