Cabaletta Bio™

Correlative findings following DSG3-CAART infusion with & without preconditioning in patients with Pemphigus Vulgaris (DesCAARTes™ trial)

ESGCT 2024

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Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements.

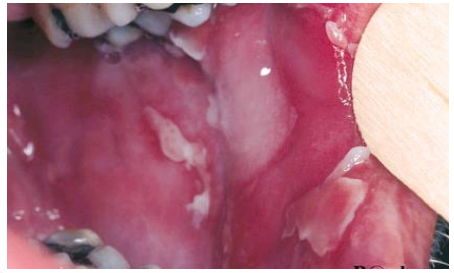
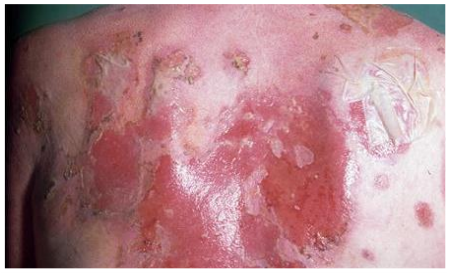
Various risks, uncertainties and assumptions could cause actual results to differ materially from those anticipated or implied in our forward-looking statements. Such risks and uncertainties include, but are not limited to, risks related to the success, cost, and timing of our product candidate development activities and preclinical studies and clinical trials, risks related to our ability to demonstrate sufficient evidence of safety, efficacy and tolerability in our preclinical studies and clinical trials of CABA-201 and MuSK-CAART, the risk that the results observed with the similarly-designed construct, including, but not limited to, due to dosing regimen, are not indicative of the results we seek to achieve with CABA-201, the risk that signs of biologic activity or persistence may not inform long-term results, the risk that persistence observed with effective CD19-CAR T oncology studies in combination with lymphodepletion is not indicative of, or applicable to, clinical responses in patients with mPV, risks related to clinical trial site activation or enrollment rates that are lower than expected, our ability to demonstrate sufficient evidence of safety, efficacy and tolerability in its preclinical studies and clinical trials of CABA-201; risks that modifications to trial design or approach may not have the intended benefits and that the trial design may need to be further modified; our ability to protect and maintain our intellectual property position, risks related to our relationships with third parties, uncertainties related to regulatory agencies' evaluation of regulatory filings and other information related to our product candidates, our ability to retain and recognize the intended incentives conferred by any Orphan Drug Designations and Fast Track Designations, risks related to regulatory filings and potential clearance, the risk that any one or more of our product candidates will not be successfully developed and commercialized, the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies, and risks related to volatile market and economic conditions and public health crises. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, you are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ materially from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent annual report on Form 10-K, as well as discussions of potential risks, uncertainties, and other important factors in our other and subsequent filings with the Securities and Exchange Commission. Certain information contained in this Presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this Presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. The Company is the owner of various trademarks, trade names and service marks. Certain other trademarks, trade names and service marks appearing in this Presentation are the property of third parties. Solely for convenience, the trademarks and trade names in this Presentation are referred to without the ® and TM symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Outline

- Pemphigus Vulgaris overview
- DSG3 CAART design overview
- Emerging translational and clinical data from DSG3 program
  - Overview of trial design
  - Safety
  - Persistence
  - Impact of lymphodepletion
  - Auto-antibody changes
  - Efficacy
  - Impact of CAAR expression
- Emerging translational data from MuSK CAART program (see poster P0744)
  - Persistence

Overview of pemphigus vulgaris & current treatment landscape

Current treatments require broad immunosuppression associated with safety risks and transient efficacy

	Mucosal PV[1] (25%)	Mucocutaneous PV[2] (75%)
		
Associated Antibody	**Anti-DSG3**	**Anti-DSG3 + Anti-DSG1**
Clinical Signs	Painful blisters of the mucous membranes (mouth, nose, larynx, esophagus, eyes, genitalia, rectum)	Blisters on orifices and skin
U.S. Disease Prevalence	**3,250 to 4,750**	**9,750 to 14,250**

CROT = 8+ weeks without lesions while off systemic therapy

Broad immunosuppression[3,6]

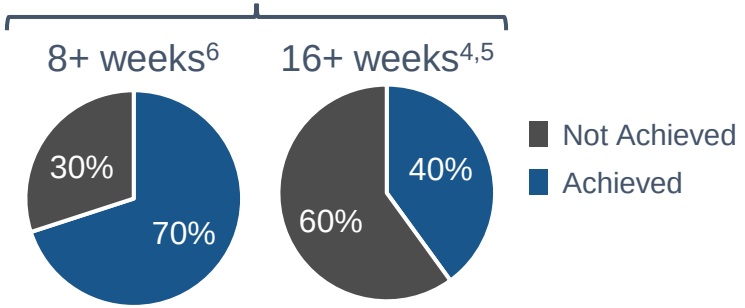
Modestly effective & poorly tolerated

Rituximab plus steroids (~3,500 mg/yr)[4]

Transient remission

~30% relapse in 1 year & >50% relapse in 2 years[6]

% of patients failing to achieve any 8+ or 16+ weeks without lesions or medicines



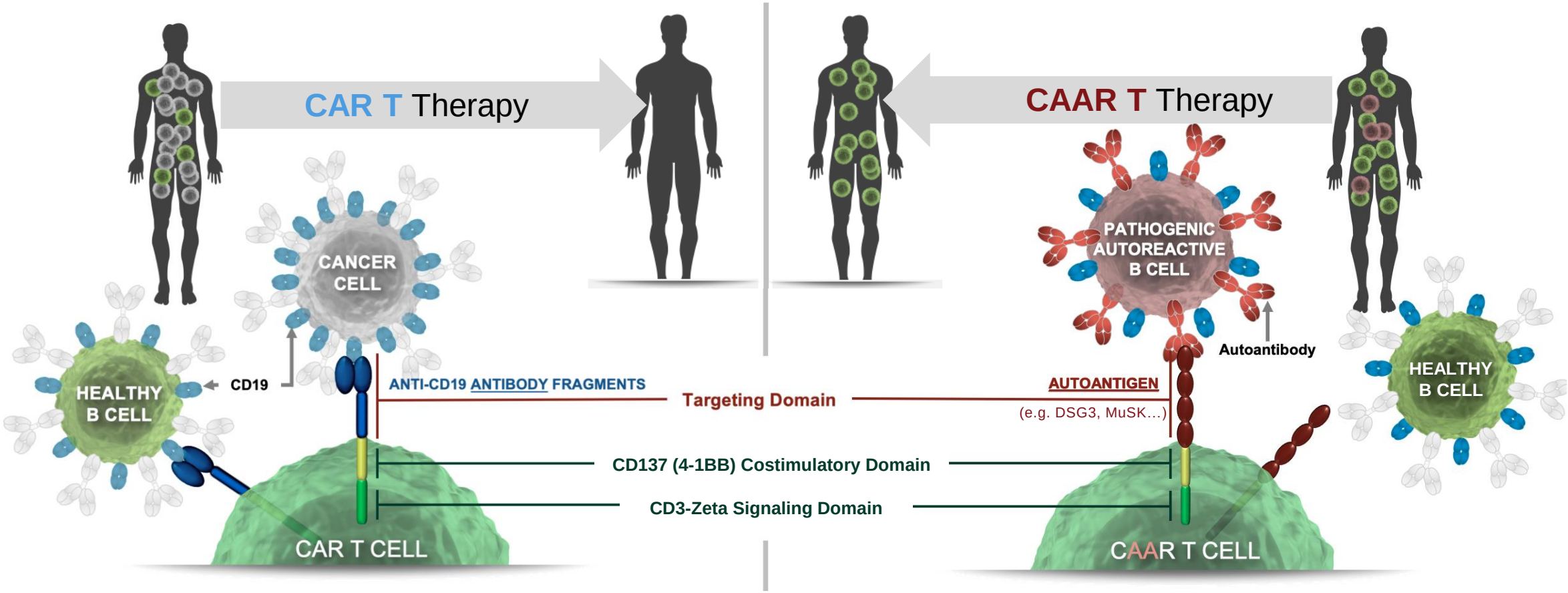
Safety risks

- 22% annual serious adverse event (SAE) rate[4]
- 4-9%[3,4,5] annual risk of severe infection in PV
- ~1.9% lifetime risk of fatal infection[7]

1. Image credit: D@nderm.
2. http://www.vgrd.org/archive/cases/2004/pv/DSCN4996%20copy.JPG
3. Joly, Pascal, et al. "First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial." The Lancet 389.10083 (2017): 2031-2040.
4. Werth, Victoria P., et al. "Rituximab versus Mycophenolate Mofetil in Patients with Pemphigus Vulgaris." New England Journal of Medicine (2021).
5. Rituximab label, 08/2020 revision.
6. Kushner, Carolyn J., et al. "Factors Associated With Complete Remission After Rituximab Therapy for Pemphigus." JAMA dermatology (2019).
7. Tony, Hans-Peter, et al. "Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID)." Arthritis research & therapy 13.3 (2011): 1-14.

