Cabaletta Bio®

RESET-Myositis™: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), a Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Idiopathic Inflammatory Myopathies

Tahseen Mozaffar[1], Elie Naddaf[2], Nizar Chahin[3], Erin Wilfong[4], Courtney Little[5], Carl DiCasoli[5], Claire Miller[5], Jenell Volkov[5], Daniel Nunez[5], Thomas Furmanak[5], Jason Stadanlick[5], Larissa Ishikawa[5], Zachary Vorndran[5], Alexandra Ellis[5], Jazmean Williams[5], Steve Flanagan[5], Quynh Lam[5], Fatemeh Hadi-Nezhad[5], **Raj Tummala[5],** Samik Basu[5], David Chang[5]

1. University of California, Irvine, Irvine, USA; 2. Mayo Clinic, Rochester, USA; 3. Oregon Health and Science University, Portland, USA; 4. Vanderbilt University Medical Center, Nashville, USA; 5. Cabaletta Bio, Philadelphia, USA

RESET Myositis™

June 2025

Disclaimer

This presentation, including any printed or electronic copy of these slides, the talks given by the presenters, the information communicated during any delivery of the presentation and any question and answer session and any document distributed at or in connection with the presentation (collectively, the "Presentation") has been prepared by Cabaletta Bio, Inc. ("we," "us," "our," "Cabaletta" or the "Company") and may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, and include, but are not limited to, express or implied statements regarding our current beliefs, expectations and assumptions regarding: our business, future plans and strategies for our technology; our ability to grow our autoimmune-focused pipeline; the ability to capitalize on and potential benefits resulting from our research and translational insights, including those related to any similarly-designed constructs or dosing regimens; the anticipated market opportunities for rese-cel in patients with autoimmune diseases; our expectations around the potential success and therapeutic and clinical benefits of rese-cel, as well as our ability to successfully complete research and further development and commercialization of our drug candidates in current or future indications, including the timing and results of our clinical trials and our ability to conduct and complete clinical trials; expectation that clinical results will support rese-cel's safety and activity profile; our plan to leverage increasing clinical data and a unique development program for rese-cel; the clinical significance and impact of clinical data read-outs, including the progress, results and clinical data from each of the patients dosed with rese-cel in the Phase 1/2 RESET-Myositis, RESET-SLE and the RESET-SSc trials and our other planned activities with respect to rese-cel; our belief that rese-cel has the potential to provide drug-free, durable meaningful clinical responses, through an immune reset, including the potential for achieving drug-free remission in patients with refractory myositis; the Company's advancement of separate Phase 1/2 clinical trials of rese-cel and advancement of the RESET-PV and RESET-MS trials, including updates related to status, safety data, efficiency of clinical trial design and timing of data read-outs or otherwise; our ability to leverage our experience in autoimmune cell therapy; our ability to enroll the requisite number of patients, dose each dosing cohort in the intended manner and timing thereof, and advance the trial as planned in our Phase 1/2 clinical trials of rese-cel; the timing any planned regulatory filings for our development programs, including IND applications and interactions with regulatory authorities, including such authorities' review of safety information from our ongoing clinical trials and potential registrational pathway for rese-cel; our ability to increase enrollment from our rapidly expanding clinical network in the RESET clinical trial program in the US and Europe; our ability to obtain and maintain regulatory approval of our product candidates, including our expectations regarding the intended incentives conferred by and ability to retain regulatory designations and the anticipated initiation of registrational cohorts and potential BLA submission; our belief regarding alignment with FDA on registrational trial design and timing thereof; our ability to accelerate our pipeline to approval and launch and to develop meaningful therapies for patient and the ability to optimize collaborations on our development programs; our ability to contract with third-party suppliers and manufacturers; our ability to execute our manufacturing strategy to enable expansion of clinical supply and efficiently scale commercial supply for rese-cel; our potential commercial opportunities, including value and addressable market, for our product candidates. 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 development activities and clinical trials, risks related to our ability to demonstrate sufficient evidence of safety, efficacy and tolerability in our clinical trials, the risk that the results observed with the similarly-designed construct, including, but not limited to, dosing regimen, are not indicative of the results we seek to achieve with rese-cel, the risk that signs of biologic activity or persistence may not inform long-term results, risks related to clinical trial site activation or enrollment rates that are lower than expected, 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 regulatory 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, risks related to volatile market and economic conditions and our ability to fund operations and continue as a going concern. 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 and quarterly report on From 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our other 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.

Disclosures

Author		Disclosures
Raj Tummala		**Employee**: Cabaletta Bio
Tahseen Mozaffar		Sanofi, Amicus; AnnJi; Argenx; Astellas Gene Therapy; AstraZeneca; Janssen; Spark Therapeutics; UCB; Arvinas; AskBio; Horizon Therapeutics; Maze Therapeutics; Sarepta; Fate Therapeutics; Bristol Myers Squibb (BMS); Cartesian Therapeutics; Grifols; ML-Bio; Valerion
Elie Naddaf		Johnson & Johnson
Nizar Chahin		No relevant disclosures
Erin Wilfong		AstraZeneca, Boehringer Ingelheim
Courtney Little Carl DiCasoli Claire Miller Jenell Volkov Thomas Furmanak Fatemeh Hadi Nezhad Quynh Lam Larissa Ishikawa Daniel Nunez	Jason Stadanlick Zachary Vorndran Alexandra Ellis Jazmean Williams Steve Flanagan Samik Basu David Chang	**Employees:** Cabaletta Bio

Cabaletta Bio®

Myositis: A Disease of Significant Unmet Need

~80K U.S. patients and ~85K patients in Europe with IIM subtypes which are frequently severe, with limited treatment options[1–7]

Idiopathic inflammatory myopathies (IIMs)[1]

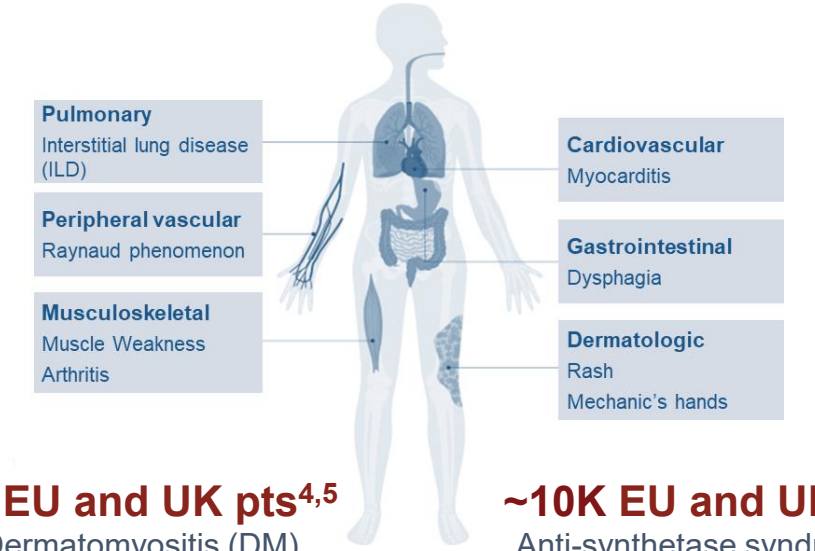
- A group of systemic autoimmune diseases characterized by multi-organ inflammation and muscle weakness

