Idecabtagene vicleucel chimeric antigen receptor T-cell therapy for relapsed/refractory multiple myeloma with renal impairment

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Abstract

We evaluated patients with relapsed multiple myeloma with renal impairment (RI) treated with standard of care idecabtagene vicleucel (ide-cel), as outcomes with chimeric antigen receptor (CAR) T-cell therapy are unknown in this population. RI was defined as creatinine clearance (CrCl) <50 mL/min. CrCl of <30 mL/min or dialysis dependence were defined as severe RI. The study cohort included 214 patients, 28 (13%) patients with RI, including 11 patients severe RI (dialysis, N=1). Patients with RI were older, more likely to be female and had higher likelihood of having Revised International Staging System stage 3 disease. Rates and severity of cytokine release syndrome (89% *vs.* 84%, grade ≥3: 7% *vs.* 2%) and immune effector cell-associated neurotoxicity syndrome (23% *vs.* 20%) were similar in patients with and without RI, respectively. Patients with RI had higher incidence of short-term grade ≥3 cytopenias, although cytopenias were similar by 3 months following CAR T-cell therapy. Renal function did not worsen after CAR T-cell therapy in patients with RI. Response rates (93% *vs.* 82%) and survival outcomes (median progression-free survival: 9 *vs.* 8 months; *P*=0.26) were comparable in patients with and without RI, respectively. Treatment with ide-cel is feasible in patients with RI, with a comparable safety and efficacy profile as patients without RI, with notable exception of higher short-term high-grade cytopenias.

Introduction

Idecabtagene vicleucel (ide-cel) is an autologous B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapy that was approved in United States in March 2021 for the treatment of patients with relapsed/refractory multiple myeloma (RRMM) who have received four or more prior lines of therapy, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody.[1-5] This approval was based on the pivotal phase II KarMMa trial of ide-cel which evaluated 128 patients who had received a median of six prior lines of therapy and were mostly triple-class refractory. In this heavily pretreated population, ide-cel resulted in an overall response rate (ORR) of 73%, a complete response (CR) of 33%, and minimal residual disease (MRD)

negativity rate of 26%.[6,7] This was significantly higher than response rates seen with other therapies that have been historically available for a similar indication, with response rates around 30% and median progression-free suvival (PFS) of 3-4 months.[4,6-9]

However, the KarMMa trial, akin to many other CAR T-cell therapy trials excluded patients with impaired renal function at the time of screening, excluding patients with creatinine clearance (CrCl) <45 mL/min.[10-14] At diagnosis, around 20% of patients with multiple myeloma (MM) have renal impairment (RI) due to cast nephropathy or other reasons.[15] Although exact estimates are not available in patients with relapsed disease, several patients do not recover renal function post-diagnosis or develop impaired renal function during the course of the treatment or due to disease relapse. This limits access of this novel therapy to a significant proportion of patients who have impaired renal function.

There are two main concerns for use of CAR T-cell therapy in patients with RI. First is lack of safety and efficacy data with CAR T cells in this patient population, and second is concern about using fludarabine as part of lymphodepletion chemotherapy, which is 40% renally cleared.[16-18] Most CAR T-cell therapy clinical trials have traditionally used fludarabine and cyclophosphamide lymphodepletion chemotherapy, though some clinical trials have used cyclophosphamide alone.[19-21] We hypothesized that ide-cel CAR T-cell therapy will result in similar efficacy and acceptable safety profile in patients with MM with RI compared to patients without RI, after adjusting lymphodepletion chemotherapy (specifically fludarabine) doses for renal function. The goal of this study was to evaluate the real-world outcomes of relapsed/refractory MM (RRMM) patients with RI treated with standard of care (SOC) ide-cel.

Methods

This was a retrospective multicenter observational study of patients with and without RI treated with SOC ide-cel under commercial label for RRMM from 11 medical centers in the US Multiple Myeloma Immunotherapy Consortium. Each center obtained independent institutional review board approval and informed consent per institutional requirements.