Our scientific platform leverages FDA-approved CAR T technology

CAAR T product candidates are designed for selective and specific elimination of the pathogenic B cells



Chimeric **A**ntigen **R**eceptor **T** cell

Kymriah

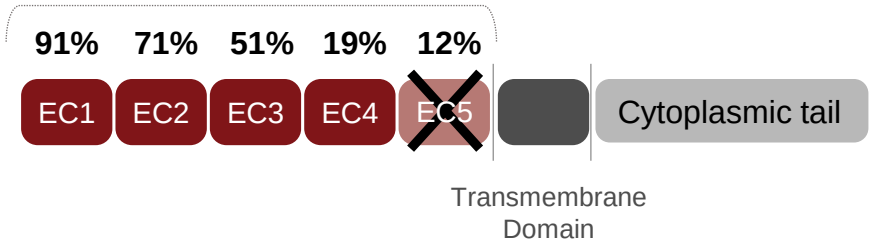
Chimeric **A**uto**A**ntibody **R**eceptor **T** cell

CABA CAAR T

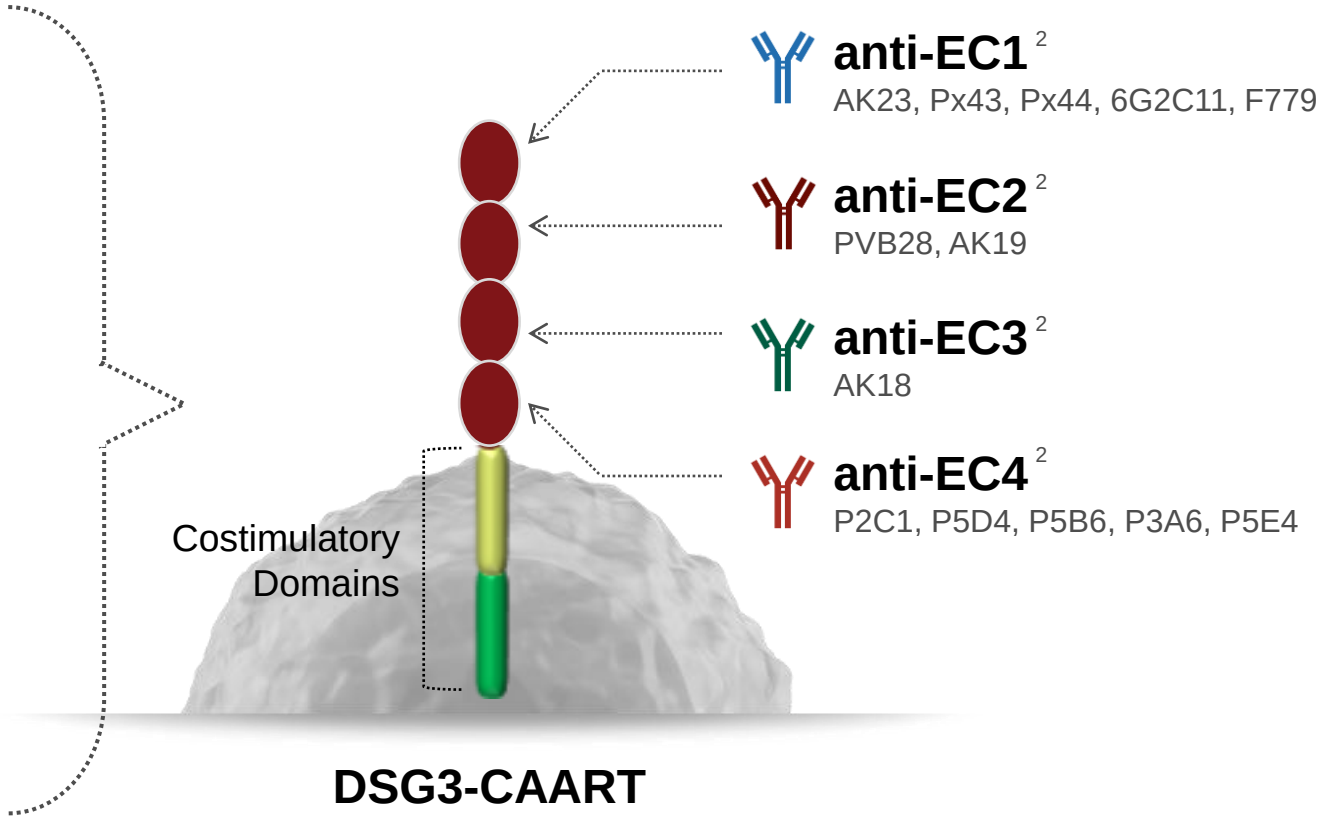
DSG3-CAART encompasses all known pathogenic epitopes

Antibodies or B-cell receptors against the EC5 domain of DSG3 are not known to be pathogenic

% of PV sera targeting each domain[1]

