Factors associated with refractoriness or early progression after idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma: US Myeloma Immunotherapy Consortium real world experience

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Abstract

While response rates and survival outcomes have been very promising for idecabtagene vicleucel (ide-cel), a proportion of patients do not respond or relapse early after this B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T-cell therapy. Understanding the characteristics of these patients is important for patient selection and development of novel strategies to improve outcomes. We evaluated factors associated with early progression (progression or death due to myeloma ≤3 months after CAR T-cell infusion) in patients treated with standard of care ide-cel at 11 US academic centers. Among 211 patients that received ide-cel, 43 patients had a progressive event ≤3 months of infusion. Patients with a history of extramedullary disease, prior BCMA targeted therapy, elevated ferritin at lymphodepletion, use of bridging therapy, Hispanic ethnicity, plasma cell leukemia and t(4;14) were more likely to progress ≤3 months of infusion (P<0.05). Of these risk factors for early progression identified in univariate analyses, history of extramedullary disease, prior BCMA targeted therapy, elevated ferritin at lymphodepletion, plasma cell leukemia, and t(4;14) were associated with worse progression-free survival (PFS) in multivariable analysis. Presence of three or more of these factors had a significant negative impact on PFS (P<0.001; median PFS for ≥3 factors, 3.2 months *vs*. 0 factors, 14.1 months). This study helps identify patients at high risk of early progression after CAR T-cell therapy who may benefit from specific interventions pre and post CAR T-cell therpy to improve outcomes.

Introduction

Patients with relapsed/refractory multiple myeloma (RRMM) to all three classes of drugs including immunomodulatory agents (IMiD), proteasome inhibitors (PI), and anti-CD38 monoclonal antibodies have poor prognosis with a median progression-free survival (PFS) of 3 to 4 months and an overall survival (OS) ranging from 5.6 to 13 months.[1,2] For these RRMM patients, the B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T-cell therapy ide-cabtagene vicleucel (ide-cel) has demonstrated remarkable efficacy and reasonable safety leading to approval from the Food and Drug Agency in March 2021 for commercial use in patients with ≥4 prior lines of therapy including an IMiD, PI, and anti-CD38 monoclonal antibody.[3] In the pivotal phase II KarMMa trial, patients infused with ide-cel demonstrated an overall response rate (ORR) of 73%, ≥ complete response (CR) rate of 33%, median PFS of 8.6 months, and median OS of 24.8 months.[4] The US Myeloma CAR T consortium has previously published real-world outcomes for patients with RRMM treated with commercially available standard of care (SOC) ide-cel.[5] A majority of the patients receiving

ide-cel in the analysis did not meet the eligibility criteria of the KarMMa trial; however, efficacy and safety outcomes were fairly comparable between the real-world and clinical trial settings. While response rates and survival outcomes have been very promising, a proportion of patients do not respond or relapse early after ide-cel. In the KarMMA trial, lower CAR T-cell dose and less than very good partial response (VGPR) were factors associated with inferior PFS.[3] However, lower CAR T-cell doses used in earlier cohorts of the trial are not reflective of the higher target cell dose administered with the commercial product in clinical practice. Similarly, depth of response determined after administration of CAR T-cell therapy is not an actionable predictor of progression for CAR T. A multivariate analysis of the depth of response identified immunglobulin (Ig)G heavy chain, high serum BCMA, and elevated prothrombin time-international normalized test as negative correlates of complete remission (CR)/stringent CR, and high vector copy number as a positive correlate of CR/sCR.[6] In the CARTITUDE-1 trial that led to the commercial approval of a second BCMA targeted CAR T-cell therapy for RRMM in February 2022; advanced stage disease, high-risk cytogenetics and high tumor burden were associated with shortened duration of response (DOR).[7,8] Identification of risk factors associated with early progression after CAR T-cell therapy in the real-world setting is important to help guide patient selection and development of novel strategies to improve outcomes, as well as to spare patients who would not derive benefit from this treatment, its potential toxicities, and costs of therapy. To this end, we evaluated factors associated with early progression (≤3 months after CAR T-cell infusion) for patients treated with SOC ide-cel.

Methods

Study treatment and data collection

This was a multicenter retrospective analysis of patients with RRMM who received SOC ide-cel from April 1, 2021, to May 1, 2022, at one of 11 US medical centers. Institutional review board approval was obtained independently by each center.

Following leukapheresis, patients were observed or received bridging treatment with chemotherapy or radiation therapy at the discretion of the treating physician. Lymphodepleting chemotherapy was administered on days -5 through -3 with SOC cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 or renally-dose adjusted per institutional guidelines. Cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS) were graded as per the American Society for Transplantation and Cellular Therapy criteria.[9] Hematologic toxicities were graded as per Common Terminology Criteria for Adverse Events, Version 5.0. Response to therapy was assessed by each institution as per International Myeloma Working Group criteria.[10] Supportive care measures including infectious disease prophylaxis, use of growth factors, and treatment of CRS and ICANS were managed per institutional guidelines.

For this analysis, early progression was defined as a progressive event or death due to myeloma that occurred ≤3 months from infusion. Because of this, we excluded any patient that did not have an event and did not reach 3 months of follow-up time as we cannot be certain whether they did or did not progress ≤3 months of infusion. Any patient that died ≤3 months due to other causes (not myeloma) were included in the cohort of patients that did not progress ≤3 months from infusion. We investigated differences in patient, disease, and CAR T-cell therapy related characteristics as well as safety and efficacy by early progression using χ^2 or Kruskal-Wallis tests.

Two survival outcomes were considered, OS and PFS. OS was calculated as the time between the date of CAR T-cell infusion and date of death from any cause or last contact. PFS was calculated as the time between the date of CAR T-cell infusion and date of progression, death (any cause), or last contact. We performed multivariable Cox proportional hazard regression to examine the association of the risk factors associated with early progression at $P<0.05$ with OS and PFS. We additionally created a variable summing the early progression risk factors that remained statistically significant in the multivariable analyses and examined the association of this variable (0, 1, 2, or ≥3 factors) with OS and PFS using Kaplan-Meier survival curves, log-rank tests, and Cox proportional hazard regression models. All statistical tests were two-sided and *P* values of <0.05 were considered statistically significant. Statistical analyses were conducted using R version 4.2.2.

Results

Patients and treatment

As of May 1, 2022, 215 patients had received ide-cel and 211 patients had at least 3 months follow-up available, with a median follow-up of 9.9 months. Of those, 43 patients experienced a progressive event (progression or death due to myeloma), ≤3 months post CAR T-cell therapy, and were considered the early progression cohort, in contrast to the cohort of patients who did not progress within 3 months of CAR T-cell therapy (N=168), which served as the comparison cohort for the analysis (Figure 1).

