Reply to R. Chakraborty et al

We thank Chakraborty and Al Hadidi[1] for their interest and comments in response to our study[2] reporting on the safety and efficacy of standard-of-care idecabtagene vicleucel (ide-cel) in patients with relapsed/refractory multiple myeloma (RRMM).

The first point raised is about patient selection and intention-to-treat analysis. The purpose of our study was to compare outcomes of real-world patients receiving ide-cel with patients treated on the KarMMa clinical trial to provide data for clinicians in an expedient manner regarding this novel therapy.[2,3] We agree that waitlists for chimeric antigen receptor (CAR) T-cell therapy (CAR T) in myeloma are long, and the limited manufacturing availability creates significant access issues. In fact, our clinical experience suggests that many patients decline in terms of performance status and comorbidities while waiting for CAR T such that they may be in worse condition when they receive the treatment. Even if there is some selection given the attrition due to factors outside the control of the treating physician, most patients have suboptimal performance status, significant comorbidities, and disease that is refractory to other treatments.

We would like to note that patients in our study were heavily pretreated with seven median previous lines of therapy and 84% and 44% having triple- and penta-refractory disease, respectively, similar to the KarMMa trial. In contrast to the trial, patients in our study were more likely to have comorbidities and worse performance status, which can unfavorably affect outcomes. Three fourths of patients receiving standard-of-care ide-cel would have been trial ineligible because of organ dysfunction, poor performance status, or cytopenias, yet the safety and efficacy profile was similar to the trial.[2] In the manuscript, an as-treated analysis was conducted as in the trial publication to allow for comparison to the KarMMa trial.[4] We also provided granular data on all patients who underwent apheresis with intent to manufacture ide-cel to allow for an intention-to-treat analysis. The baseline characteristics of all patients who underwent apheresis are provided in Supplementary Table 1. The turnaround time for manufacturing is an inherent limitation of any therapy that requires individualized manufacturing and not unique to our study or myeloma CAR T. The authors note that some patients may be better served by bispecific antibody therapies. However, bispecific antibodies were not US Food and Drug Administration approved in the United States at the time of our analysis.[5] We agree that the velocity of relapse and availability of CAR T may influence the type of treatment received by patients. Ultimately, the choice of therapy lies with the treating physician and the patient.

The second point raised is regarding baseline patient characteristics and progression before CAR T infusion. Most of our patients (95%) were progressing before referral for CAR T, including those patients who were relapsing after initial response to the last line of therapy or truly refractory without any response to the last line of therapy. Because of longer wait times for CAR T slots, many patients required further therapy to be able to wait their turn. Bridging therapy options were not limited in the real world as they were on trial. Nevertheless, few patients responded to bridging chemotherapy at 11% in our cohort and 5% in the clinical trial.

Third, the authors discuss the higher percentage of patients requiring stem-cell boost in our cohort than the clinical trial. This is likely attributable to a higher proportion of patients in our study having baseline cytopenias compared with the trial population as patients with cytopenias would not have been eligible for the trial. Moreover, the practice and protocols for stem-cell boost at each institution differ widely outside the context of a clinical trial. We agree that this information is important and should be investigated in future studies.

Finally, the authors comment on inclusion of information on race and ethnicity. We agree that this information is critical. Of the 159 patients infused, patients from underrepresented minority groups represented a fourth of our cohort. Given that this topic is of utmost importance, we are continuing to investigate the impact of race and ethnicity on outcomes with ide-cel in our cohort[6] and a subsequent manuscript is in progress.

Although we agree that our study has limitations because of its retrospective nature, our large multi-institutional study of patients treated with ide-cel within the first year of its approval in the United States fills a key area of need. This study provides data for clinicians and researchers considering CAR T for patients with RRMM and for development of future trials, including broadening eligibility criteria to represent a real-world population.

Doris K. Hansen, MD
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Surbhi Sidana, MD
Stanford University School of Medicine, Stanford, CA

Lauren C. Peres, PhD
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Krina K. Patel, MD
The University of Texas MD Anderson Cancer Center, Houston, TX

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00568.

ACKNOWLEDGMENT

This work was in part supported by the Moffitt Cancer Center National Cancer Center Institute (NCI) Core Grant No. (P30-CA076292) and a generous donation from the Hyer family. S.S. is supported by Stanford Clinical and Translational Science KL2 Career Development Award program, Award No. KL2 TR003143, and Stanford Cancer Institute/American Cancer Society Pilot Grant 2022. D.K.H. is supported by the International Myeloma Society Young Investigator Award for Exemplary Abstract and by the Pentecost Family Myeloma Research Center.

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DOI: https://doi.org/10.1200/JCO.23.00568; Published at ascopubs.org/journal/jco on May 26, 2023.

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Doris K. Hansen
Consulting or Advisory Role: Bristol Myers Squibb Foundation
Research Funding: Bristol Myers Squibb/Celgene

Surbhi Sidana
Consulting or Advisory Role: Janssen, Bristol Myers Squibb/Celgene, Oncopeptides, Magenta Therapeutics, Sanofi
Research Funding: Janssen (Inst), Magenta Therapeutics (Inst), Allogene Therapeutics (Inst), Bristol Myers Squibb/Celgene (Inst)

Lauren C. Peres
Research Funding: Bristol Myers Squibb Foundation (Inst)

Krina K. Patel
Consulting or Advisory Role: Celgene, Bristol Myers Squibb, Janssen, Pfizer, Arcellx, Karyopharm Therapeutics, Merck, Cellectis, Caribou Biosciences, Takeda, AbbVie
Research Funding: Celgene/Bristol Myers Squibb, Takeda, Janssen, Cellectis, Nektar, AbbVie/Genentech, Precision Biosciences, Allogene Therapeutics
Travel, Accommodations, Expenses: Bristol Myers Squibb

No other potential conflicts of interest were reported.