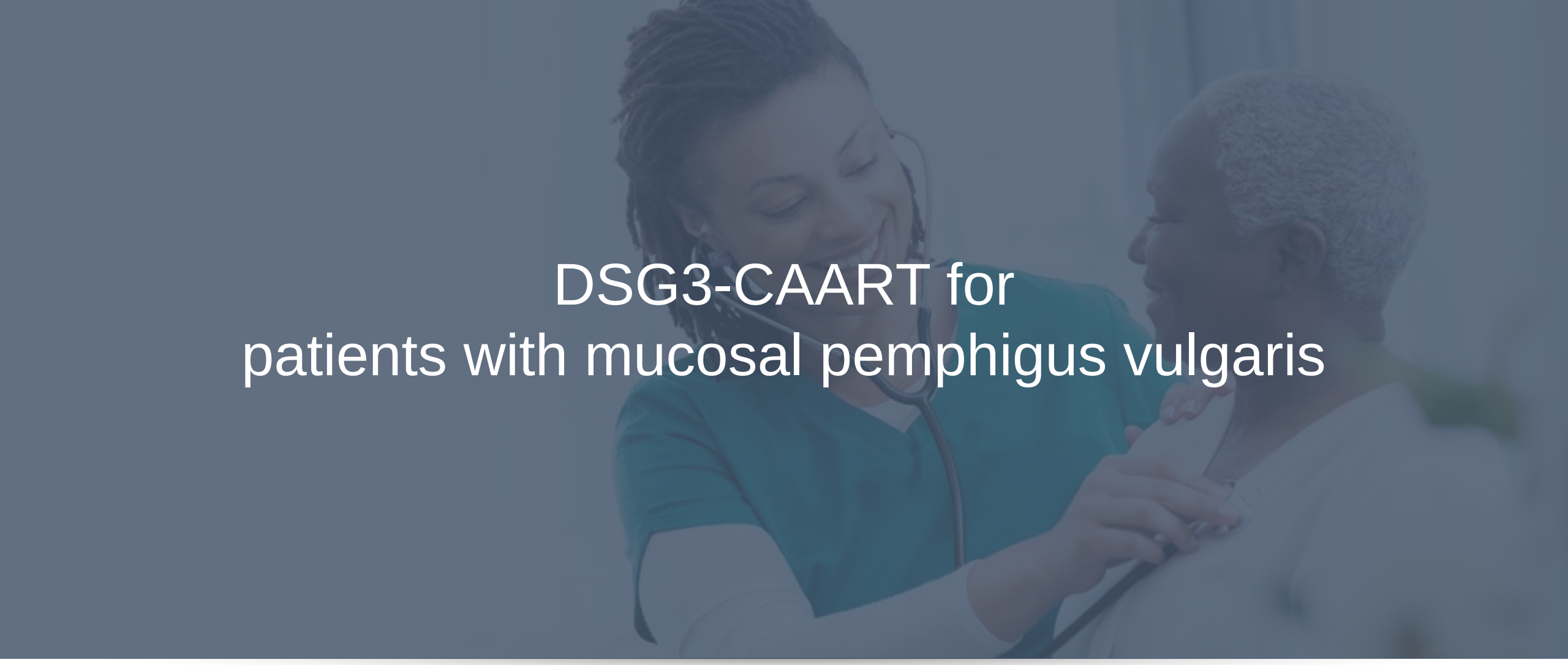


DSG3 Protein



DSG3-CAART

1. Ohyama, Bungo, et al. Journal of investigative dermatology 132.4 (2012): 1158-1168.
2. Antibodies that target the specific extracellular domain are shown below each extracellular domain.



DSG3-CAART for patients with mucosal pemphigus vulgaris

Cabaletta Bio™

DesCAARTes™ Phase 1 study of DSG3-CAART

Orphan Drug Designation

Fast Track Designation

Trial in patients with mPV evaluating up to 750x dose range (2×10^7 - *1.5×10^{10} cells)*

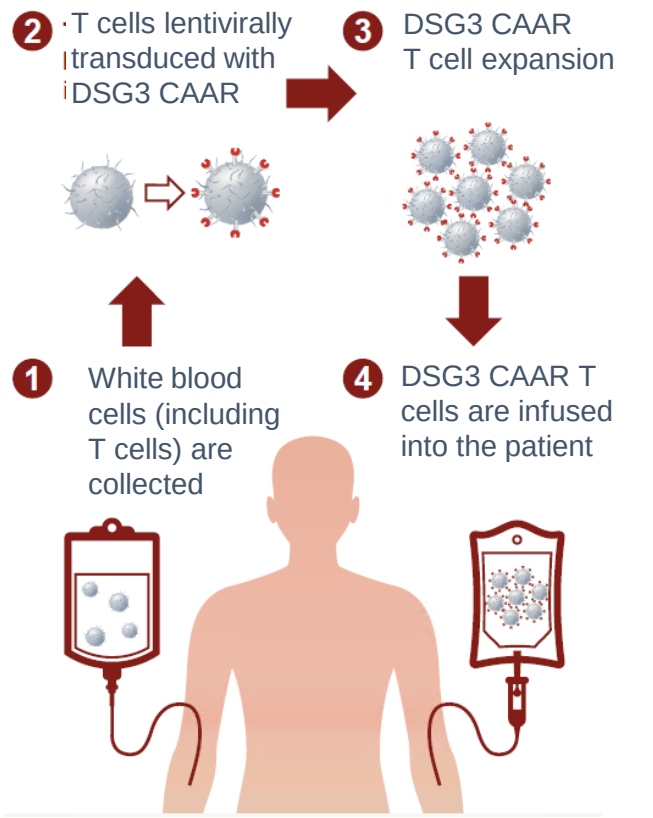
Screening → Apheresis → **DSG3-CAART INFUSION** → TREATMENT & FOLLOW-UP PERIOD → Next Patient

Major Inclusion Criteria

- Age: ≥18, confirmed diagnosis
- Inadequately managed by standard immunosuppressive therapies
- Confirmed diagnosis
- 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
- ALC < 1,000 at screening



Adjunctive immunosuppressants are stopped; prednisone tapered to low dose prior to infusion

Part A Cohorts	Subjects	Cell Dose
A1	3 (+3)	2×10^7
A2	3 (+3)	1×10^8
A3	3 (+3)	5×10^8
A4	3 (+3)	2.5×10^9
A5	3 (+3)	$5 - 7.5 \times 10^9$
A6m	*3 (+3)*	*$1 – 1.5 \times 10^{10}$*
P4 (cy + IVIG)	*3(+3)*	2.5×10^9
P4F (cy/flu + IVIG)	*3(+3)*	2.5×10^9

Up to 750-fold dose escalation

Primary objective:
Determine the maximum tolerated dose of DSG3-CAART

Primary endpoint:
AEs, DLTs, related to DSG3-CAART within 3 months of infusion

Secondary objectives:
- Manufacturing success rate
- **DSG3-CAART persistence**
- **Anti-DSG3 antibody titer changes**
- **Clinical disease activity score changes**

Baseline characteristics of enrolled patients

All patients enrolled in cohorts A1 (2×10^7) to P4F (2.5×10^9)

	Cohort A1 2×10^7 (n=3)	Cohort A2 1×10^8 (n=3)	Cohort A3[1] 5×10^8 (n=4)	Cohort A4 2.5×10^9 (n=3)	Cohort A5 $5 – 7.5 \times 10^9$ (n=4)	Cohort A6m $1 – 1.5 \times 10^{10}$ (n=3)	Cohort P4[2] 2.5×10^9 (n=3)	Cohort P4F[3] 2.5×10^9 (n=3)	Overall (n=23)
Age, years, median (range)	39 (32-57)	53 (50-54)	59 (47-70)	60 (56-70)	48 (34-57)	44 (30-50)	57 (45-58)	47 (44-60)	50 (30-70)
Female (%)	67%	67%	50%	67%	0%	67%	33%	33%	48%
Disease Duration, years, median (range)	3.4 (0.5-4.3)	4.3 (4.0-13.0)	2 (0.3-15.4)	3.5 (0.1-12.4)	1.6 (0.5-5.3)	1.4 (0.3-1.4)	1.8 (1.8-4.2)	1.6 (1.6-2.7)	1.8 (0.1-15.4)
Anti-DSG3 Ab Level, U/mL, median (range)	92 (32-119)	131 (124-169)	141 (71-166)	101 (87-160)	142 (128-165)	45 (9-95)	153 (135-188)	161 (156-164)	130 (9-188)
Pemphigus Disease Area Index, median (range)	17 (5-20)	9 (7-14)	15 (2-37)	3 (1-5)	5 (4-18)	3 (1-7)	12 (4-79)	11 (6-13)	6 (1-79)
Prior use of corticosteroids (%)	3 (100%)	3 (100%)	3 (75%)	3 (100%)	3 (75%)	3 (100%)	3 (100%)	3 (100%)	21 (91%)
Prior use of mycophenolate (%)	1 (33%)	3 (100%)	2 (50%)	1 (33%)	3 (75%)	1 (33%)	2 (67%)	1 (33%)	12 (52%)
Prior use of rituximab (%)	3 (100%)	3 (100%)	1 (25%)	2 (67%)	1 (25%)	1 (33%)	1 (33%)	1 (33%)	12 (52%)

1. Cohort A3 includes one retreated patient from Cohort A1, A1-1
2. Cohort P4 includes one retreated patient from Cohort A5, A5-1
3. Cohort P4F includes on retreated patient from Cohort A3, A3-3