Patient baseline characteristics are presented in Table 1 stratified by early progression. Similar to patients who did not progress within 3 months of CAR T-cell therapy, the median age of patients that progressed ≤3 months was 61 years and 65% were male. However, there were a significantly higher number of Hispanic patients in the early progression cohort (23% *vs*. 7.1%; *P*=0.03). There were no significant differences in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 at time of lym-

phodepletion (24% *vs*. 15%; *P*=0.14), Revised International Staging System (R-ISS) stage III disease (29% vs. 27%; P=0.4), penta-refractory disease (47% *vs*. 42%; *P*=0.6) or median number of prior lines of therapy (7 *vs*. 6; *P*=0.075), between the two cohorts. A higher proportion of patients in the early progression cohort compared to the cohort that did not progress ≤3 months had received prior BCMA targeted therapy (40% *vs*. 21%; *P*=0.01), had history of extramedullary disease (EMD) (60% *vs*. 41%; *P*=0.02), and received bridging therapy (88% *vs*. 74%; *P*=0.04). High-risk cytogenetics defined by the presence of t(4;14), or t(14;16), or deletion (17p) on fluorescence *in situ* hybridization (FISH) were present in 42% of patients in the early progression cohort and 30% of patients in the comparison cohort (*P*=0.2). While this difference, and the presence of t(14;16) and deletion (17p), did not reach statistical significance, a higher number of patients in the early progression cohort had t(4:14) (21% *vs*. 8.9 %; *P*=0.04). Although the total number of patients with plasma cell leukemia that received CAR T-cell therapy were low (N=12, 6%), half of them experienced early progression. There were no differences in most baseline laboratory values between the two cohorts, including serum albumin, β^2 microglobulin, lactate dehydrogenase, blood counts or C-reactive protein. However, a higher proportion of patients in the early progression cohort had ferritin levels above the upper limit of normal at the time of lymphodepletion (400 ng/mL; 60% *vs*. 39%; *P*=0.01). In summary, patients with Hispanic ethnicity, presence of t(4;14) on FISH prior to CAR T-cell therapy, plasma cell leukemia, prior use of BCMA therapy, history of extramedullary disease, use of bridging therapy, and elevated ferritin at lymphodepletion were more likely to have progressed early (≤3 months).

Safety

Adverse events for each cohort are summarized in Table 2A, B. The median duration of hospitalization for the early progression cohort was 9 days (range, 5-69), and five patients (12%) required intensive care unit level of care for toxicity management during their inpatient stay, similar to the comparison cohort. The overall incidence of CRS for the early progression cohort was 67% and lower than in the comparison cohort, where the overall incidence of CRS was 89% (*P*<0.001), resulting in a smaller proportion of patients receiving tocilizumab in the early progression cohort (44% *vs*. 76%; *P*<0.001). There were no differences in median time to onset of maximum grade CRS, or grade 3-4 CRS events between the cohorts, as shown in Table 2A. In terms of ICANS, there were no differences in the incidence of all grades (20% *vs*. 19%; *P*>0.9) and grade ≥2 (15% *vs*. 9.3%; *P*=0.4) events between the cohorts. Similarly, there were no differences in rates of infection or grade ≥3 cytopenias between the cohorts on day 30 and day 90 post CAR T-cell infusion, but interestingly, a higher number of patients recovered to grade 2 or lower neutropenia by day 30 in the early progression cohort than the comparison cohort (78% *vs*. 59%; *P*=0.03). In contrast, as shown in Table 2B, there was more anemia (any grade) at days 30 and 90 amongst patients with early progression.

Efficacy

As expected, given the analysis being performed, patients in the early progression cohort had a significantly lower best ORR (42% *vs*. 93%), best ≥ VGPR (19% *vs*. 81%), best ≥ CR (7% *vs*. 60%), and best minimal residual disease (MRD) negative (10^{-5}) CR (2.3% *vs*. 42%), than patients who did not have a progressive event ≤3 months from infusion (Figure 2). Median PFS for this cohort was understandably short at 1.9 months (95% confidence interval [CI]: 1.4-2.7) *versus* 10.7 months (95% CI: 9.0-12.2) (*P*<0.0001) for the comparison cohort, and this was also reflected in an inferior OS (median estimate 7.3 months [95% CI: 6.5-9.9] *versus* not reached [NR]; *P*<0.0001) compared to the comparison cohort (Figure 3).

Of the variables associated with progression in univariate analysis at *P*<0.05 (i.e., Hispanic ethnicity, presence of t(4;14) on FISH prior to CAR T-cell theraphy, plasma cell leukemia, prior use of BCMA therapy, history of EMD, use of bridging therapy, and elevated ferritin at lymphodepletion),

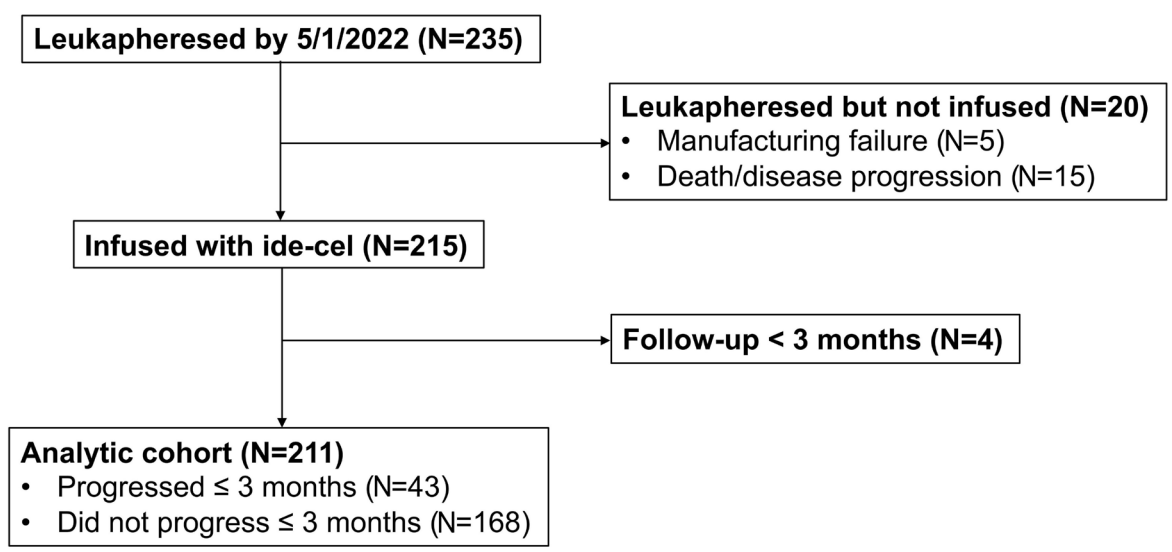


Figure 1. Consort diagram of study inclusion. Ide-cel: idecabtagene vicleucel.

Table 1. Baseline characteristics overall and by early progression.

