In response to: "Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee" by Greco et al.

James F. Howard, Jr.[a,*] Susan M. Manzi,[b] Milos D. Miljkovic,[c] Tuan Vu,[d] and Tahseen Mozaffar[e]

[a]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b]Allegheny Health Network, Lupus Center of Excellence, Pittsburgh, PA, USA
[c]Cartesian Therapeutics, Gaithersburg, MD, USA
[d]University of South Florida, Tampa, FL, USA
[e]University of California Irvine, CA, USA

We would like to highlight four points regarding recent EBMT recommendations for the use of chimeric antigen receptor (CAR) T cells in autoimmune diseases.[1] First, the recommendations are based on conventional, integrating vector-based CAR-Ts, which require lymphodepletion chemotherapy, inpatient administration and prolonged post-infusion monitoring. In phase 1/2 trials in generalized myasthenia gravis, mRNA CAR-Ts were administered outpatient, without lymphodepletion, and resulted in no cytokine release syndrome or neurotoxicity.[2] Different monitoring recommendations are needed for mRNA CAR-T and other cellular therapies associated with an improved safety profile. Second, "stable disease" is noted as a contraindication for administering cellular therapy in patients with neurologic autoimmune disease, in contrast to the statement that advanced cell therapies should be considered "in case of fluctuating or inadequate clinical response to second-line immunosuppressive treatment". While we agree with the latter phrasing, the common meaning of "stable disease" implies unchanged symptoms over time regardless of severity. The term should thus be clearly defined or reconsidered. Third, many specialties have already defined criteria for what constitutes meaningful response and unacceptable toxicity. For example, International Consensus Guidelines for myasthenia gravis emphasize that medication side effects should be no greater than grade 1.[3] These considerations should be integrated for each specialty. Lastly, the referenced methodology by the EBMT practice harmonization and guidelines committee[4] does not state which if any consensus methodology was used (e.g., modified Delphi appropriateness method).[5] As the recommendations affect many stakeholders across several disciplines, the method by which inter and intra-disciplinary consensus was reached should be clarified.

Contributors
James F. Howard, Jr. and Milos D. Miljkovic wrote the original draft. Tahseen Mozaffar, Tuan Vu and Suzan M. Manzi reviewed and edited the letter. All authors have read and approve the final manuscript.

Declaration of interests
James F Howard Jr: Research funding (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, PCORI, and UCB Pharma; Consulting fees from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd, Biologix Pharma, F. Hoffmann-LaRoche Ltd, Horizon Therapeutics plc (now Amgen), Merck EMB Serono, NMD Pharma, Novartis Pharma, Regeneron Pharmaceuticals, Sanofi US, UCB Pharma, and Zai Labs; Speaker fees from AcademicCME, argenx, CheckRare CME, Medscape CME, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, UCB Pharma; He served on advisory boards for Alexion AstraZeneca Rare Disease, argenx, Amgen, F. Hoffmann-LaRoche Ltd, Merck EMB Serono, Novartis Pharma, UCB Pharma and has received travel support from Alexion AstraZeneca Rare Disease, argenx, UCB Pharma and Zai Labs.

Suzan M Manzi: Research funding: HGS/GSK, AstraZeneca, AbbVie, Amgen, Cartesian Therapeutics, BMS; Consulting: AstraZeneca, Cartesian, Exagen, GSK, Lily, UCB; Participation in DSMB: NIAID, NIH, Miltenyi; Board Member, Medical Director: Lupus Foundation of America.

Milos D Miljkovic: Employee and equity ownership: Cartesian Therapeutics.

Tuan Vu: USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, Dianthus Therapeutics, Immunovant, Johnson & Johnson, Regeneron Pharmaceuticals, and UCB Pharma, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx, and CSL Behring. He served on advisory boards and/or performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Amgen, Dianthus Therapeutics, Johnson & Johnson, ImmunAbs, and UCB Pharma.

Tahseen Mozaffar: Grants or contracts: the Myositis Association, the Muscular Dystrophy Association, the National Institutes for Health and from the following sponsors: Alexion, Amicus, AnnJi, Argenx, Audentes (now Astellas Gene Therapy), Cabaletta, Cartesian Therapeutics, Grifols, ML-Bio, Momenta, Ra Pharmaceuticals, Sanofi, Spark Therapeutics, and Valerion; Consulting fees: Alexion, Amicus, AnnJi, Argenx, Arvinas, Ask Bio, Audentes, AvroBio, Horizon Therapeutics, Immunovant, Maze Therapeutics, Shionogi, Momenta (now Janssen), Sanofi-Genzyme,

eClinicalMedicine 2024;78: 102918
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102918

DOI of original article: https://doi.org/10.1016/j.eclinm.2024.102476
*Corresponding author.
E-mail address: howardj@neurology.unc.edu (J.F. Howard).

Spark Therapeutics, UCB, and Zogenix; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Sanofi, Alexion; Support for attending meetings and/or travel: Amicus, Audentes, Sanofi; Participation on a Data Safety Monitoring Board or Advisory Board: Acceleron, Applied Therapeutics (Chair), Sarepta, Sirolimus in IBM trial (Chair), and the NIH. Leadership or Fiduciary role: the Myositis Association and the Neuromuscular Disease Foundation.

References

1 Greco R, Alexander T, Papa ND, et al. Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee. *eClinicalMedicine*. 2024;69. https://doi.org/10.1016/j.eclinm.2024.102476.

2 Granit V, Benatar M, Kurtoglu M, et al. Safety and clinical activity of autologous RNA chimeric antigen receptor T-cell therapy in myasthenia gravis (MG-001): a prospective, multicentre, open-label, non-randomised phase 1b/2a study. *Lancet Neurol*. 2023;22:578.

3 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419.

4 Yakoub-Agha I, Greco R, Onida F, et al. Practice harmonization workshops of EBMT: an expert-based approach to generate practical and contemporary guidelines within the arena of hematopoietic cell transplantation and cellular therapy. *Bone Marrow Transplant*. 2023;58:696.

5 Jandhyala R. Delphi, non-RAND modified Delphi, RAND/UCLA appropriateness method and a novel group awareness and consensus methodology for consensus measurement: a systematic literature review. *Curr Med Res Opin*. 2020;36:1873.