Safety data in the first 3 months following infusion

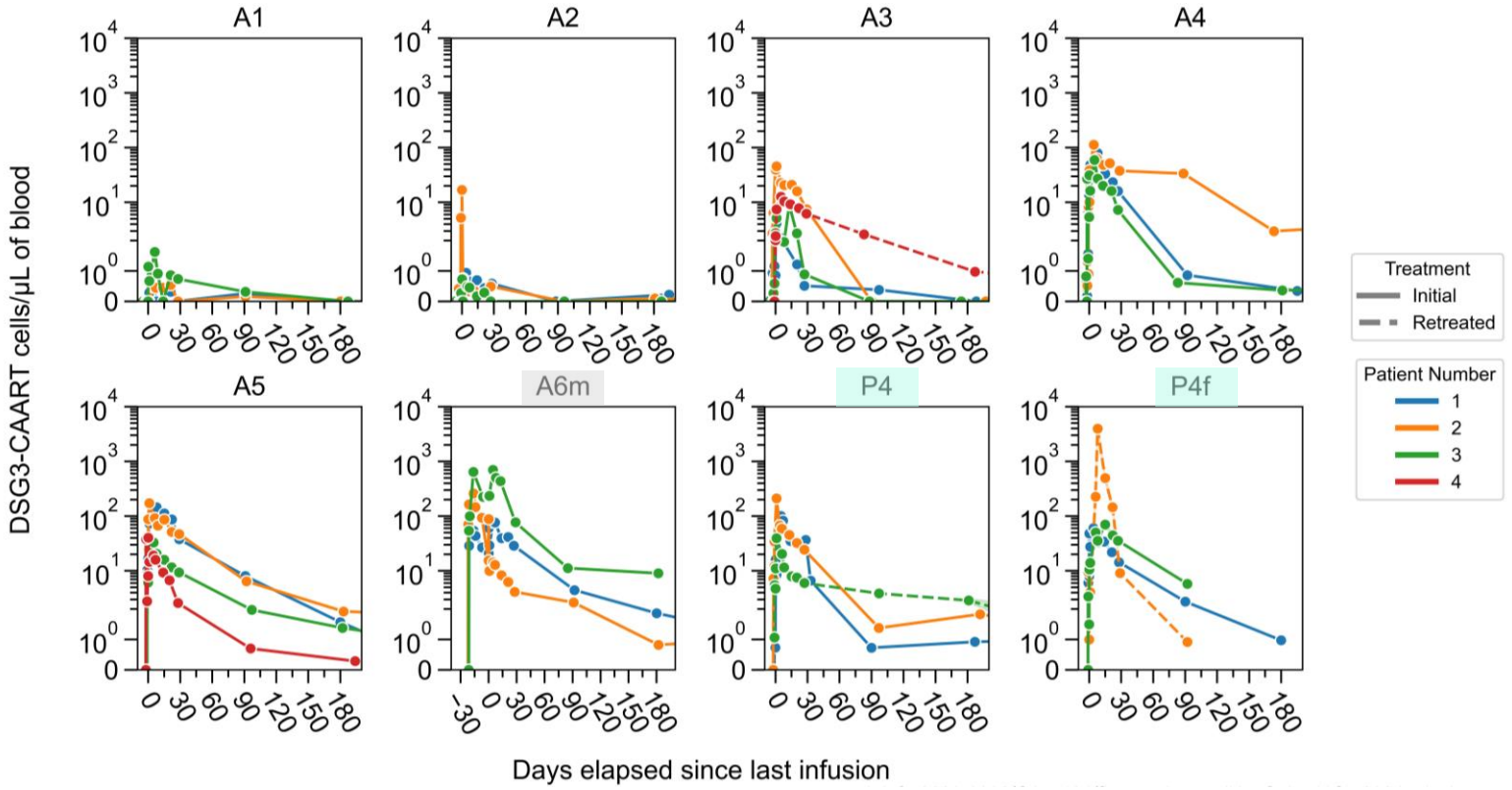
No DLTs observed throughout dose escalation

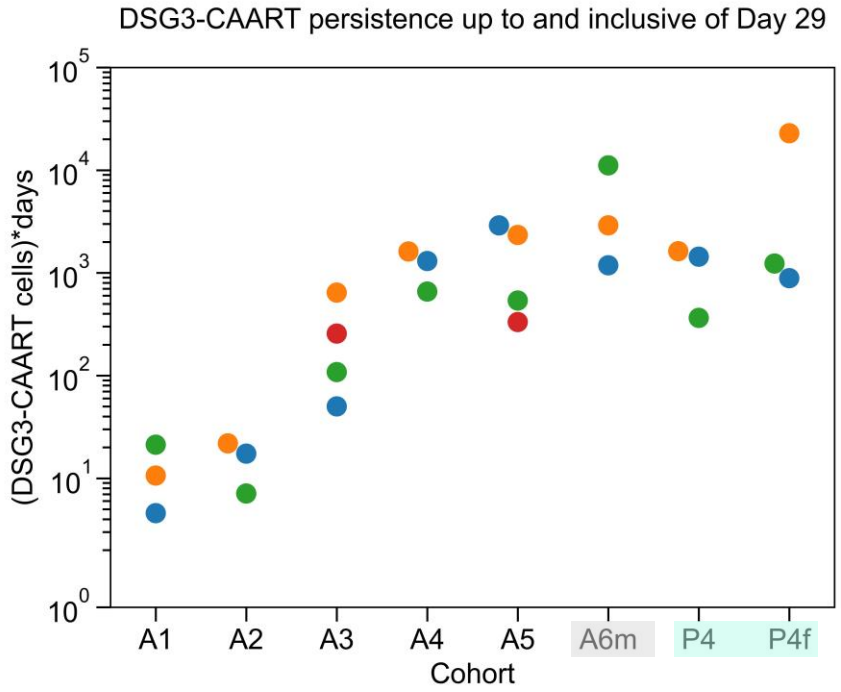
	Cohort A1 2×10^7 (n=3)	Cohort A2 1×10^8 (n=3)	Cohort A3 5×10^8 (n=4)	Cohort A4 2.5×10^9 (n=3)	Cohort A5 $5 – 7.5 \times 10^9$ (n=4)	Cohort A6m $1 – 1.5 \times 10^{10}$ (n=3)	Cohort P4[2] 2.5×10^9 (n=3)	Cohort P4F[3] 2.5×10^9 (n=3)	Overall (n=26)
# Subjects with ≥1 AEs (%)	3 (100%)	3 (100%)	4 (100%)	3 (100%)	4 (100%)	3 (100%)	3 (100%)	2 (67%)	25 (96%)
# Subjects with ≥1 Related AEs* (%)	3 (100%)	2 (67%)	3 (75%)	3 (100%)	2 (50%)	3 (100%)	1 (33%)	2 (67%)	19 (73%)
# Subjects with ≥1 SAEs (%)	2 (67%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	4 (15%)
# Subjects with ≥1 Related SAEs (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
# Subjects with Cytokine Release Syndrome (CRS) (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
# Subjects with Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (%)	0 (0%)	0 (0%)	0 (0%)	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%)	0 (0%)	0 (0%)	0 (0%)

1. Cohort A3 includes one retreated patient from Cohort A1, A1-1
2. Cohort P4 includes one retreated patient from Cohort A5, A5-1
3. Cohort P4F includes on retreated patient from Cohort A3, A3-3

