Dear Editor,

Due to the advent of novel agents such as proteasome inhibitors (PI), immunomodulatory agents (IMiD), and anti-CD38 monoclonal antibodies (MoAbs), the survival of patients with multiple myeloma (MM) has improved and is expected to continue to improve [1, 2]. Nonetheless, relapse is inevitable with multiple myeloma (MM) has improved and is expected to continue to improve [1, 2]. Nonetheless, relapse is inevitable with

Subsequent anti-myeloma therapy after idecabtagene vicleucel treatment in patients with relapsed/refractory multiple myeloma: A single center analysis

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We reviewed the treatment outcomes of 7 patients who developed progressive disease (PD) and were treated with sAMT following treatment with ide-cel on a clinical trial at Mayo Clinic Florida between December 2019 and November 2020. All patients had received 2–4 prior lines of therapy and prior treatment with at least one PI, and IMiD and an anti-CD38 MoAb. Data were collected retrospectively from hospital records. Response rates were defined based on the International Myeloma Working Group Criteria [7]. PFS and OS were analyzed using Kaplan–Meier analysis and Cox regression. Time-to-event variables were compared using unadjusted Cox proportional hazards regression models.

Patient characteristics are shown in Table 1. The median follow-up time following initiation of first line therapy following CAR-T relapse was 8 months (95% CI 2-NR). One (14.2%) patient was R-ISS I, 5 (71.4%) were R-ISS II, and 1 (14.2%) was R-ISS-III at the time of CAR-T therapy. Two (33%) patients had high risk FISH abnormalities. Seven (100%) patients were triple-class exposed, 7 (100%) were triple-class refractory, and none were pentarefractory at the time of CAR-T therapy. Following CAR-T therapy, 2 (28.5%) patients were MRD positive even at 90 days post CAR-T and 5 (71.4%) patients achieved MRD negativity in the bone marrow by day 90. Two (28.5%) patients had a PET-CT that was negative post CAR-T, 4 (57.1%) patients had a persistently positive PET-CT post-CAR-T, one patient did not have a post-CAR-T PET-CT. The median time to progressive disease following CAR-T therapy was 211 days (range 57–277).

Following disease progression, all 7 patients received a subsequent line of therapy. Regimens are shown in Table 1; 2 (28.5%) patients received alkylator-based therapy, 4 (57.1%) patients received carfilzomib-based therapy and 2 (28.5%) received MoAb-based therapy with 1 (14.2%) receiving a quadruplet containing daratumumab and carfilzomib. The median number of treatment cycles was 1 (range 1–4). The ORR to the first sAMT was 28.5% with 1 patient achieving a very good partial response (VGPR) and one patient achieving a partial response (PR). The clinical benefit rate was 57.1% with one patient each achieving a VGPR, PR, minor response (MR), and stable disease (SD). Patients who received a carfilzomib-based regimen (n = 4) were the only responders with one each achieving a VGPR, PR, and MR. 3 of these patients had never been exposed to carfilzomib. The median PFS following 1st post-CAR-T sAMT was 2 months (95% CI 0-NR).

Four (57.1%) patients went on to receive a second and/or third sAMT. Two patients received carfilzomib-based therapy, 1 patient received elotuzumab-based therapy and 1 received high dose cyclophosphamide 1500 mg/m² for 2 consecutive days. The ORR to second sAMT was 50% with 2 patients achieving a VGPR. The CBR was 75% (n = 3) with 2 patients achieving a VGPR and one achieving an MR. The median number of cycles was 1.5 (range 1–4). The median PFS after second sAMT was 1 month (95% CI 1-NR). Two patients received belantamab mafodotin as a third-line, post-CAR-T sAMT and the ORR was 0% with both patients developing progressive disease as the best response to therapy.

The median OS after initiation of sAMT in the post-CAR-T relapse setting was 5 months (95% CI 4-NR). In our small cohort of 7 patients who progressed following anti-BCMA CAR-T cell therapy with ide-cel, outcomes were dismal with short-lived ORR and PFS and a median OS of 5 months following sAMT. Carfilzomib-based therapy appears to be transiently active in both the first and second-line of therapy following progression on anti-BCMA CAR-T, however, responders were mainly carfilzomib-naïve and responses were short-lived. While previous reports [8, 9] have shown that anti-BCMA agents can be sequenced, 2 patients in our cohort who received the anti-BCMA antibody-drug conjugate belantamab mafodotin as third line sAMT following anti-BCMA CAR-T progression did not respond.