High burden on function & quality of life[1]

- Moderate to severe disability in ~50% of patients[2]
- The risk of mortality is ~3 times higher than the general population, primarily due to cancer and lung & cardiac complications[3]
- Mainstay of therapy is glucocorticoids with immunomodulators (e.g., methotrexate, azathioprine, mycophenolate, rituximab)
  - Limited approved therapies in the EU and UK
  - Many patients have disease that remains refractory
  - Therapies carry potential long-term side effects

Potential manifestations & subtype prevalence in Europe

Key myositis subtypes based on underlying immune mechanisms & clinical characteristics[1]



~59K EU and UK pts[4,5]
Dermatomyositis (DM)

~10K EU and UK pts[4,6,7]
Anti-synthetase syndrome (ASyS)

~16K EU and UK pts[4]
Immune-mediated necrotizing myopathy (IMNM)

1. Lundberg IE, et al. *Nat Rev Dis Primers.* 2021;7(1):86. 2. Opinc AH, et al. *Rheumatol Int.* 2019;39(7):1213-1220. 3. Marie I. Morbidity and mortality in adult polymyositis and dermatomyositis. Curr Rheumatol Rep. 2012;14(3):275-285. 4. Khoo T, et al. *Nat Rev Rheumatol.* 2023;19(11):695–712. 5. Kronzer VL, et al. *Arthritis Care Res (Hoboken).* 2023;75(2):348–355. 6. Coffey C, et al. *Arthritis Rheumatol.* 2021;73 (Suppl 9). Abstr. No. 1022. 7. Orphanet: Antisynthetase syndrome. Available at: https://www.orpha.net/en/disease/detail/81 (accessed June 2025).

B Cells Play a Central Role in the Pathogenesis of Myositis

Current therapeutic options may result in incomplete B cell depletion in tissues and lymphoid organs[1]

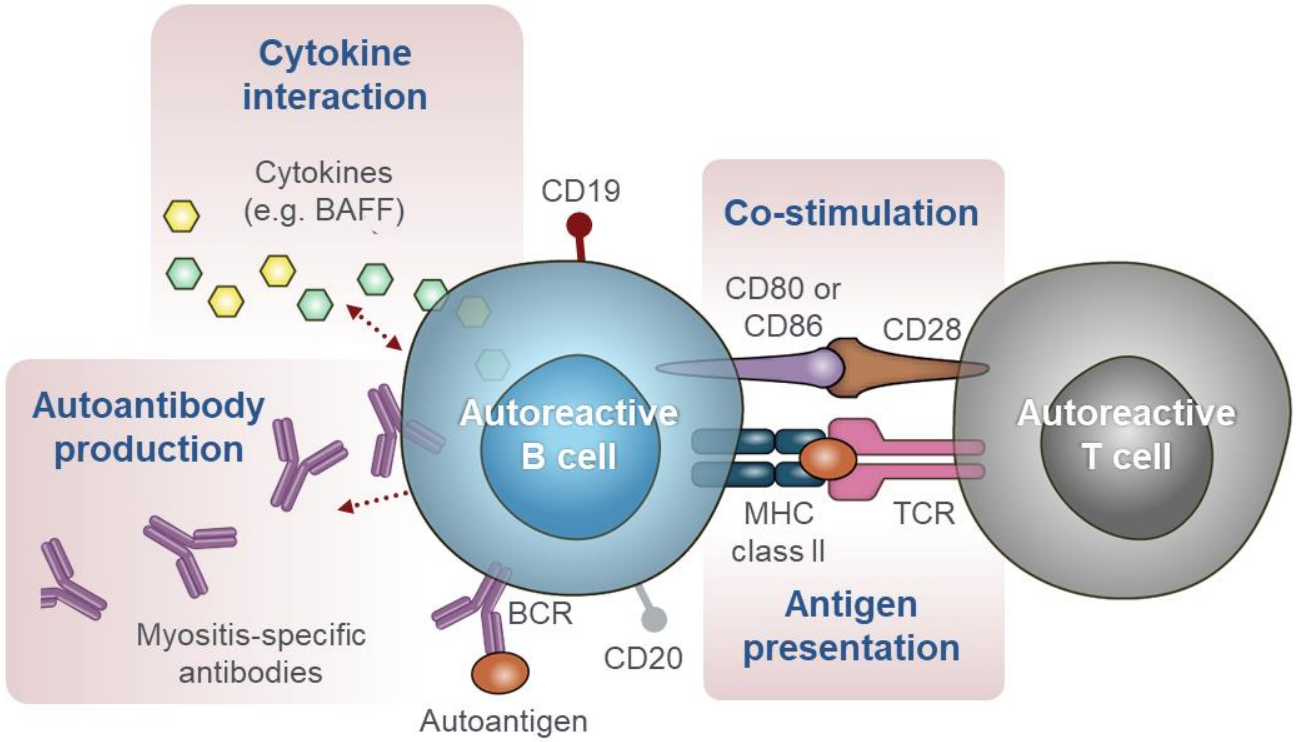


Image adapted from Rubin SJS, et al. 2019[2]

In myositis:

- B cells are key drivers of immune dysregulation through multiple mechanisms[3]
- B cell-targeted therapies offer a promising approach for treatment-refractory cases[3]
- Persistent B cell activity in muscle and lung tissue may contribute to treatment resistance using currently available therapies[3]

BAFF, B cell activating factor; BCR, B cell receptor; CD, cluster of differentiation; MHC, major histocompatibility complex; TCR, T cell receptor.

1. Schett G, et al. *Ann Rheum Dis*. 2024;83(11):1409–1420. 2. Rubin SJS, et al. *Nat Rev Rheumatol.* 2019;15(5):303–315. 3. Liu T, et al. *Clin Rev Allergy Immunol*. 2025;68(1):40.