Characteristic	Study cohorts			*P*
	Overall N=211	Progressed ≤3 months N=43	Did not progress ≤3 months N=168	
Patient age in years, median (range) [IQR]	64.0 (36.0-83.0) [57.0-69.0]	61.0 (43.0-78.0) [55.5-66.5]	65.0 (36.0-83.0) [58.0-69.0]	0.090
Male sex, N (%)	127 (60)	28 (65)	99 (59)	0.5
Race and ethnicity, N (%) Hispanic Non-Hispanic Black Other Non-Hispanic White	 22 (10) 36 (17) 8 (3.8) 145 (69)	 10 (23) 5 (12) 1 (2.3) 27 (63)	 12 (7.1) 31 (18) 7 (4.2) 118 (70)	0.030
Plasma cell leukemia, N (%)	12 (6)	6 (14)	6 (4)	0.018
Extramedullary disease, N (%)	95 (45)	26 (60)	69 (41)	0.023
High marrow burden (>=50%), N (%) Unknown	58 (30) 17	13 (35) 6	45 (29) 11	0.4
ECOG at LD of 0-1, N (%) Unknown	169 (83) 8	31 (76) 2	138 (85) 6	0.14
R-ISS stage at CAR T infusion, N (%) I II III Unknown	 37 (23) 82 (50) 44 (27) 48	 5 (14) 20 (57) 10 (29) 8	 32 (25) 62 (48) 34 (27) 40	0.4
High-risk cytogenetics, N (%) Unknown	60 (33) 27	16 (42) 5	44 (30) 22	0.2
t(4;14) at Infusion, N (%) Unknown	21 (11) 27	8 (21) 6	13 (8.9) 21	0.046
Deletion 17p at infusion, N (%) Unknown	40 (21) 21	10 (26) 4	30 (20) 17	0.4
t(4;16) at infusion, N (%) Unknown	7 (4) 27	1 (3) 6	6 (4) 21	>0.9
Bridging therapy, N (%)	162 (77)	38 (88)	124 (74)	0.044
N of prior lines of therapy, median (range) [IQR]	6.0 (3.0-19.0) [5.0-9.0]	7.0 (4.0-18.0) [5.0-9.5]	6.0 (3.0-19.0) [5.0-8.0]	0.075
> 4 prior lines of therapy, N (%)	180 (85)	40 (93)	140 (83)	0.11
Prior treatment with BCMA-targeted therapy, N (%)	52 (25)	17 (40)	35 (21)	0.011
Triple-refractory, N (%)	176 (83)	36 (84)	140 (83)	>0.9
Penta-refractory, N (%)	90 (43)	20 (47)	70 (42)	0.6
Baseline ferritin, median (range) [IQR]	345.0 (9.0-27,260.0) [124.5-959.5]	635.0 (15.4-4,960.0) [228.5-1,704.5]	283.5 (9.0-27,260.0) [116.0-752.8]	0.013
Ferritin >ULN at LD (400 ng/mL), N (%)	91 (43)	26 (60)	65 (39)	0.010
Baseline CRP, median (range) [IQR]	0.9 (0.0-286.0) [0.4-3.7]	1.5 (0.1-84.4) [0.4-7.6]	0.8 (0.0-286.0) [0.4-3.4]	0.3
Baseline B2M, median (range) [IQR] Unknown	3.0 (0.7-15.3) [2.4-4.6] 64	3.1 (1.6-13.5) [2.5-4.9] 8	3.0 (0.7-15.3) [2.3-4.6] 56	0.6
Patient did not meet criteria for KarMMa1 pre-CAR T, N (%)	160 (76)	37 (86)	123 (73)	0.079
Albumin pre-infusion, median (range) [IQR]	3.6 (1.7-4.8) [3.2-4.0]	3.6 (2.1-4.7) [3.3-4.0]	3.7 (1.7-4.8) [3.2-3.9]	0.7
LDH pre-infusion, median (range) [IQR] Unknown	216.5 (78.0-1,597.0) [173.2-275.0] 1	217.0 (93.0-1,597.0) [177.0-295.0] 0	216.0 (78.0-1,408.0) [173.0-266.5] 1	0.7

ECOG: Eastern Cooperative Oncology Group performance; RISS: Revised International Staging System; LD: lymphodepletion; IQR: inter quartile range; BCMA: B-cell maturation antigen; CRP: C-reactive protein; B2M: β-2 microglobulin; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Table 2. SAFETY: Incidence and severity of cytokine release syndrome, immune cell effector associated neurotoxicity syndrome and cytopenias overall and by early progression.

Characteristic	Study cohorts			*P*
	Overall N=211	Progressed ≤3 months N=43	Did not progress ≤3 months N=168	
Any CRS, N (%)	179 (85)	29 (67)	150 (89)	<0.001
CRS grade, N (%) No CRS Grade 1 or 2 Grade ≥3	 32 (15) 173 (82) 6 (2.8)	 14 (33) 27 (63) 2 (4.7)	 18 (11) 146 (87) 4 (2.4)	0.001
Relative day of max. CRS (relative to infusion), median (range) [IQR]	1.0 (0.0-21.0) [1.0-2.0]	1.0 (0.0-13.0) [1.0-2.0]	1.0 (0.0-21.0) [1.0-2.0]	0.4
Any ICANS, N (%) Unknown	39 (19) 10	8 (20) 3	31 (19) 7	>0.9
ICANS grade, N (%) No ICANS Grade 1 or 2 Grade ≥3 Unknown	 162 (81) 26 (13) 13 (6.5) 10	 32 (80) 3 (7.5) 5 (12) 3	 130 (81) 23 (14) 8 (5.0) 7	0.2
Relative day of max. ICANS (relative to infusion), median (range) [IQR]	3.0 (0.0-36.0) [2.0-4.0]	4.0 (0.0-24.0) [1.5-9.0]	3.0 (0.0-36.0) [2.0-4.0]	0.4
Length of hospital stay (total days including readmission), median (range) [IQR]	9.0 (5.0-69.0) [8.0-14.0]	9.0 (5.0-69.0) [8.0-13.5]	9.0 (5.0-68.0) [8.0-14.0]	0.7
ICU admission, N (%)	18 (8.5)	5 (12)	13 (7.7)	0.4
Tocilizumab, N (%)	146 (69)	19 (44)	127 (76)	<0.001
Steroid use, N (%)	57 (27)	10 (23)	47 (28)	0.5
Anakinra use, N (%)	9 (4)	5 (12)	4 (2)	0.02
Infection, N (%)	68 (32)	15 (35)	53 (32)	0.7
Day 30 cytopenia				
Anemia, N (%) Any grade Grade ≥3 Unknown	 168 (82) 38 (18) 5	 38 (95) 6 (15) 3	 130 (78) 32 (19) 2	 0.015 0.5
Thrombocytopenia, N (%) Any grade Grade ≥3 Unknown	 182 (88) 92 (45) 5	 38 (95) 16 (40) 3	 144 (87) 76 (46) 2	 0.2 0.5
Neutropenia, N (%) Any grade Grade ≥3 Unknown	 136 (66) 76 (37) 6	 21 (52) 9 (22) 3	 115 (70) 67 (41) 3	 0.039 0.033
Day 90 cytopenia				
Anemia, N (%) Any grade Grade ≥3 Unknown	 113 (63) 15 (8.3) 31	 19 (83) 3 (13) 20	 94 (60) 12 (7.6) 11	 0.035 0.4
Thrombocytopenia, N (%) Any grade Grade ≥3 Unknown	 114 (63) 41 (23) 31	 18 (78) 7 (30) 20	 96 (61) 34 (22) 11	 0.11 0.3
Neutropenia, N (%) Any grade Grade≥ 3 Unknown	 68 (38) 24 (13) 32	 9 (39) 5 (22) 20	 59 (38) 19 (12) 12	 >0.9 0.2