DSG3 CAART persistence increases linearly from 2 x 10^7 to 2.5 x 10^9

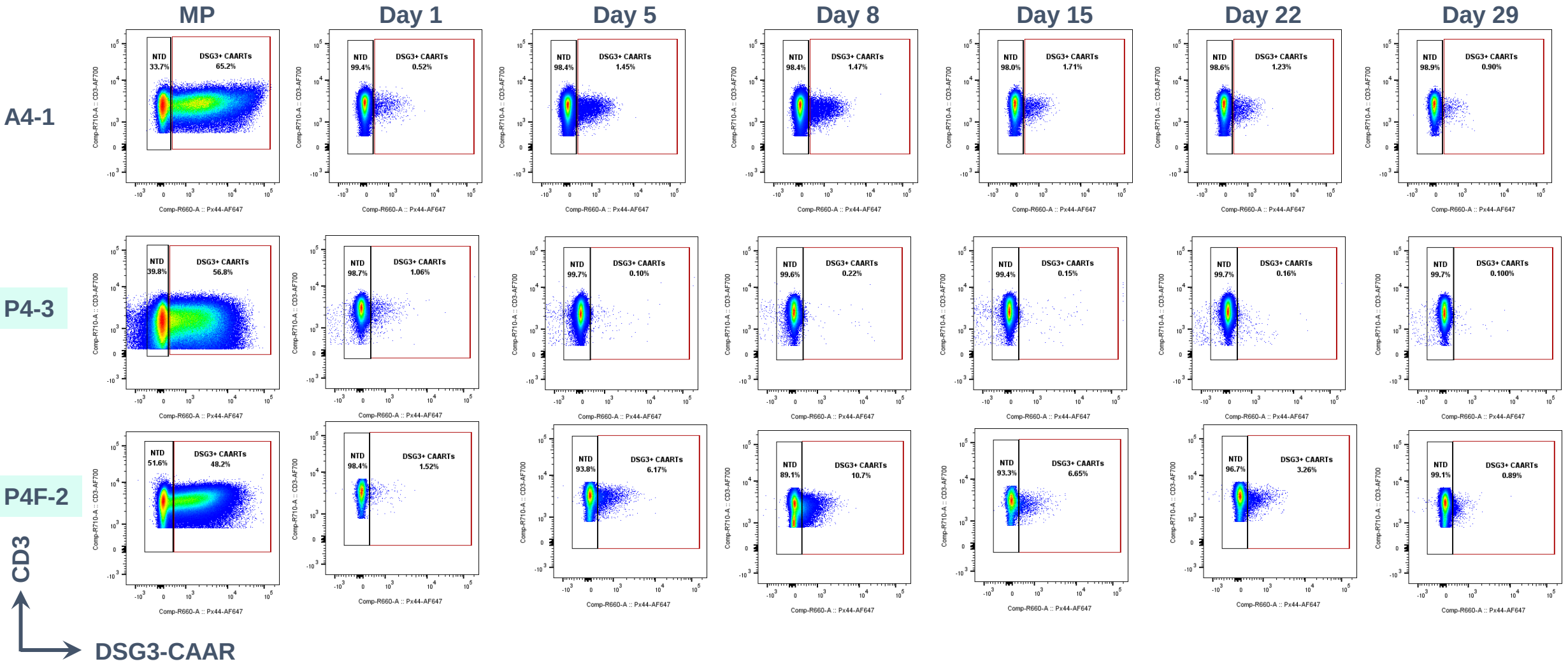
Conditioning with cyclophosphamide or fludarabine and cyclophosphamide does not impact persistence





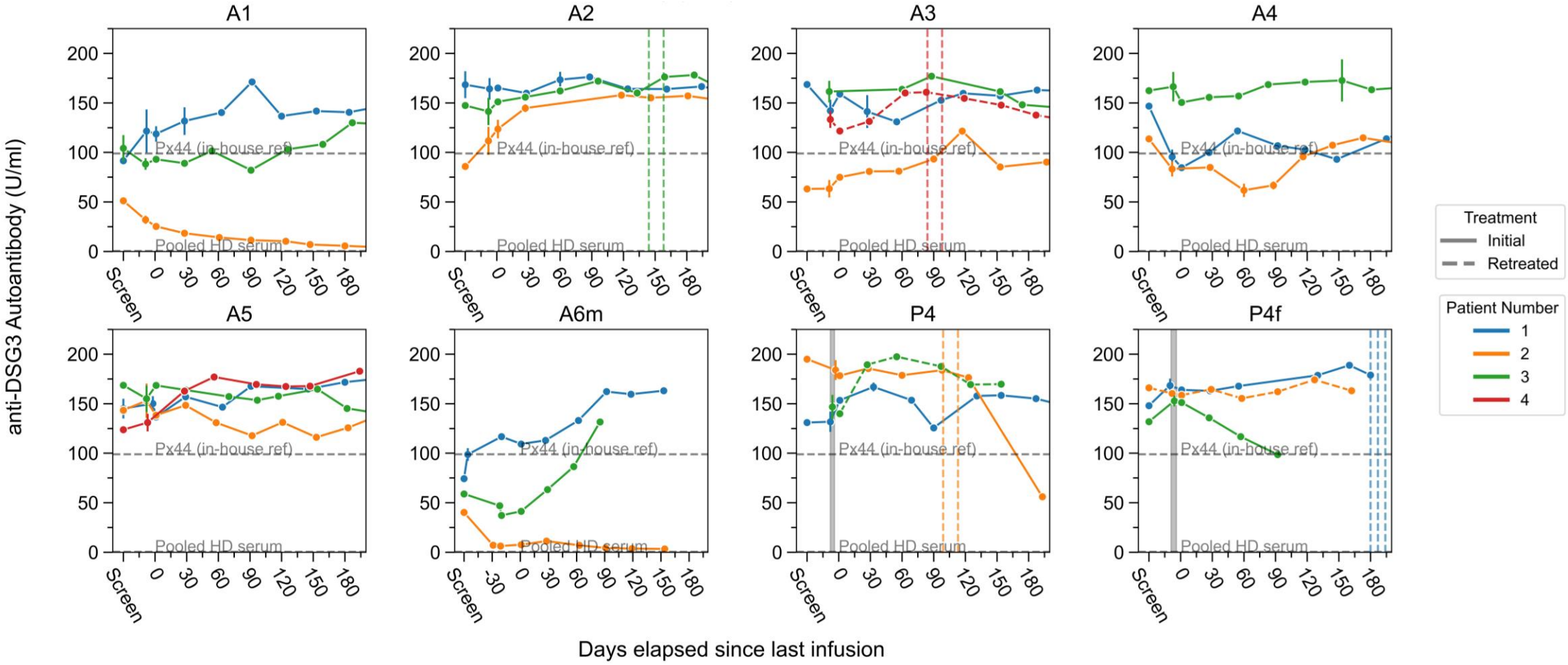
Conditioning does not impact persistence over the 1st month post-infusion