Rese-cel (CABA-201): CD19-CAR T Designed For Autoimmunity

Cabaletta's CD19 binder with similar in vitro & in vivo activity to FMC63[1,2] (binder used in academic report[3])

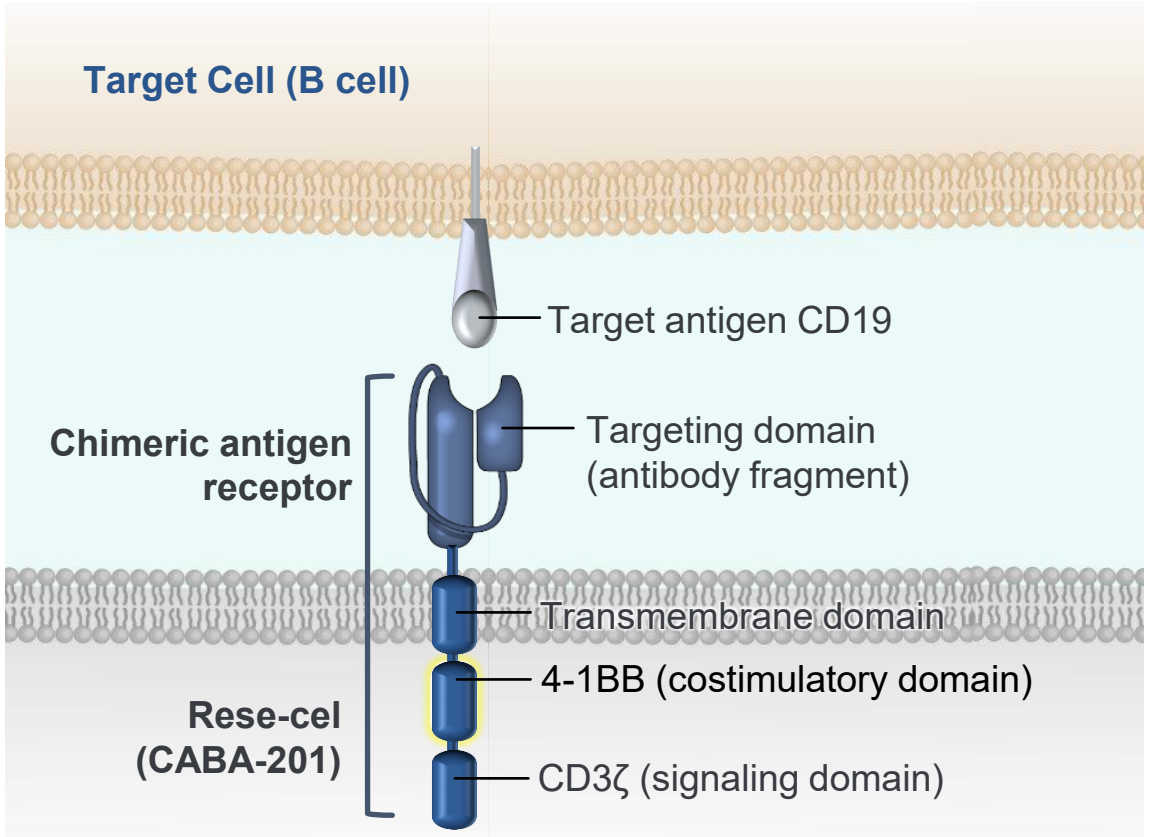


Image adapted from June CH and Sadelain M. 2018.[4]

Rese-cel product design and clinical/translational data

4-1BB costimulatory domain with fully human binder[1]

- Binder with similar affinity and biologic activity to academic FMC63 binder while binding to the same epitopes[1,2]

Same weight-based dose as in academic studies[3,5]

- Potential to provide immune reset based on initial clinical and translational data[5]

Initial patients treated with rese-cel have shown clinical responses with safety data that supports development in autoimmune diseases[6]

CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel.

1. Peng BJ, et al. *Mol Ther Methods Clin Dev*. 2024;32(2):101267. 2. Dai Z, et al. *J Cell Physiol*. 2021;236(8):5832–5847. 3. Müller F, et al. *N Engl J Med*. 2024;390(8):687–700. 4. June CH, Sadelain M. *N Engl J Med*. 2018;379(1):64–73. 5. Volkov J, et al. *Mol Ther*. 2024;32(11):3821–3828. 6. Sheikh S, et al. *Arthritis Rheumatol*. 2024;76 (Suppl 9). Abstr. No. 1733.

Autologous CAR T Cell Therapy: How Rese-cel is Manufactured

Designed to combine antibodies' targeting ability with the cell-killing machinery of a patient's own T cells[1,2]