CRS: cytokine release syndrome; ICANS: immune cell effector associated neurotoxicity syndrome; IQR: interquartile range; ICU: intensive care unit.

multivariable analysis showed that patients with history of EMD (hazard ratio [HR] =1.71, 95% CI: 1.16-2.51), prior BCMA targeted therapy (HR=1.64, 95% CI: 1.08-2.50), elevated ferritin at lymphodepletion (HR=1.95, 95% CI: 1.33-2.88), plasma cell leukemia (HR=4.27, 95% CI: 2.06-8.87) and t(4;14) (HR=1.82; 95% CI: 1.07-3.09) were associated with worse PFS (Table 3). Similarly, patients with EMD (HR=1.69, 95% CI: 1.00-2.86), elevated ferritin at lymphodepletion (HR=2.56, 95% CI: 1.51-4.35), plasma cell leukemia (HR=3.97, 95% CI: 1.66-9.46) were associated with worse OS (Table 3). Taking into account the early progression risk factors associated with PFS in the multivariable analysis (history of EMD, prior BCMA targeted therapy, elevated ferritin at lymphodepletion, plasma cell leukemia, and t(4;14)), patients with a higher number of these risk factors had inferior PFS (P< 0.001; ≥3 risk factors, 3.2 months *vs*. 2 risk factors, 4.6 months *vs*. 1 risk factor, 9.6 months *vs*. 0 risk factors, 14.1 months; Figure 4A). A similar pattern was observed for the association of the number of early progression risk factors with OS (P<0.001; Figure 4B).

Discussion

To our knowledge, this is the largest study of RRMM patients receiving ide-cel in the real-world setting evaluating factors associated with early progression or failure of CAR T-cell therapy. While patient and disease related characteristics predictive of early progression have been an area of interest in pivotal trials of CAR T-cell therapy,[4-7] there have been no clearly established measurable and potentially actionable or modifiable risk factors associated with early progression after CAR T-cell therapy for myeloma.

In the pivotal trial evaluating ide-cel in RRMM, a lower cell dose and less than VGPR as best response were associated with an inferior PFS.[3] There was no difference in outcomes among patients with high-risk features, including advanced stage disease, extramedullary myeloma, and high-risk cytogenetics. This could be related to the relatively small number of patients included in the trial. In a subgroup analysis of phase II KarMMa trial participants,[6] elevated serum BCMA levels at baseline and presence of EMD were negatively associated with attainment of CR/sCR post CAR T-cell therapy. However, serum soluble BCMA assays are not readily available and hence their utility in routine clinical practice remains unclear. On the contrary, in the CARTITUDE 1 trial; ISS stage III disease, high-risk cytogenetics, EMD and high tumor burden were associated with shortened duration of response and a lower PFS and OS,[8] similar to the results reported in our study. A recent meta-analysis of 17 studies including 723 patients with RRMM that received

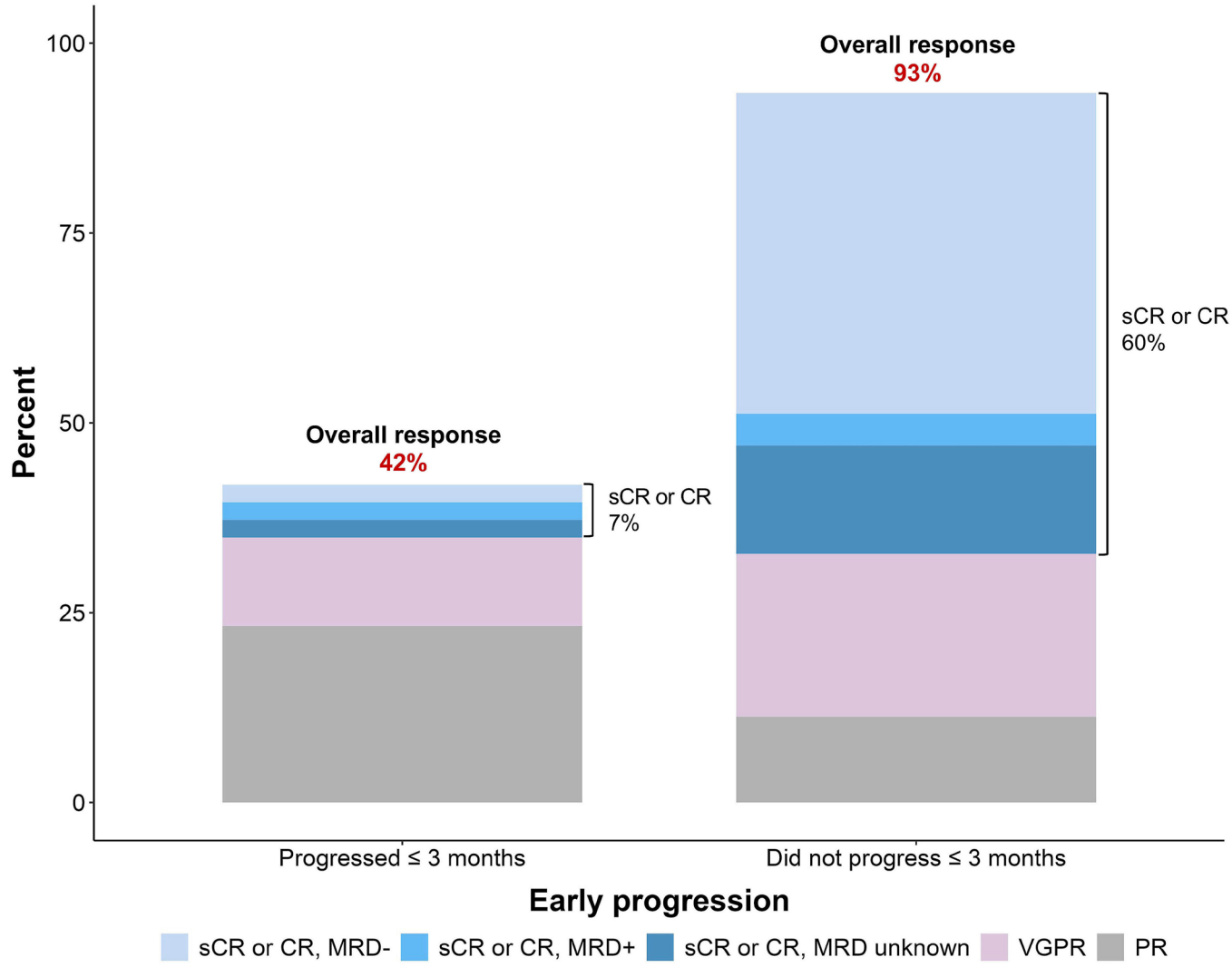


Figure 2. Best response by early progression. Any patient who was not evaluable by International Myeloma Working Group criteria or was missing a response but reached day 30 was considered as a partial response (PD) response. CR: complete response; sCR: stringent complete response; VGPR: very good partial response; MRD: minimal residual disease.