DSG3-CAART expression (MFI) decreases rapidly after infusion



Anti-DSG3 antibody levels do not decrease post DSG3-CAART infusion

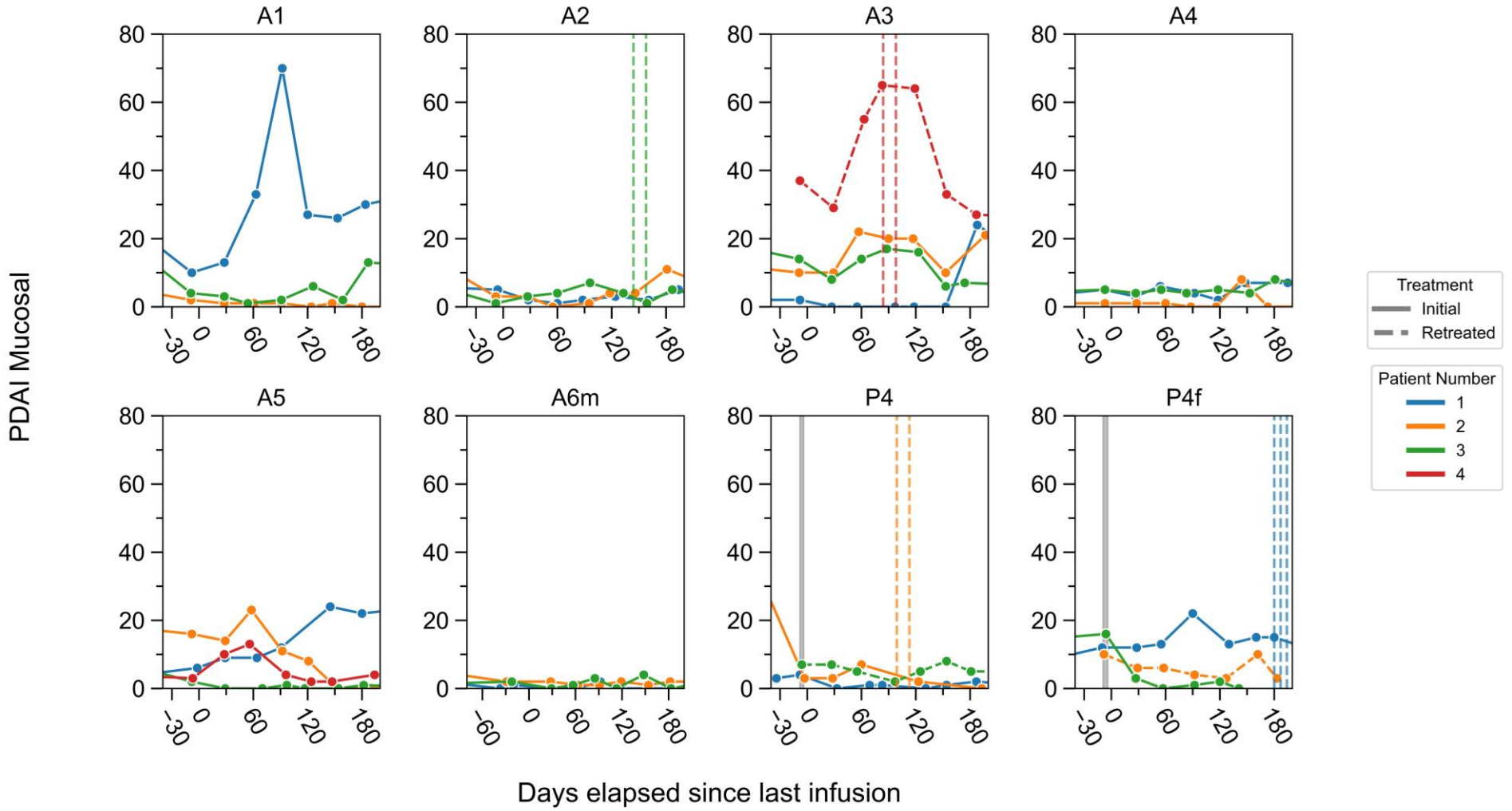
Rituximab elicits a decrease in subject P4-2 post-infusion



1. Vertical dashed lines indicate use of Rituximab
2. Horizontal dashed line indicates average U/mL value for anti-DSG3 reference control

No significant decreases observed in PDAI[1] scores post-CAART infusion

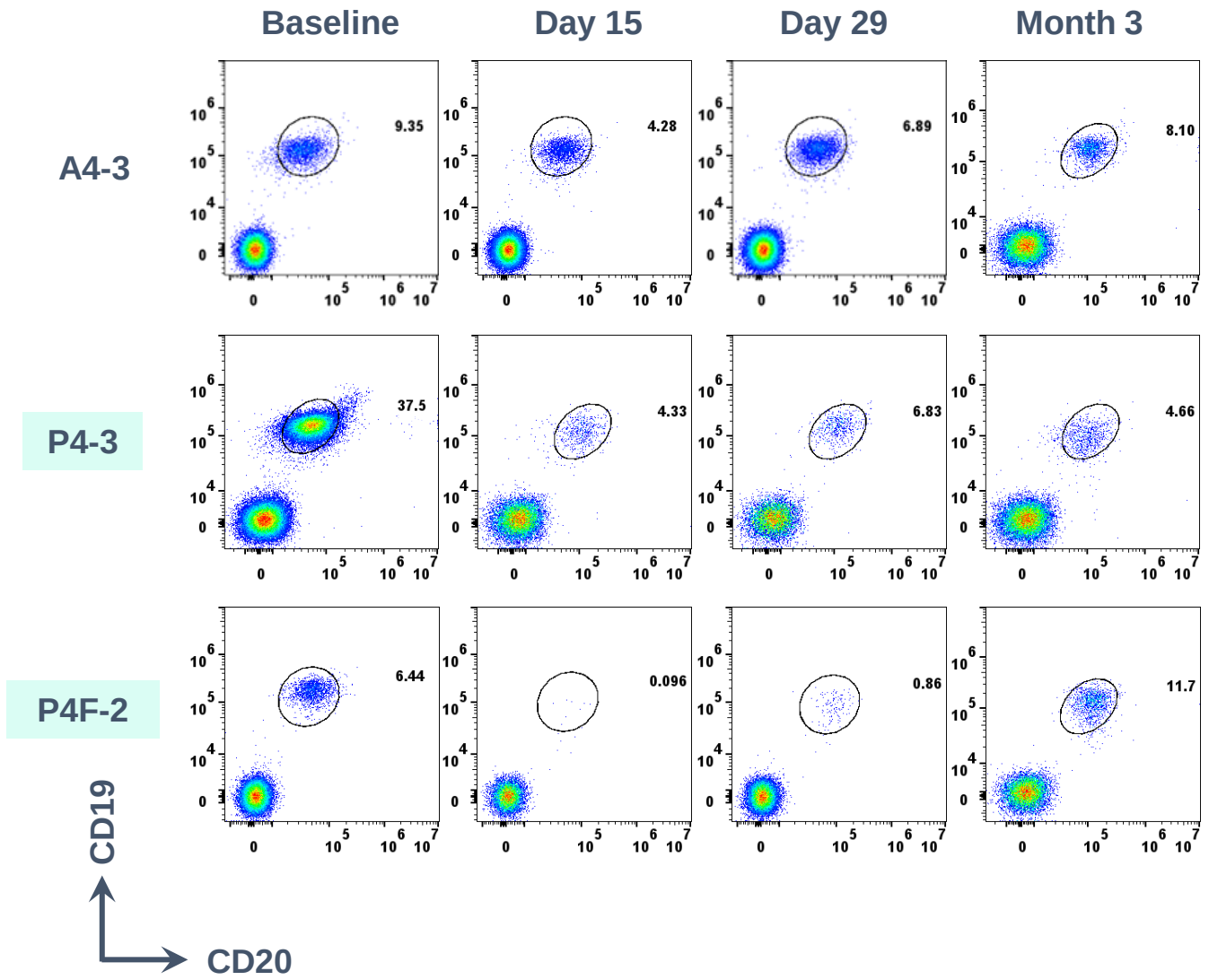
Mucosal PDAI scores



1. PDAI – pemphigus disease area index

Conditioning transiently impacts circulating B-cells following infusion

$CD19^{+}CD20^{+}$ B-cells return at one-month post-infusion; no long-term impact of conditioning observed

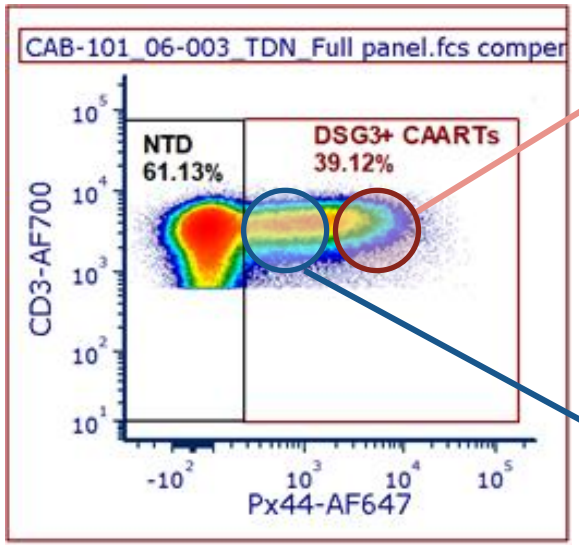


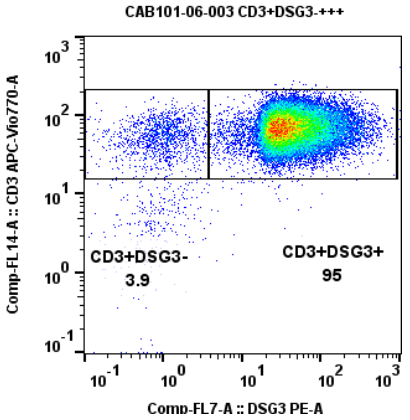
LLOQ of B-cell detection is 0.06%

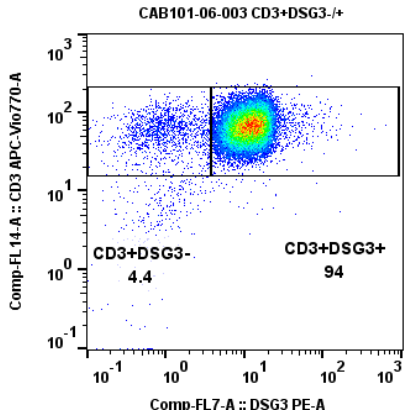
DSG3-CAAR expression appears to impact cytolytic capacity