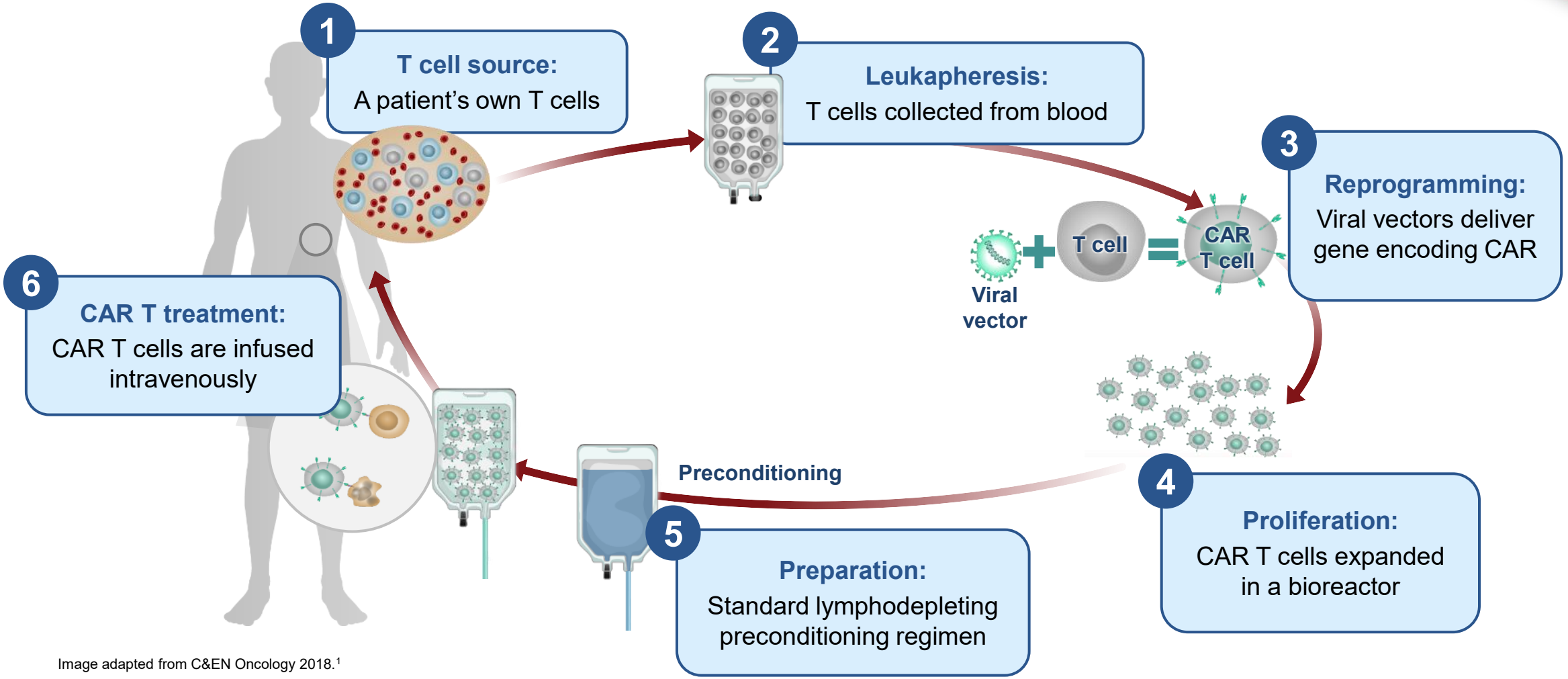


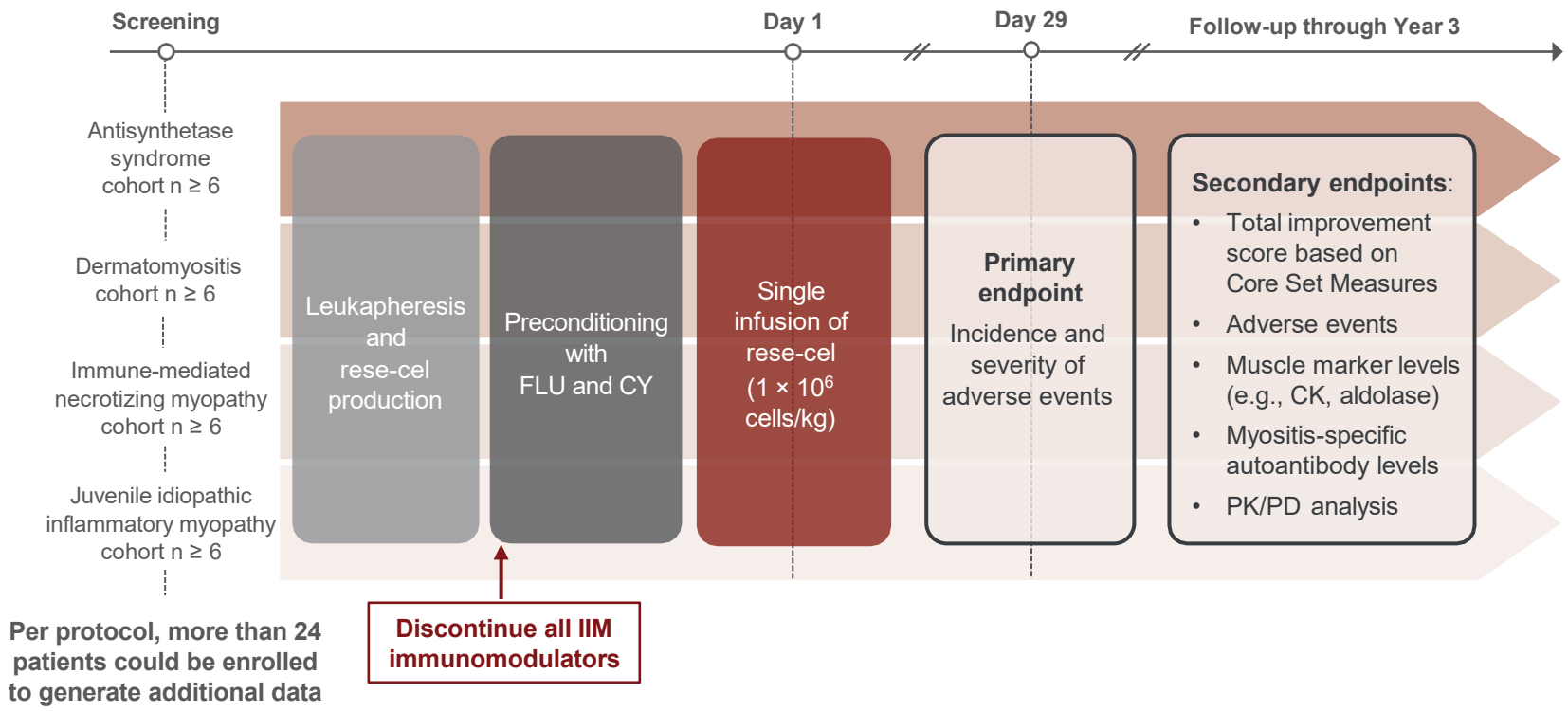
Image adapted from C&EN Oncology 2018.[1]

CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel.

1. C&EN Oncology. 2024. Available at: https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19 (accessed May 2025). 2. Peng BJ, et al. *Mol Ther Methods Clin Dev*. 2024;32(2):101267.

RESET *Myositis*™ Study Design [1,2]

Enrolling patients with moderate to severe disease that is refractory to standard of care



Key Inclusion Criteria[1,2]

- A definite or probable clinical diagnosis of IIM (2017 EULAR/ACR classification criteria)
- **For adult IIM cohorts**: Age ≥18 and ≤75 with a diagnosis of **antisynthetase syndrome, dermatomyositis, or immune-mediated necrotizing myopathy** based on presence of serum myositis-specific antibodies (MSA)
- **For JIIM cohort:** Age ≥6 and ≤17 with presence of at least one MSA or myositis-associated antibody (MAA)

Key Exclusion Criteria[1,2]

- Cancer-associated myositis or malignancy within the last 5 years
- Significant lung or cardiac impairment
- Previous CAR T cell therapy and/or HSCT
- Treatment with B cell-depleting agent within prior ~6 months

ACR, American College of Rheumatology; CAR T, chimeric antigen receptor T cells; CK, creatine kinase; CY, cyclophosphamide; EULAR, European Alliance of Associations for Rheumatology; FLU, fludarabine; HSCT, hematopoietic stem cell transplant; IIM, idiopathic inflammatory myopathy; JIIM, juvenile IIM; MAA, myositis-associated antibody; MSA, myositis-specific antibodies; PK/PD, pharmacokinetic/pharmacodynamic; rese-cel, resecabtagene autoleucel; RESET™, REstoring Self Tolerance.