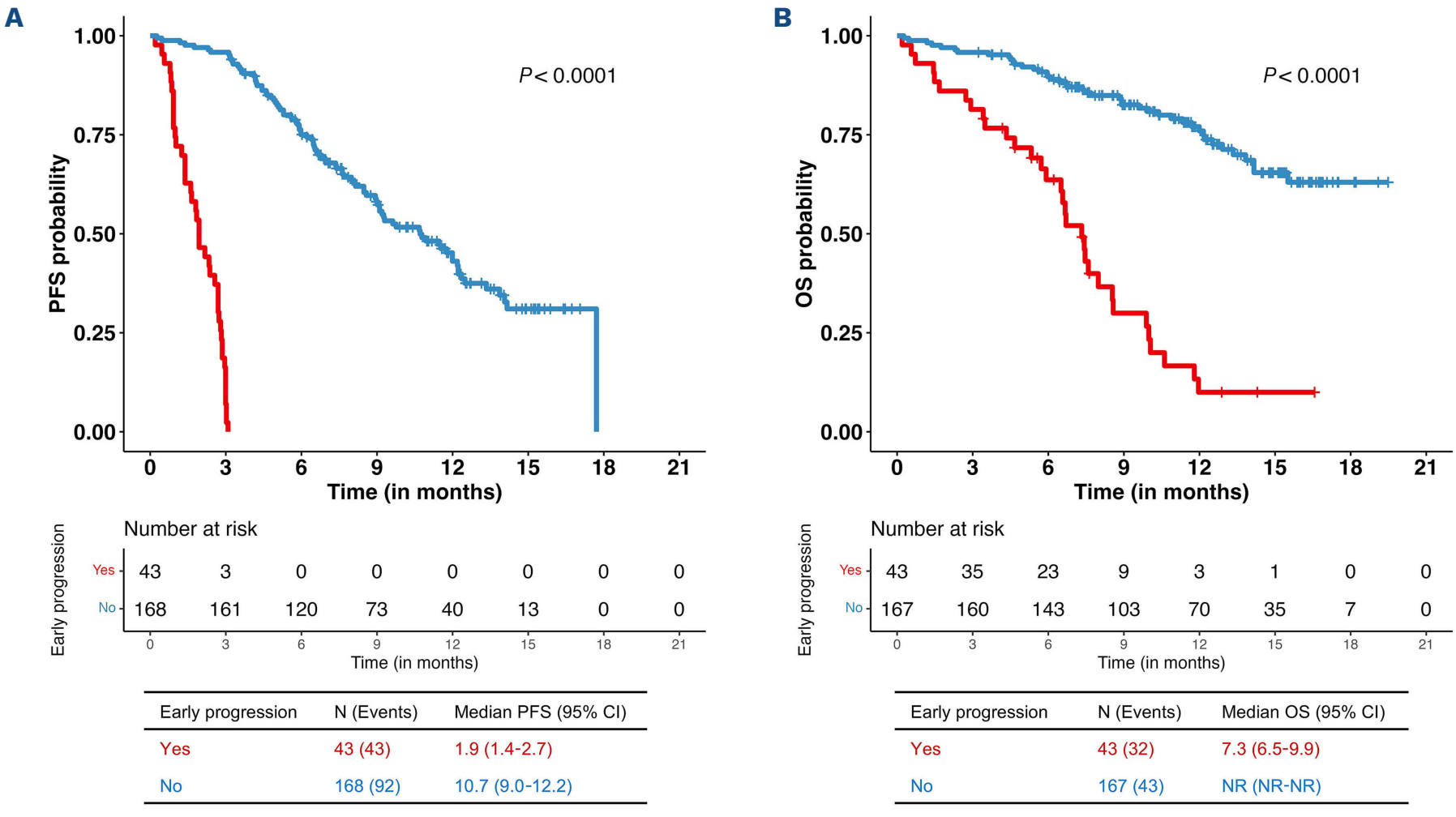
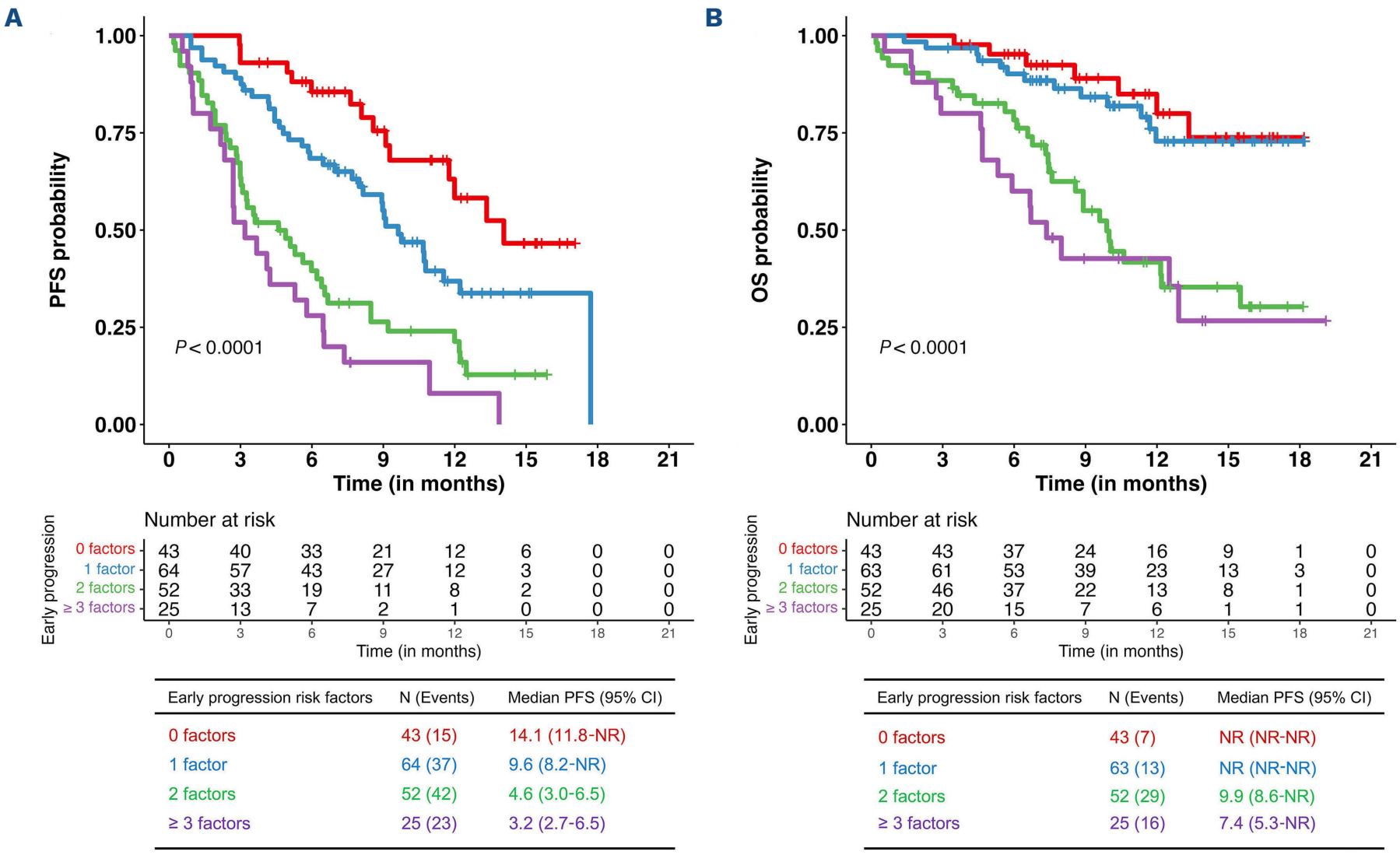