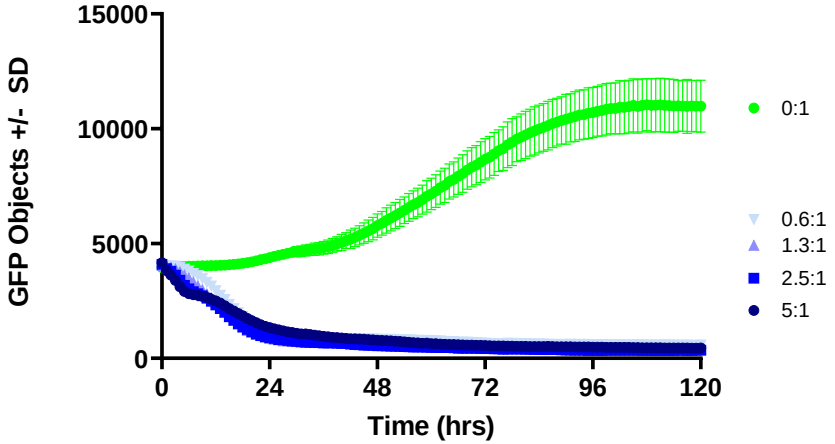
Loss of DSG3-CAAR^{HI} expressors could contribute to minimal activity post-infusion

MP[1]

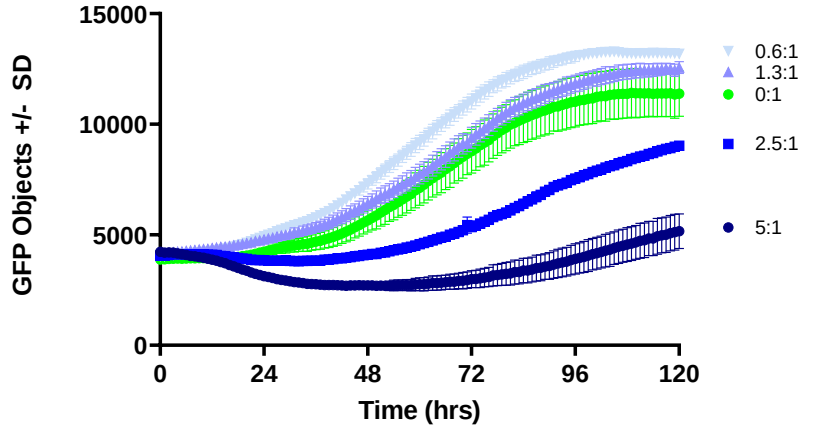








MP DSG3^{HI}



MP DSG3^{LO}

CD3

DSG3-CAAR

1. MP – Manufactured product of representative patient

Conclusions

Implications for adoptive cell therapy in autoimmune disease (CAART and CD19 approaches)

- DSG3-CAART is well-tolerated across a large dose range
- DSG3-CAART does not impact clinical scores in pemphigus vulgaris at 6 months post-infusion
- DSG3-CAART persistence increases linearly with dose from a 2×10^7 to 2.5×10^9 cell dose
  - After 2.5×10^9 cells, there is a plateau in exposure
  - Loss of high DSG3-CAAR expressing cells observed post-infusion
- Lymphodepletion does not impact the persistence of DSG3-CAART
- Lymphodepletion does not deeply deplete B-cell levels
- Lymphodepletion has no direct impact on clinical efficacy in pemphigus
  - No substantial changes in PDAI observed at 6 months post-infusion
- DSG3-CAART expression impacts cytolytic activity
  - Low expressing DSG3-CAART cells have inferior cytolytic activity compared to high expressing DSG3-CAART cells

Potential hypotheses for translational/clinical outcomes seen to date

Hypotheses are not mutually exclusive

- CAART cells target a small number of B-cells (low antigen burden)
  - DSG3 memory B-cells represent < 1% of all B-cells
  - Antigen load in oncology and autoimmune disease with CD19 or BCMA directed approaches is ~10^2 - 10^5 fold higher
  - Insufficient antigen load to drive expansion of CAART cells
- Relatively high levels of circulating auto-antibodies could impact DSG3-CAART function or DSG3-CAAR function
  - Anti-DSG3 antibodies could inhibit DSG3-CAART activity or DSG3-CAAR expression
- DSG3 could be a non-optimal extracellular domain for the CAART approach

Question: How do we evaluate and/or address potential hypotheses?

Answer: Use the MuSK CAART in MuSK subtype myasthenia gravis (see poster P0744)

- CAART cells target a small number of B-cells (low antigen)
  - Memory B-cells represent a < 1% of all B-cells
  - Antigen load in oncology and autoimmune disease with CD19 or BCMA directed approaches is ~10^2 - 10^5 fold higher
  - Insufficient antigen load to drive expansion of CAART cells

- Relatively high levels of circulating auto-antibodies could impact DSG3-CAART function or DSG3-CAAR function
  - Anti-DSG3 antibodies could inhibit DSG3-CAART activity or DSG3-CAAR expression

➢ MuSK subtype MG has 10^1 - 10^2 lower levels of circulating auto-antibody

- DSG3 is a non-optimal extracellular domain for the CAART approach

➢ MuSK-CAART utilizes a different extracellular domain

MuSK-CAART for patients with MuSK subtype Myasthenia Gravis

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MuSKCAART™ Phase 1 study of DSG3-CAART

Orphan Drug Designation

Fast Track Designation

Trial in patients with MuSK MG evaluating up to 5x dose range (5 x 10^8 up to 2.5 x 10^9 cells)

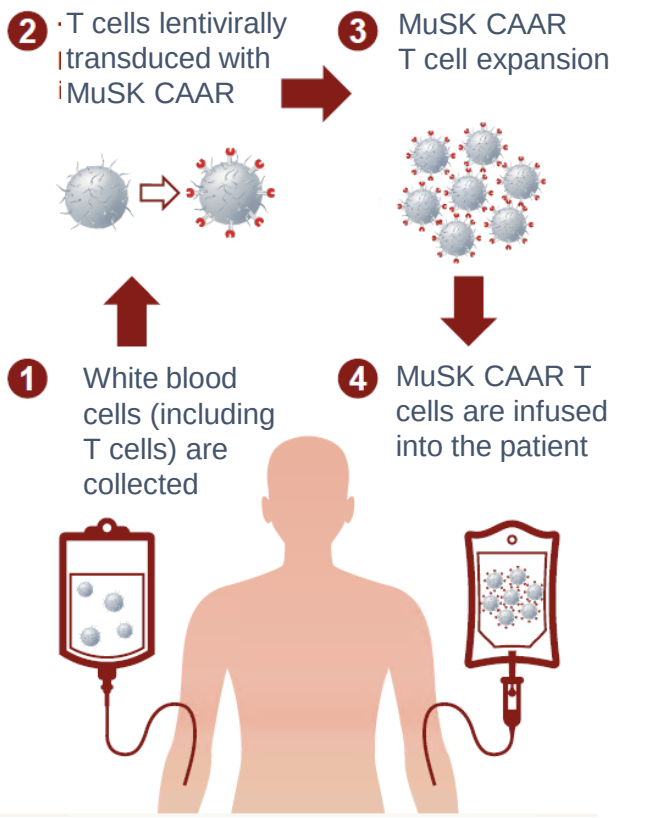
Screening → Apheresis → **MuSK-CAART INFUSION** → TREATMENT & FOLLOW-UP PERIOD → Next Patient