1. Cabaletta Bio – Data on File. 2. NCT06154252. Available online at: www.clinicaltrials.gov/study/NCT06154252 (accessed May 2025).

Cabaletta Bio®

Baseline Characteristics: First 8 Patients in RESET-Myositis*

All patients had active, refractory disease and most had failed IVIg and B cell-targeting therapies

	RESET-Myositis™							
Cohort	**DM**		**ASyS**		**IMNM**			
Patient	**DM-1**	**DM-2**	**ASyS-1**	**ASyS-2**	**IMNM-1**	**IMNM-2**	**IMNM-3**	**IMNM-4**
Age, sex	57 M	45 F	39 M	48 F	33 M	60 M	55 M	64 M
Disease duration (y)	~4	~2	~4	~15	~2	~4	~1	~6
Autoantibodies	SAE	NXP-2; Ro	Jo-1; Ro-52	Jo-1; Ro-52	SRP	HMGCR	SRP; Ro-52	HMGCR
Baseline disease activity†	**MMT-8**							
	131	117	119	140	130	126	105	108
	CK (U/L)							
	94	39	502	121	617	4725	1447	529
Therapies at Screening	GC, MMF, HCQ	IVIg, MMF, HCQ	GC, IVIg, TAC	GC, IVIg, MMF, TAC	GC, MTX	GC, IVIg	MTX, AZA	GC, IVIg, MMF
Other prior therapies	IVIg	GC, RTX, TAC	RTX, MMF, TOC, AZA	RTX, MTX, MMF, AZA	RTX, IVIg	RTX, MTX, MMF	GC	AZA
GC dose at Screening (mg/day)	20	NA	10	5	5	5	NA	10

*As of May 6, 2025.
†Baseline disease activity = activity before preconditioning.
ASyS, antisynthetase syndrome; AZA, azathioprine; CK, creatine kinase; DM, dermatomyositis; GC, glucocorticoid; HCQ, hydroxychloroquine; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IMNM, immune-mediated necrotizing myopathy; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; MTX, methotrexate; NXP, nuclear matrix protein; RESET, REstoring SElf-Tolerance; RTX, rituximab; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TAC, tacrolimus; TOC, tocilizumab; U/L, units per liter; y, years.
Cabaletta Bio: Data on File.

Incidence of Relevant and Related Serious Adverse Events*

No CRS in 4 of 8 patients and no ICANS in any patients

	RESET-Myositis™							
Cohort	**DM**		**ASyS**		**IMNM**			
Patient	**DM-1**	**DM-2**	**ASyS-1**	**ASyS-2**	**IMNM-1**	**IMNM-2**	**IMNM-3**	**IMNM-4**
CRS†	None	Grade 1	Grade 1	Grade 1	None	None	Grade 1	None
ICANS†	None	None	None	None	None	None	None	None
Serious infections‡	None	None	None	None	None	None	None	None
Related SAEs (Grade)§ (excluding CRS and ICANS)	None	None	None	None	None	None	None	None

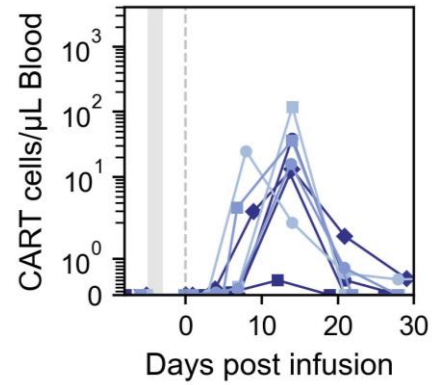
*As of May 6, 2025; primary endpoint is incidence and severity of adverse events through Day 29.
†Graded per ASTCT Consensus Grading Criteria. DM-1, DM-2, ASyS-1, ASyS-2, and IMNM-3 **received** medication for seizure prophylaxis. Tocilizumab was administered for CRS for DM-2, ASyS-1, ASyS-2, and IMNM-3.
‡Coded in System Organ Class of Infections and Infestations and meets seriousness criteria.
§As assessed per US Food and Drug Administration guidelines.
ASTCT, American Society for Transplantation and Cellular Therapy; ASyS, antisynthetase syndrome; CRS, cytokine release syndrome; DM, dermatomyositis; ICANS, immune effector cell-associated neurotoxicity syndrome; IMNM, immune-mediated necrotizing myopathy; SAE, serious adverse event; RESET, REstoring SElf-Tolerance.
Cabaletta Bio: Data on File.

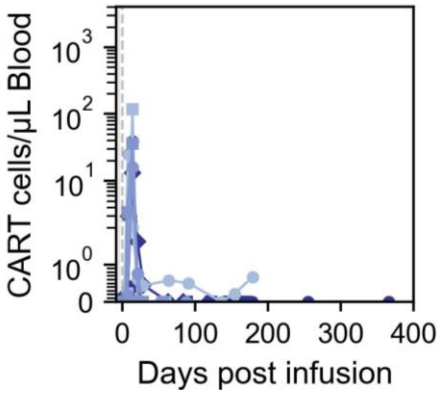
Cabaletta Bio®

Rese-cel Expansion and B Cell Kinetics

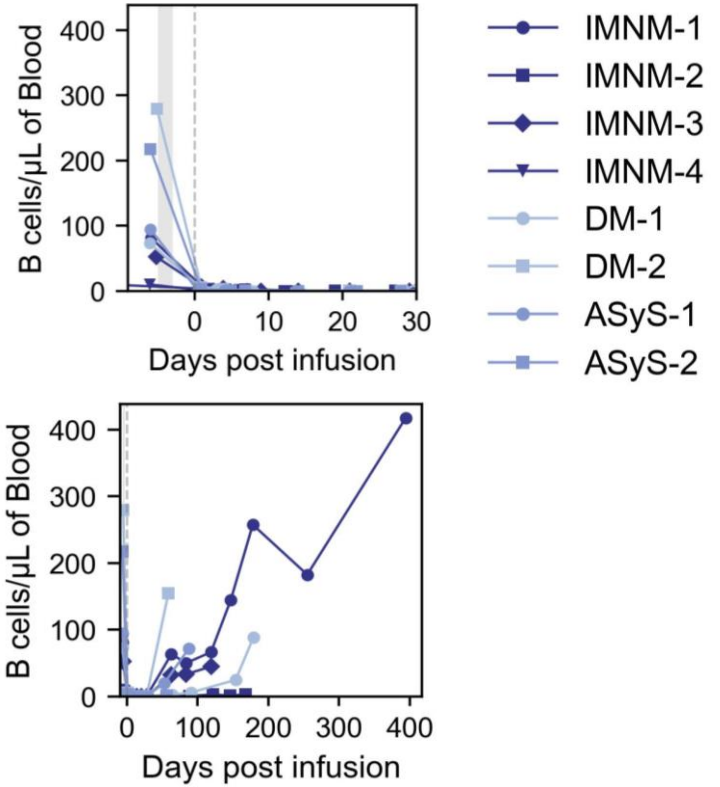
Peak rese-cel expansion and transient peripheral B cell depletion occurred within 1-2 weeks post-infusion