Patients

All RRMM patients who underwent apheresis for SOC ide-cel by May 1, 2022 and infusion by June 21, 2022 were included. If the CAR T-cell product did not meet release criteria, patients were treated under an expanded access protocol. RI was defined as CrCl <50 mL/min at the time of CAR T-cell therapy based on the Cockroft Gault equation. CrCl of <30 mL/min or being on dialysis was defined as severe RI. The cutoffs were selected as these are commonly used cutoffs for fludarabine dose reduction. Dosing of lymphodepletion chemotherapy and toxicity management was per institutional guidelines. High-risk cytogenetics were defined by the presence of del (17p), t(4;14), and t(14;16) at any time point prior to CAR T-cell infusion. Cytokine release syndrome (CRS) and neurotoxicity were graded based on the American Society for Transplantation and Cellular Therapy (ASTCT) criteria and hematologic toxicity was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[22,23] Response was assessed based on the International Myeloma Working Group Criteria (IMWG),[24] per investigator discretion, but due to the retrospective nature of our study, all of the IMWG criteria were not required to be fulfilled. Patients who died due to toxicity are included in the response assessment and considered as non-responders. Patients with insufficient follow-up, non-evaluable disease or where response data was not available are not included in the response-evaluable population. Cyclophosphamide (Cy) 300 mg/m^2 and fludarabine (Flu) were administered according to Food and Drug Adminstration-approved standard-dose labeling for LD chemotherapy on days -5, -4, and -3 prior to CAR T-cell infusion. All patients received fludarabine, however, fludarabine was dose adjusted per institutional protocol. Each center's instituional guidelines for fludarabine dose reduction from the conventional 30 mg/m^2 dose are described in detail in *Online Supplementary Table S1*. Toxicity management was also per institutional guidelines.

Statistical analyses

The distribution of patient and clinical characteristics, safety, and efficacy were examined by RI using χ^2 or Fisher exact tests for categorical variables or Kruskal-Wallis rank sum tests for continuous variables. PFS was calculated as time from infusion until progression or death, whichever occurred earlier. Patients who were alive and progression-free were censored at last follow-up. Overall survival (OS) was calculated as time between the date of infusion and date of death from any cause or last contact. Patients who were alive were censored at last follow-up. Kaplan Meier curves were used to depict survival data and survival outcomes by RI were compared using the log-rank test. Multivariable Cox proportional hazard regression models were used to examine the association of RI with PFS and OS, while adjusting for *a priori* selected patient characteristics (prior BCMA-targeted therapy, age at infusion, high-risk cytogenetics). The proportional hazard assumption was tested using covariate x time interaction terms individually and collectively. No violations of proportional hazards were observed. All analyses were conducted using R (Version 4.1.2.).

Results

The study cohort includes 214 patients from 11 medical centers who received ide-cel, of which 28 (13%) patients had RI. Among these, 11 (39%) patients had severe RI including one patient who was on dialysis. Table 1 describes patient

characteristics. Patients with RI were older (median age 69 *vs.* 63 years; *P*=0.001), more likely to be female (68% *vs.* 36%; *P*=0.001) and had higher likelihood of having R-ISS stage 3 disease (43% *vs.* 24%; *P*=0.03), driven by lower albumin and higher β-2-microglobulin levels. Overall, 33% of patients had high-risk cytogenetics with higher proportion of patients with high-risk cytogenetics in the RI cohort (48% *vs.* 21%; *P*=0.09). At baseline, patients with RI had lower platelet counts, with 32% of patients having platelets <50x10^9/L (grade 3 or 4 thrombocytopenia) compared to 17% in the normal renal function group (*P*=0.06). Patients with RI were more heavily pretreated with median of eight lines of therapy compared to six prior lines of therapy in patients without RI; *P*=0.03. There was no difference in the proportion of patients with penta-refractory disease (36% *vs.* 45%; *P*=0.4) or prior exposure to another BCMA-targeted therapy (25% each; *P*>0.9) Bridging therapy was more commonly used in patients with RI (93% *vs.* 75%; *P*=0.04). Dose reduction of fludarabine was more common in patients with RI (79% *vs.* 21%; *P*<0.001). Amongst patients with RI who underwent fludarabine dose reduction, 86% of patients had >20% dose reduction. There was no difference in CAR T-cell dose infused (median: 416 *vs.* 406 million cells) or proportion of patients receiving ≥400 million CAR T cells.