Figure 3. Survival analysis by early progression. (A) Kaplan-Meier survival curve of progression-free survival (PFS) by early progression. (B) Kaplan-Meier survival curve of overall survival (OS) by early progression. The *P* value is from a log-rank test of the association of early progression with PFS and OS. CI: confidence interval, NR: not reached.

Table 3. Multivariable analysis of the association of early progression risk factors with progression-free survival and overall survival.

Early progression risk factors	PFS			OS		
	N (N event)	HR (95% CI)	*P*	N (N event)	HR (95% CI)	*P*
Prior BCMA therapy						
No	135 (79)	1.00 Ref.		134 (42)	1.00 Ref.	
Yes	49 (38)	1.64 (1.08-2.50)	0.02	49 (23)	1.56 (0.90-2.71)	0.1
Extramedullary disease						
No	100 (53)	1.00 Ref.		99 (28)	1.00 Ref.	
Yes	84 (64)	1.71 (1.16-2.51)	0.006	84 (37)	1.69 (1.00-2.86)	0.048
Baseline ferritin at LD						
Normal	100 (53)	1.00 Ref.		100 (22)	1.00 Ref.	
≥ULN	84 (64)	1.95 (1.33-2.88)	<0.001	83 (43)	2.56 (1.51-4.35)	<0.001
Bridging therapy						
No	40 (19)	1.00 Ref.		40 (6)	1.00 Ref.	
Yes	144 (98)	1.42 (0.84-2.38)	0.2	143 (59)	2.23 (0.94-5.26)	0.07
Race and ethnicity						
Non-Hispanic White	126 (81)	1.00 Ref.		126 (45)	1.00 Ref.	
Non-Hispanic Black	33 (21)	1.48 (0.90-2.46)	0.1	32 (12)	1.45 (0.75-2.79)	0.3
Hispanic	19 (12)	1.15 (0.60-2.17)	0.7	19 (7)	1.45 (0.61-3.25)	0.4
Other	6 (3)	0.56 (0.18-1.81)	0.3	6 (1)	0.27 (0.04-2.04)	0.2
Plasma cell leukemia						
No	175 (108)	1.00 Ref.		174 (58)	1.00 Ref.	
Yes	9 (9)	4.27 (2.06-8.87)	<0.001	9 (7)	3.97 (1.66-9.46)	0.002
t(4;14) at infusion						
No	163 (98)	1.00 Ref.		162 (52)	1.00 Ref.	
Yes	21 (19)	1.82 (1.07-3.09)	0.03	21 (13)	1.58 (0.80-3.11)	0.2

HR: hazard ratio; CI: confidence interval; BCMA: B-cell maturation antigen; Ref.: referent; LD: lymphodepletion chemotherapy; ULN: upper limit of normal.



Early progression risk factors	N (Events)	Median PFS (95% CI)
0 factors	43 (15)	14.1 (11.8-NR)
1 factor	64 (37)	9.6 (8.2-NR)
2 factors	52 (42)	4.6 (3.0-6.5)
≥ 3 factors	25 (23)	3.2 (2.7-6.5)

Early progression risk factors	N (Events)	Median PFS (95% CI)
0 factors	43 (7)	NR (NR-NR)
1 factor	63 (13)	NR (NR-NR)
2 factors	52 (29)	9.9 (8.6-NR)
≥ 3 factors	25 (16)	7.4 (5.3-NR)

Figure 4. Survival analysis by number of early progression risk factors. (A) Kaplan-Meier survival curve of progression-free survival (PFS) by number of early progression risk factors. (B) Kaplan-Meier survival curve of overall survival (OS) by number of early progression risk factors. Early progression risk factors included prior B-cell maturation antigen therapy, extramedullary disease, baseline ferritin, plasma cell leukemia, and t(4;14). The *P* value is from a log-rank test examining the association of the number of early progression risk factors (0, 1, 2, ≥3 factors) with PFS and OS. CI: confidence interval; NR: not reached.

BCMA targeted CAR T-cell therapy revealed that the high risk cytogenetics and presence of EMD at the time of CAR T-cell infusion were associated with worse outcomes.[11] While our analysis identified several patient and disease related factors associated with early progression, we focused on risk factors that had a statistically significant impact on PFS in the multivariable analysis. Hispanic ethnicity was one of these risk factors where when compared to the other racial and ethnic groups, Hispanic patients were more likely to progress early. However, race and ethnicity were not associated with PFS or OS after adjusting for other early progression risk factors in the multivariable analysis. These findings may be due to the small number of Hispanic patients in our study or differences in high-risk features across race and ethnicity.[12] Presence of t(4;14) cytogenetic abnormality as well as plasma cell leukemia were considered inherent part of disease biology and not modifiable risk factors prior to CAR T-cell infusion. It remains important that these risk factors are identified as early as time of initial consultation and leukapheresis for CAR T-cell therapy. This will not only offer prognostic information for the patients undergoing treatment but also help plan consolidation/maintenance strategies.

In two of the previous studies from this consortium,[13] it was shown that prior BCMA targeted therapy was associated with inferior depth and duration of response. One study also showed that with a shorter duration of exposure to the prior BCMA targeted therapy and a significantly longer time from the last BCMA targeted therapy exposure to leukapheresis as well as ide-cel infusion, patients seemed to achieve better outcomes with ide-cel as a sequential therapy. In the present study, the median time to ide-cel infusion from last exposure to BCMA targeted therapy was 202.5 days (range, 16-1,118) for all patients, 201 days (range, 32-425) for those with early progression, and 238 days (range, 16-1,118) for those without early progression. These inferior outcomes seen in patients with prior BCMA exposure could potentially be explained by emergence of clones with loss of BCMA leading to acquired resistance to retreatment with BCMA targeted therapy, as postulated in a previously reported case.[14] Loss of BCMA expression in these patients could not be confirmed due to the retrospective nature of the study. While it seems prudent to avoid exposure to BCMA targeted therapy as the last line of therapy prior to CAR T-cell infusion, it is not always possible to avoid exposure to other BCMA targeted therapy for

triple class refractory myeloma patients in need of urgent therapy. Hence, exposure to alternative non BCMA therapies after BCMA targeted cellular therapy and before ide-cel, as a 'BCMA free treatment interval,' may help mitigate the negative impact of prior BCMA targeted therapy exposure. There also remains a need for future research to explore techniques for sensitive and deep sequencing of BCMA locus prior to sequential BCMA targeted therapies.