Rese-cel Pharmacokinetics





B Cell Kinetics

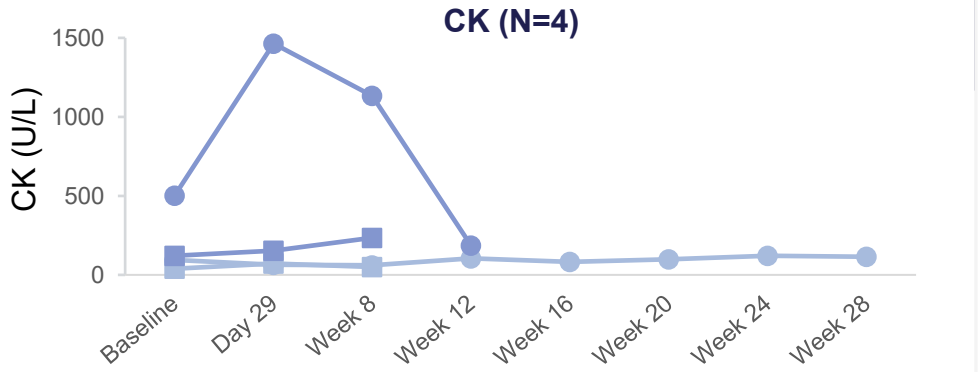


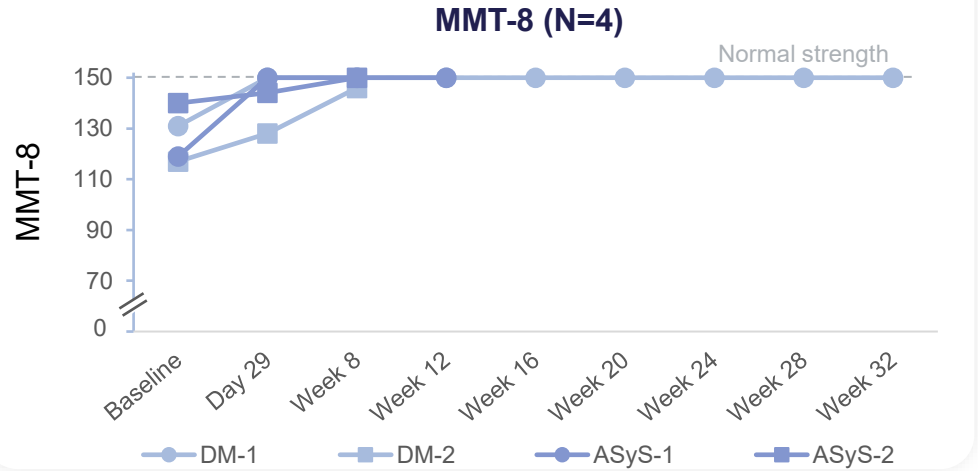
Peripheral B cells began repopulating 2 to 3 months after rese-cel in patients with sufficient follow-up

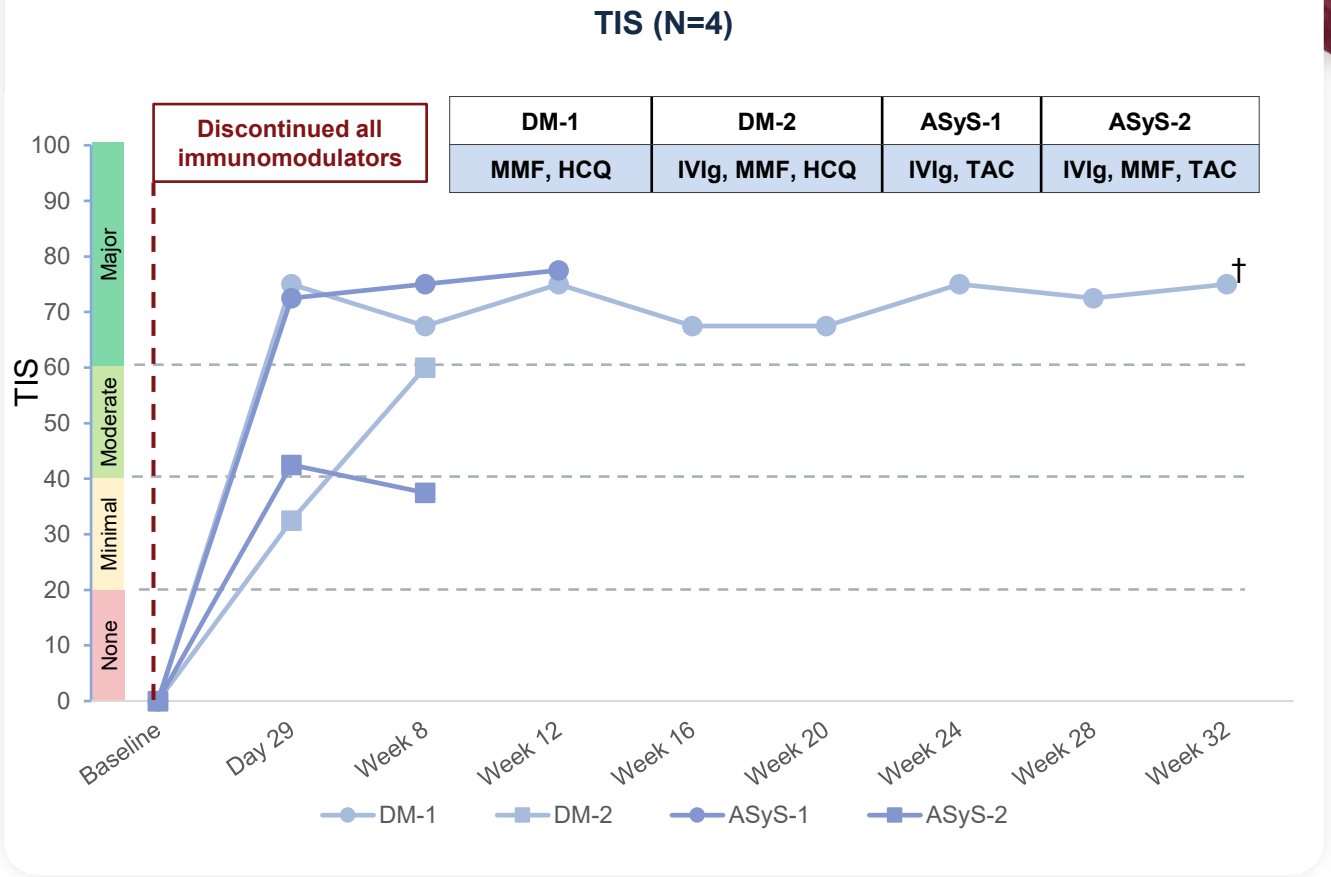
ASyS, antisynthetase syndrome; CAR, chimeric antigen receptor; DM, dermatomyositis; IMNM, immune-mediated necrotizing myopathy; rese-cel, resecabtagene autoleucel.
Cabaletta Bio: Data on File.