Major Inclusion Criteria

- Age: ≥18, confirmed diagnosis
- Inadequately managed by standard immunosuppressive therapies
- Confirmed diagnosis
- Active disease

Major Exclusion Criteria

- Recent rituximab
- Prednisone > 0.25 mg/kg/day
- Other autoimmune disorder requiring immunosuppressive therapies
- Recent investigational treatment
- ALC < 1,000 at screening



Adjunctive immunosuppressants are stopped; prednisone tapered to low dose prior to infusion

Part A Cohorts	Subjects	Dose
A1	2 (+4)	5 x 10^8
A2	2 (+4)	2.5 x 10^9

5-fold dose escalation

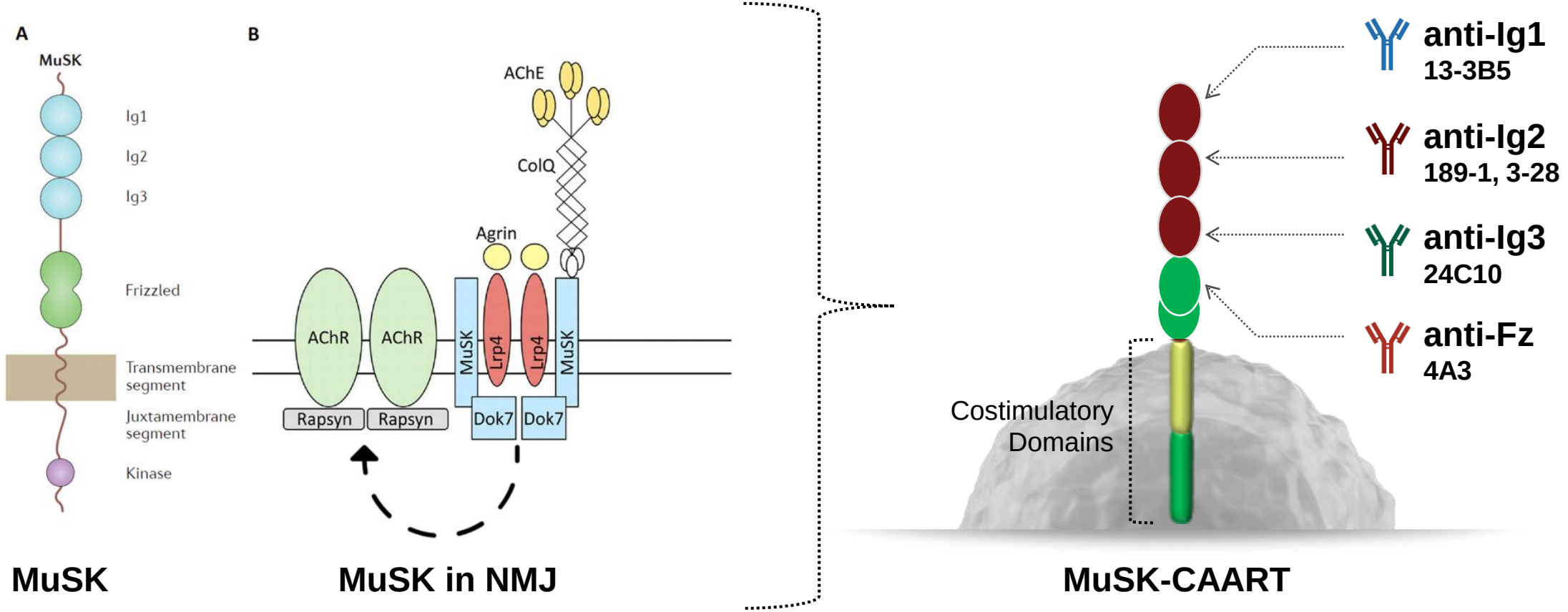
Primary objective:
Determine the maximum tolerated dose of MuSK-CAART

Primary endpoint:
AEs, DLTs, related to MuSK-CAART within 3 months of infusion

Secondary objectives:
- Manufacturing success rate
- **MuSK-CAART persistence**
- **Anti-MuSK antibody titer changes**
- **Clinical disease activity score changes**

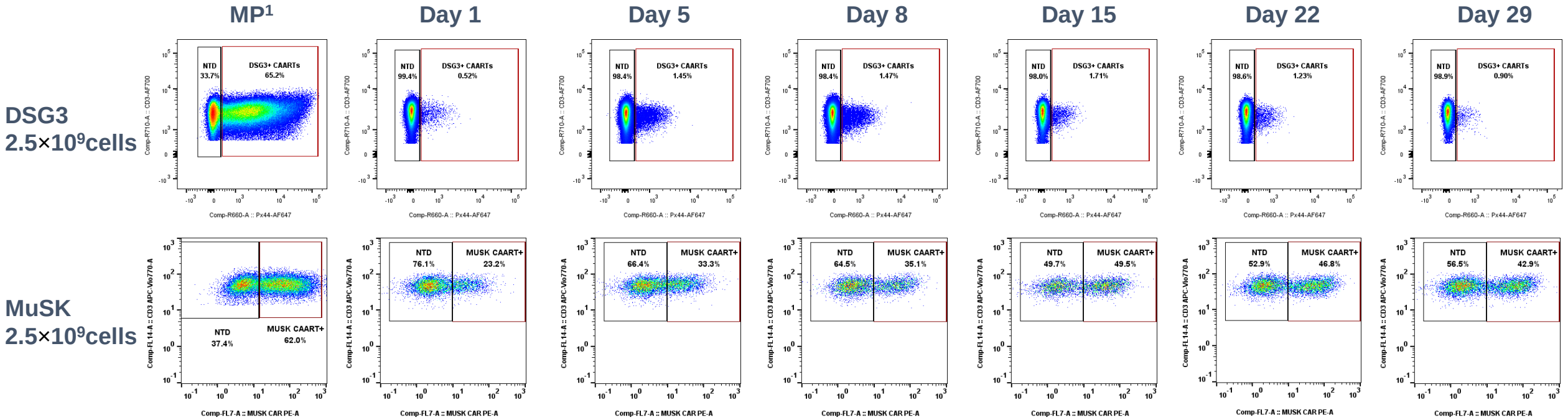
MuSK-CAART design

Extracellular domain of the CAAR T is designed to bind all MuSK reactive BCRs

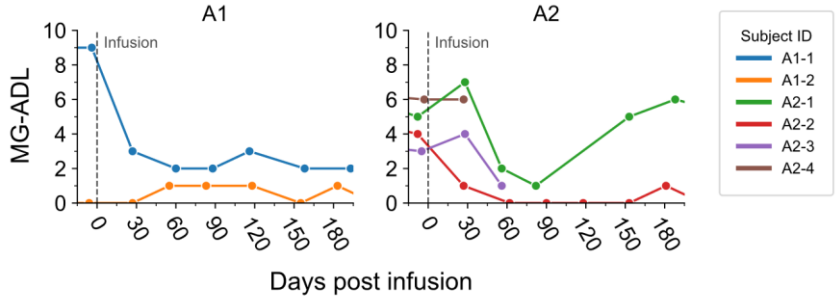


DSG3- versus MuSK-CAAR expression in T cells post-infusion

MuSK-CAAR MFI remains comparable to that in the MP



T cell expansion is seen with biological activity in the absence of preconditioning



1. MP – Manufactured product

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