Elevated ferritin at the time of lymphodepletion, after bridging therapy and before CAR-T cell infusion, is a marker of systemic inflammation. It has been previously shown that a high tumor burden is associated with worse efficacy outcomes among patients with large cell lymphoma.[15] Similarly, high metabolic tumor volume was found to be associated with an increased risk of CAR T-cell therapy specific adverse events and inferior outcomes in patients with RRMM receiving CAR T-cell therapy.[16] These patients with high metabolic tumor volume have immune dysregulation characterized by significantly higher levels of serum inflammatory markers and tumor interferon signaling.[17] This leads to poor CAR T-cell expansion and persistence explaining inferior outcomes in comparison to patients who had a lower baseline state of inflammation.[17] While we did not collect samples for measurement of specific inflammatory cytokines, tumor microenvironment, and metabolic tumor volumes; this deleterious state of inflammation as measured by serum ferritin level prior to lymphodepletion may have utility as a predictive marker of early disease progression.

With an improvement in OS in the era of novel therapeutics, there is an increasing incidence of EMD for MM, especially at the time of relapse. Based on meta-analysis by Blade *et al.*, high-risk cytogenetics and EMD have been associated with worse outcomes after CAR T-cell therapy for RRMM[18] and our study also confirms the negative impact of EMD on post CAR T-cell therpy outcomes. The underlying pathophysiology is complex and may be explained by systemic inflammation and a more suppressive tumor microenvironment associated with large and highly avid tumors on positron emission tomography. Based on one reported study,[19] prior EMD remains the predominant site of post CAR T-cell therapy relapse, raising the possibility of EMD as site of immunological sanctuary susceptible to tumor relapse. Tumor-driven inhibition of T-cell function, whether it be T cells collected for manufacture or the CAR T cells themselves after infusion, adds to the effector: target disparity because large tumors as seen in EMD require the highest expansion of CAR T for deep and durable responses. While this indeed highlights the need for more effective bridging therapy including radiotherapy for maximum debulking prior to CAR T-cell infusion, this novel goal of effective disease control may not be attainable in many patients. Investigating the mechanisms of CAR T-cell trafficking and exhaustion in patients with EMD will be essential to optimizing responses to CAR T cells and may identify factors leading to the rare responses to therapy as seen in our study.

Univariable analysis showed that patients who did not receive bridging therapy had better outcomes. The need for bridging therapy is dependent on disease status (response to last line of therapy, disease burden, site of disease, and rate of progression) prior to CAR T-cell therapy that dictates how long the patient can wait after leukapheresis and before CAR T-cell infusion without clinically significant disease progression impairing organ function.[20] For patients with low disease burden, absence of EMD as well as low baseline systemic inflammatory state as measured by ferritin, bridging therapy may not be necessary. However, this represents a minority of patients, and given that bridging therapy did not have a significant impact on PFS in the multivariable analysis, the decision needs to be carefully evaluated on an individual basis. Plasma cell leukemia is a rare and aggressive plasma cell disorder associated with dismal prognosis despite frontline multiagent chemoimmunotherapy and hematopoietic stem cell transplantation.[17] Enrollment of these patients in clinical trials is not always feasible partly due to the relative paucity of specific studies on plasma cell leukemia due to aggressive disease biology and poor prognosis, highlighting the critical need for prospective trials for this especially challenging high-risk subgroup. Although the number of patients who received SOC ide-cel was small, it is important to highlight that at least half of them did not experience early progression despite aggressive disease biology. Further exploration of the role of immunotherapies (CAR T cells, bispecific T-cell engagers, antibody-drug conjugates) with dedicated clinical trials in the treatment landscape of plasma cell leukemia as well as inclusion of these patients in MM clinical trials is much needed and eagerly awaited. Presence of t(4;14), but not any other high-risk cytogenetic abnormalities, was predictive of early progression after CAR T-cell therapy. This could again be related to a small number of patients with individual high-risk cytogenetic abnormalities as well as more than 10% of the patients with missing information on cytogenetic abnormalities prior to CAR T-cell infusion. Further research is needed to confirm these findings and elucidate potential causes of cytogenetic differences in CAR T-cell therapy response in larger sample sizes of diverse and high risk RRMM patients treated with SOC ide-cel. The study also revealed the interesting finding that patients who had early progression experienced a lower incidence of CRS and early recovery from cytopenias. This could be explained by the less robust expansion of CAR T cells and immunological reactivity leading to compromised efficacy. While presence of extramedullary disease and elevated ferritin at lymphodepletion may appear as actionable risk factors prior to CAR T-cell therapy, in real-world practice there are no effective measures that can truly modify these risk factors just in time prior to CAR T and overcome the poor prognosis associated with them. However, these risk

factors do allow us to identify patients for more applicable post CAR T interventions including close surveillance for relapse, initiation of salvage therapy at the earliest signs of disease progression and consideration of maintenance therapy in future clinical trials. Moreover, use of CAR T-cell therapy in the earlier lines of therapy where patients are not as heavily pretreated, have relatively lower disease burden, and are more likely to be BCMA-naïve are likely to mitigate the negative influence of some of these risk factors of early progression after CAR T-cell therapy.

Limitations of our study include its retrospective design, small sample size, and response assessment dependent on investigator discretion. Due to the retrospective nature of a multicenter study, some of the more informative predictors of progression after CAR T-cell therapy including serum BCMA levels[10] and metabolic tumor volume[13] could not be measured or reported. Despite the largest real-world experience of CAR T-cell therapy for RRMM, a small number of patients had a progressive event, and it remains possible that some of the predictors of early progression could not reach a statistically significant impact on outcomes. Future studies with SOC ide-cel in RRMM should focus on mechanisms of relapse, sequential treatment with other BCMA and non BCMA targeted agents, long-term outcomes including risk of infections and need for de-escalation/cessation of therapy based on quality of response, as well as comparative analyses of the safety and efficacy of other BCMA targeted bispecifics.

Conclusion

Per this multicenter retrospective study, prior use of BCMA therapy, presence of EMD, elevated ferritin at lymphodepletion, plasma cell leukemia, and t(4;14) are potential predictors of early progression after CAR T-cell therapy for RRMM. Presence of three or more of these factors negatively impacted PFS and OS.