Efficacy Data in DM and ASyS Patients Following Rese-cel Infusion*

Clinical responses have been observed off immunomodulators and glucocorticoids in all patients





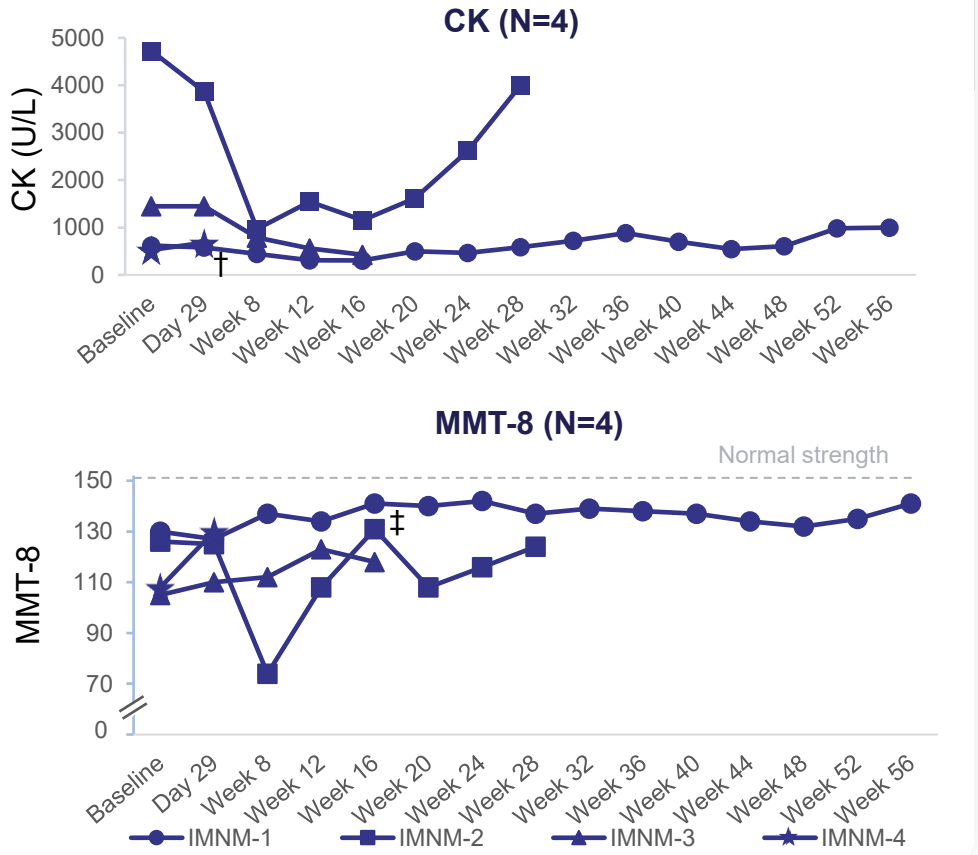


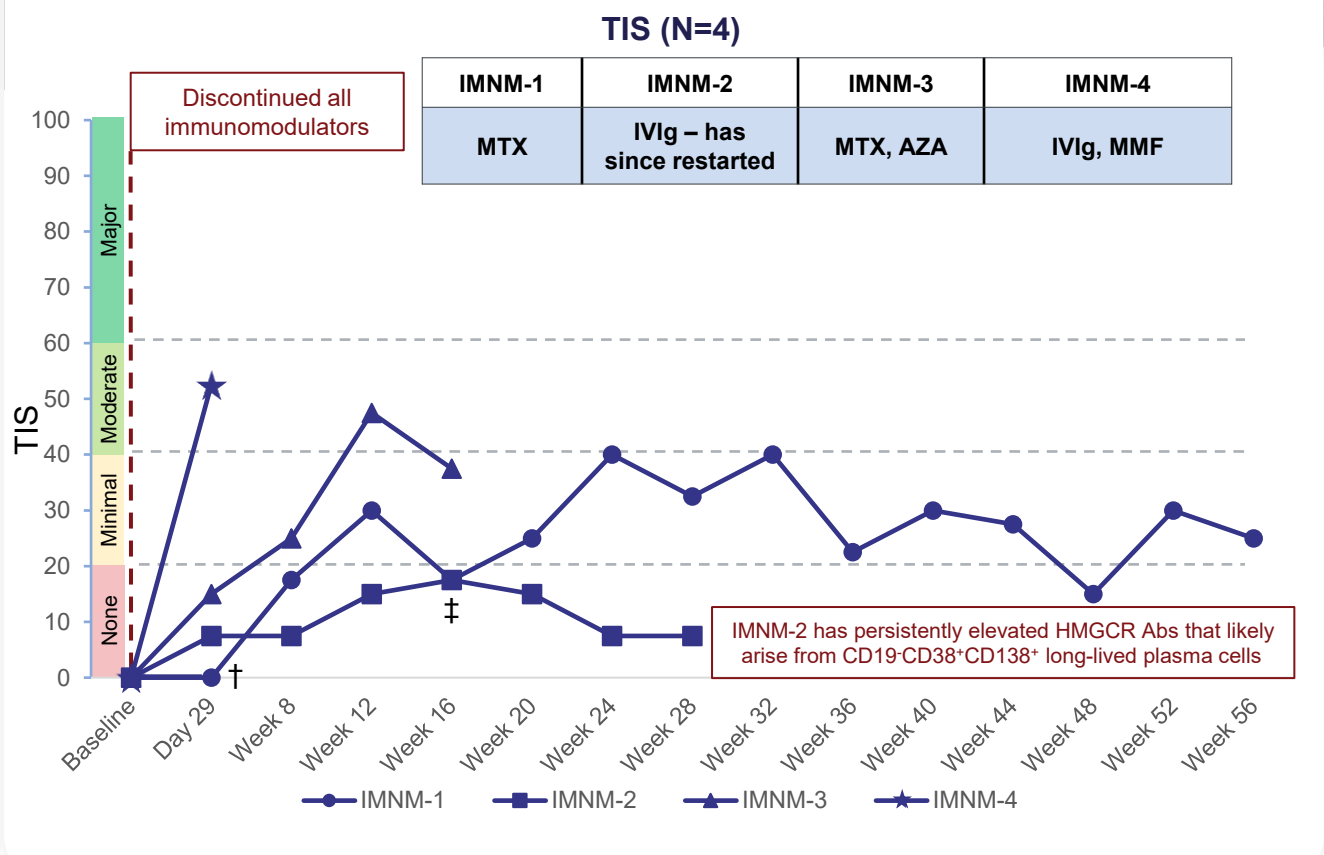
TIS responses to rese-cel among all DM and ASyS patients show potential for achieving drug-free remission in patients with refractory myositis