The ideal treatment strategy for patients who progress following anti-BCMA CAR-T cell therapy is currently unknown. Given that most patients are at least triple-class refractory, if not pentarefractory by the time they receive anti-BCMA CAR-T cell therapy, using standard FDA approved anti-myeloma agents in
the PI, IMiD, or anti-CD38 MoAb class upon relapse may not be possible. Recent data has shown that in 68 patients who progressed following ide-cel in the phase I KarMMa I study [NCT02658929] and received sAMT, the most frequent subsequent anti-myeloma drug classes were corticosteroids (n = 58) and PIs (n = 47), while the most frequent agents were dexamethasone (n = 56) and carfilzomib (n = 32). Anti-BCMA agents included antibody-drug conjugate belantamab mafodotin (n = 10). ORR to sAMT were not reported. In patients who received sAMT, the median duration of first sAMT was 48 days and PFS was 15.5 months [10]. A possible discrepancy between the KarMMa I study and our study in terms of PFS to first sAMT may be that in KarMMa 1, the median time between MM diagnosis and CAR-T was 60 months, whereas it was 37 months (range:19–95) in our cohort of patients [11]. Therefore, the patients in our study may have had more biologically aggressive disease.

In another retrospective study of 31 patients who developed PD after anti-BCMA CAR-T cell therapy on a clinical trial, patients

| Table 1. Baseline patient characteristics. |
|-------------------------------------------|
| **Characteristic** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** | **Patient 6** | **Patient 7** |
| Myeloma Type | IgA Kappa | IgG Lambda | IgG Lambda | IgG Lambda | IgA Kappa | IgG Kappa | IgD Lambda |
| High Risk FISH? | N | N | Y | +1Q, t(4;14), del(13q) | N | Y | -17p, +1Q, t(4;14) | N | N |
| ISS staging at the time of CAR-T | 2 | 1 | 2 | 3 | 1 | 2 | 2 |
| R-ISS Staging at the time of CAR-T | 2 | 1 | 2 | 3 | 2 | 2 | 2 |
| Triple Class Refractory? (PI, IMiD, anti-CD38 moAb) | Y | Y | Y | Y | Y | Y | Y |
| Lenalidomide Exposed/Refractory Status | Y/Y | Y/Y | Y/Y | Y/Y | Y/N | Y/N | Y/Y |
| Bortezomib Exposed/Refractory Status | Y/Y | Y/Y | Y/Y | Y/N | Y/Y | Y/N | Y/Y |
| Pomalidomide Exposed/Refractory Status | Y/N | Y/N | Y/N | Y/N | Y/N | Y/N | Y/N |
| Carfilzomib Exposed/Refractory Status | N/N | Y/N | Y/Y | Y/Y | Y/Y | N/N | Y/Y |
| Daratumumab Exposed/Refractory Status | Y/Y | Y/Y | Y/Y | Y/Y | Y/Y | Y/Y | Y/Y |
| Sex | F | M | F | M | M | F | M |
| IMWG Response to CAR-T | CR | CR | VGPR | VGPR | sCR | VGPR | CR |
| MRD negative to CAR-T | Y | Y | N | N | Y | Y | Y |
| Negative PET-CT After CAR-T | N | N | N | N | Y | Y | N/A |
| Days from CAR-T to Progression | 195 | 277 | 57 | 211 | 224 | 275 | 69 |
| Extramedullary Disease Prior to CAR-T | N | N | N | N | N | Y | N |
| Extramedullary Disease at CAR-T Relapse | N | N | Y | Y | Y | Y | N |
| Extramedullary Disease after CAR-T Relapse | Y | N | Y | N | Y | N | N |
| 1st Regimen Post-CAR-T | Carfilzomib Dexamethasone | Elotuzumab Pomalidomide Dexamethasone | Daratumumab Lenalidomide Carfilzomib Dexamethasone | Melflufen | High Dose Cyclophosphamide | Carfilzomib Cyclophosphamide Dexamethasone | Carfilzomib Pomalidomide Dexamethasone |
| MRD negative to 1st regimen post CAR-T | Y | Y | N | N | Y | Y | Y |
| Best Response to 1st regimen post CAR-T | PD | PD | SD | PD | PR, still on tx | VGPR |
| Did Pt Receive 2nd Regimen? | Y | Y | N | N | Y | Y | N |
| Did Pt Receive 2nd Regimen? | Y | Y | N | N | Y | Y | N |
| Best Response to 2nd regimen post CAR-T | VGPR | MR | N/A | N/A | PD | N/A | VGPR |
| Did Pt Receive 3rd Regimen? | Y | Y | N | N | Y | Y | N |
| Best Response to 3rd regimen post CAR-T | PD | PD | N/A | N/A | PD | N/A | N/A |
| Status | Dead | Alive | Dead | Alive | Dead | Alive | Dead |
received a median of 2 additional treatment lines (range 0–8). The most common initial treatment after CAR-T relapse was chemotherapy with (V)DCETP or V-DPACE (10/28, 36%). Five patients (18%) were treated with a bispecific antibody immediately after CAR-T and 12 (43%) received bispecific antibody therapy at any point after CAR-T. Selinexor-based regimens were used in 3 (11%) patients immediately after and in 10 (36%) at any point after CAR-T relapse. The ORR to the subsequent therapies in this cohort of patient was 46%. Median time to progression was 105 days (95% CI: 78–204) for the initial treatment after CAR-T [12]. In a retrospective study of 11 MM patients who relapsed after prior anti-BCMA directed therapy, use of selinexor-containing regimens resulted in an ORR of 54.5%, a 6 months PFS probability of 68.6%, and a median OS of 10.5 months [13].