Disclosures

HH reports consulting or advisory role for Janssen, Bristol-Myers Squibb, Sanofi; speakers' bureau for Sanofi, GlaxoSmithKline, and Karyopharm. SS reports consulting or advisory role for Janssen, Bristol-Myers Squibb, Magenta Therapeutics, Sanofi, Takeda, Pfizer and Legend Biotech; research funding from Janssen, Magenta Therapeutics, Allogene Therapeutics, Bristol-Myers Squibb and Novartis. LCP reports research funding from Bristol-Myers Squibb. DWS reports consulting or advisory role for Sanofi, GlaxoSmithKline, Bristol-Myers Squibb, Legend Biotech, Janssen, and Skyline Diagnostics; research funding from Janssen, BioLineRx, Sanofi, Bristol-Myers Squibb, Amgen, Cantex Pharmaceuticals, Pfizer, and Gilead Sciences. SA reports honoraria from Janssen; research funding from GlaxoSmithKline, Amgen, Karyopharm Therapeutics, Janssen, Bristol-Myers Squibb; honoraria from Janssen. CF reports consulting or advisory role for Sanofi; stock/other ownership in Affimed Therapeutics. PV reports consulting or advisory role for Oncopeptides, Abbvie/Genentech, Karyopharm Therapeutics, Bristol-Myers Squibb, Secura Bio, Pfizer, Sanofi, Janssen, GlaxoSmithKline; research funding from Abbvie, Janssen, GlaxoSmithKline, and TeneoBio; travel, accommodations, and expenses from Sanofi. RB reports consulting or advisory role for Bristol-Myers Squibb, Abbvie, Janssen, GlaxoSmithKline, Takeda, and Pfizer; research funding from Bristol-Myers Squibb, Abbvie, Karyopharm, and Janssen; member of independent response assessment committee for GlaxoSmithKline. JK reports honoraria from OncLive. MA reports consulting or advisory role for Bristol-Myers Squibb and Janssen; speaker's bureau for Janssen; honoraria from Janssen. JM reports honoraria from Kite Pharma, Juno Therapeutics, Allovir, Magenta Therapeutics, and EcoR1 Capital; speakers bureau for Kite/Gilead; research funding from Novartis, Fresenius Biotech, Astellas Pharma, Bellicum Pharmaceuticals, Novartis, Gamida Cell, Pluristem Therapeutics, Kite Pharma, and AlloVir; Honoraria from Kite, AlloVir, Juno Therapeutics, and Magenta Therapeutics; travel, accommodations, expenses from Kita Pharma. FLL reports a scientific advisory role for Allogene, Amgen, Bluebird Bio, BMS/Celgene, Calibr, Cellular Biomedicine Group, GammaDelta Therapeutics, Iovance, Kite Pharma, Janssen, Legend Biotech, Novartis, Sana, Takeda, Wugen and Umoja; research funding from Kite Pharma (institutional), Allogene (institutional), Novartis (institutional), Blue-Bird Bio (institutional), CERo Therapeutics (institutional), and BMS (institutional); patents, royalties, and other intellectual property including several patents held by the institution in his name (unlicensed) in the field of cellular immunotherapy; consulting roles for Cowen, EcoR1, Emerging Therapy Solutions, and Gerson Lehrman Group (GLG); and education or editorial activity for Aptitude Health, ASH, BioPharma Communications CARE Education, Clinical Care Options Oncology, Imedex, and Society of Immunotherapy of Cancer. KKP reports consulting or advisory role for Bristol-Myers Squibb, Janssen, Pfizer, Arcellx, and Karyopharm Therapeutics; research funding from Bristol-Myers Squibb, Poseida Therapeutics, Takeda, Janssen, Cellectis, Nektar, Abbvie/Genentech, Precision Biosciences, and Allogene Therapeutics; travel, accommodations, and expenses from Bristol-Myers Squibb. DKH reports research funding from Bristol-Myers Squibb, Janssen, and Adaptive Biotech and consulting or advisory role for Bristol-Myers Squibb, Janssen, and Pfizer. MA reports research funding from Bristol-Myers Squibb, and honoraria from Janssen and Bristol-Myers Squibb. The remaining authors have no conflicts of interest to disclose.

Contributions

HH, LCP, MA were involved in conception, data collection, data analysis, manuscript writing, and manuscript revision. DKH, OCP, CF, GDA, SS, LS, DWS, JD, CW, MHK, SA, PV, GS, CG, NK, LDA, AA, DD, JK, JM, FL, RB and KKP were involved in data collection and critical review for the manuscript.

Data-sharing statement

The investigators agree to share the de-identified data upon reasonable request addressed to the corresponding authors.

References

1. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-2275.
2. Mikhael J. Treatment options for triple-class refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2020;20(1):1-7.
3. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.
4. Larry D. Anderson J, Munshi NC, Shah N, et al. Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in relapsed and refractory multiple myeloma: updated KarMMa results. J Clin Oncol. 2021;39(Suppl 15):8016.
5. Hansen DK, Sidana S, Peres LC, et al. Idecabtagene vicleucel for relapsed/refractory multiple myeloma: real-world experience from the Myeloma CAR T Consortium. J Clin Oncol. 2023;41(11):2087-2097.
6. Shah N, Munshi NC, Berdeja JG, et al. Baseline correlates of complete response to idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy in patients with relapsed and refractory multiple myeloma: subanalysis of the KarMMa Trial. Blood. 2021;138(Suppl 1):1739.
7. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-324.
8. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti–B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol. 2023;41(6):1265-1274.
9. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
10. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
11. Gagelmann N, Ayuk FA, Klyuchnikov E, Wolschke C, Berger SC, Kröger N. Impact of high-risk disease on efficacy of CAR-T cell therapy for multiple myeloma: a meta-analysis of 723 patients. Haematologica. 2023;108(10):2799-2802.
12. Peres LC, Oswald LB, Dillard C, et al. Racial and ethnic differences in clinical outcomes among multiple myeloma patients treated with CAR T therapy. Blood. 2022;140(Suppl 1):623-625.
13. Ferreri CJ, Hildebrandt MAT, Hashmi H, et al. Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy. Blood Cancer J. 2023;13(1):117
14. Samur MK, Fulciniti M, Aktas Samur A, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. Nat Commun. 2021;12(1):868.
15. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4(19):4898-4911.
16. Villanueva R, Hansen DK, Tonseth RP, et al. High metabolic tumor volume Is associated with higher toxicity and decreased efficacy of BCMA CAR-T cell therapy in multiple myeloma. Blood. 2022;140(Suppl 1):10402-10404.
17. Jain MD, Faramand R, Staedtke V, et al. The lymphoma tumor microenvironment influences toxicity after CD19 CAR T cell therapy. Blood. 2019;134(Suppl 1):4105.
18. Bladé J, Beksac M, Caers J, Jurczyszyn A, et al. Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer J. 2022;12(3):45.
19. Richard S, Lancman G, Rossi A, et al. Extramedullary relapse post CAR-T. Blood. 2022;140(Suppl 1):4301-4302.
20. Jain MD, Jacobs MT, Nastoupil LJ, et al. Characteristics and outcomes of patients receiving bridging therapy while awaiting manufacture of standard of care axicabtagene ciloleucel CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. Blood. 2019;134(Suppl 1):245.