*As of May 6, 2025. †DM-1 Week 32 CK value not available; Week 28 CK value used for TIS calculation.
ASyS, antisynthetase syndrome; CK, creatine kinase; DM, dermatomyositis; HCQ, hydroxychloroquine; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; rese-cel, resecabtagene autoleucel; TAC, tacrolimus; TIS, total improvement score; U/L, units per liter.
Cabaletta Bio: Data on File.

Efficacy Data in IMNM Patients Following Rese-cel Infusion[1]*

Clinical responses have been observed off immunomodulators in 3 of 4 patients





Initial clinical responses in IMNM-1, IMNM-3, and IMNM-4 are consistent with published data[1,2]; slower and more modest TIS response in IMNM compared to other myositis subtypes

*As of May 6, 2025. †IMNM-1 Day 29 CK measurement was unavailable; Day 22 measurement was used in its place and in calculation of the TIS score. ‡IMNM-2 Week 16 MMT-8 measurement was normalized to a total score of 150, calculated based on the collected value (96) and the maximum possible value (110). The normalized MMT-8 score was used to calculate the TIS for IMNM-2 at Week 16.

AZA, azathioprine; CK, creatine kinase; IMNM, immune-mediated necrotizing myopathy; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MMT-8, manual muscle testing 8; MTX, methotrexate; rese-cel, resecabtagene autoleucel; TIS, total improvement score; U/L, units per liter.

1. Cabaletta Bio: Data on File. 2. Schett, G. 'CAR-T Cell Therapy: "The Future is Now."' 5th Global Conference on Myositis. iMyoS. Pittsburgh, PA.

Cabaletta Bio®

Efficacy Data Following Rese-cel Infusion*

Clinical responses have been observed in 7 of 8 patients after discontinuing all immunomodulatory medications

	RESET-Myositis™							
Cohort	**DM**		**ASyS**		**IMNM**			
Patient	**DM-1**	**DM-2**	**ASyS-1**	**ASyS-2**	**IMNM-1**	**IMNM-2**	**IMNM-3**	**IMNM-4**
Latest follow-up	32 weeks	8 weeks	12 weeks	8 weeks	56 weeks	28 weeks	16 weeks	4 weeks
TIS Response	Major	Major	Major	Minimal to moderate	Minimal to moderate†	No change‡	Minimal to moderate	Moderate
GC-free	✓	✓	✓	✓	✓	--	✓	--§
IM-free	✓	✓	✓	✓	✓	--	✓	✓

*As of May 6, 2025.
†Minimal to moderate improvement at all time points from Week 20, except for Week 48. ‡The subject experienced an unrelated life-threatening pulmonary embolism resulting in prolonged hospitalization and critical illness myopathy and was treated with intravenous immunoglobulin and prednisone after the Week 12 visit, confounding assessments of treatment response. Subject then began weekly IVIg after the Week 24 visit. § Tapering prednisone dose.
ASyS, antisynthetase syndrome; DM, dermatomyositis; GC, glucocorticoids; IM, immunomodulatory medication; IMNM, immune-mediated necrotizing myopathy; IVIg, intravenous immunoglobulin; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; TIS, total improvement score.
Cabaletta Bio: Data on File.

Summary from Clinical and Translational Data: RESET Myositis™

- Rese-cel was generally well tolerated across 8 IIM subjects treated to date
  - No CRS in 4 of 8 subjects and transient fever (grade 1 CRS) observed in 4 subjects
  - No ICANS in any of the 8 subjects
- Rese-cel provided evidence of efficacy off all immunomodulatory medications in 7 of 8 patients
  - Rapid and robust drug-free clinical responses in all 4 patients with refractory DM and ASyS
  - Clinically meaningful immunomodulatory-free responses in 3 of 4 patients with refractory IMNM
- Rese-cel peak expansion was observed at approximately 13 days after infusion
- B cells were rapidly and transiently depleted in peripheral blood following rese-cel infusion
  - B cells began repopulating 2 to 3 months after rese-cel infusion in patients with sufficient follow-up
- **Based on these data and alignment reached with the FDA, Cabaletta is planning to initiate two registrational myositis cohorts of ~15 patients each this year[1]**

*As of May 6, 2025

CRS, cytokine release syndrome; FDA, US Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; IIM, idiopathic inflammatory myopathy, rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance.

1. Cabaletta Bio. (15 May 2025), [Press Release], https://www.cabalettabio.com/news-media/press-releases/detail/128/cabaletta-bio-announces-2027-rese-cel-bla-submission

Acknowledgments

This is the collective work of many individuals

Patients and caregivers involved in the RESET clinical program

Site investigators and staff involved with these patients from the RESET clinical program

- Mayo Clinic, Rochester
- University of California, Irvine
- Oregon Health & Science University
- Vanderbilt University Medical Center

Cabaletta Bio team

- Biostatistics
- Clinical Development
- Clinical Operations
- Computational Biology
- Manufacturing
- Medical Affairs
- Translational Medicine
- Quality and Compliance
- Regulatory Affairs