It remains to be determined whether treating with another BCMA-targeted agent or switching to a sAMT that targets a different antigen or cellular pathway is the ideal treatment strategy following progression on anti-BCMA CAR-T. A better understanding of the mechanisms of resistance to anti-BCMA CAR-T will be key to determining if anti-BCMA agents can be sequenced. It is currently postulated that antigen loss, BCMA shedding from plasma cell surface, secretion of anti-drug antibodies, T-cell exhaustion, and the emergence of a nonpermissive microenvironment are potential mechanisms of resistance to BCMA-directed therapies, and understanding which resistance mechanism occurs in an individual patient will be key to helping tailor sAMT [9].

Anti-myeloma agents that are not IMiDs, Ps, anti-CD38 MoAb, alkylators, corticosteroids, or anti-BCMA directed therapies have been evaluated in the post-BCMA directed therapy setting and have shown efficacy. In a phase I study evaluating talquetamab, a G-protein-coupled receptor family C group 5 member D x CD3-targeting bispecific antibody (NCT03399799), 31 evaluable patients achieved an ORR of around 70% and 30% of those patients had received prior anti-BCMA directed therapy [14]. In a phase I trial of cevatomabat (NCT03275103), an Fc receptor-homolog 5 × CD3 bispecific antibody, out of 158 evaluable patients, 33.8% of patients had received ≥1 prior anti-BCMA targeting agent. At target dose levels >90 mg, ORRs in pts with prior exposure to CAR-Ts, bispecific antibodies, antibody-drug conjugates, and anti-BCMA targeting agents were 44.4% (4/9 pts), 33.3% (3/9), 50.0% (7/14), and 36.4% (8/22), respectively [15].

In conclusion, the prognosis of MM patients following progression on anti-BCMA CAR-T cell therapy in the relapsed/refractory setting is dismal, and novel therapeutic strategies are necessary to improve the outcomes of these patients. As patients are likely to have exhausted all FDA-approved therapeutic options when they progress following progression on anti-BCMA CAR-T cell therapy, in relapsed and refractory multiple myeloma: Updated KarMMa results. J Clin Oncol. 2021;39:8016.

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AUTHOR CONTRIBUTIONS
RDP wrote the manuscript; RDP, KS, and AR collected data; VR, VA, TS, AC-K, and SA edited and finalized the manuscript.

COMPETING INTERESTS
RDP, VA, TR, TS, and AC-K declare no competing interests. SA receives honoraria from Celgene and Takeda as well as research funding from Amgen, Janssen, Pharmacyclics, Cellectar, Bristol Myers Squibb, Medimmune, and Phosplatin.

ADDITIONAL INFORMATION
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