Safety

Table 2 describes toxicities experienced post CAR T-cell therapy in patients with and without RI, respectively. Patients with RI had similar incidence, severity and timing of CRS (any grade CRS: 89% *vs.* 84%; *P*=0.8 and grade ≥3: 7% *vs.* 2%; *P*=0.2) as patients without RI. The median time to maximum severity of CRS was 1 day in both groups. Similarly, patients with RI had comparable incidence and severity of ICANS as patients without RI (any grade ICANS: 23% *vs.* 20%; *P*=0.8 and grade ≥3: 12% *vs.* 6%; *P*=0.2). Patients with RI had a longer duration of hospital stay (median: 13.5 days *vs.* 9 days; *P*=0.03) and a trend towards higher incidence of intensive care unit admission (18% *vs.* 8%; *P*=0.07). Tocilizumab (79% *vs.* 68%; *P*=0.3) or anakinra use (4% *vs.* 5%; *P*>0.9) were similar, though patients with RI had a trend towards higher use of steroids (43% *vs.* 26%; *P*=0.07). Infection rates were similar amongst patients with and without RI (43% *vs.* 31%; *P*=0.2).

At day 7, patients with RI had higher incidence of severe cytopenias, including grade ≥3 anemia (43% *vs.* 25%; *P*=0.046) and grade ≥3 thrombocytopenia (75% *vs.* 45%; *P*=0.004). At day 30 post CAR T-cell therapy, patients with RI continued to have more severe cytopenias, with higher incidence of grade ≥3 neutropenia (54% *vs.* 34%; *P*=0.047) and grade ≥3 thrombocytopenia (75% *vs.* 41%; *P*<0.001). Cytopenias recovered over time and by 3 months post CAR T-cell therapy, there was no difference in grade ≥3 cytopenias amongst the two groups. Patients with RI required more supportive care for cytopenias with higher use of thrombopoietin (TPO) agonists (36% *vs.* 14%; *P*=0.01) and a trend towards higher use of granulocyte colony-stimulating factor (G-CSF, 89% *vs.* 74%; *P*=0.09). There was no difference in use of stem cell boost (5% *vs.* 4%; *P*>0.9).

Safety outcomes followed a similar trend when analyzing renal function as three groups: severe RI (CrCl <30 mL/min or dialysis dependence), moderate RI (CrCl 30-49 mL/min) and no RI (CrCl ≥ 50 mL/min), as shown in the *Online Supplementary Table S2*.

Renal function improved in some patients; importantly, renal function did not deteriorate in any patient with baseline RI. Amongst patients with paired baseline and day 30 data, no patient with CrCl 30-49 mL/min (N=16) experienced worsening of CrCl to <30 mL/min at day 30, with 12 of 16 patients remaining in the same same renal function group of CrCl 30-49 mL/min, while four of 16 patients experienced improvement in renal function to CrCl ≥50 mL/min. Amongst ten patients with CrCl <30 mL/min, three patients experienced improvement in CrCl to 30-49 mL/min, while seven patients had similar CrCl at day 30. Amongst 167 patients with CrCl ≥50 mL/min at CAR T-cell therapy, renal function worsened in 11 patients (7%) at day 30 post CAR T-cell therapy (CrCl <30 mL/min, N= 5 and CrCl 30-49 mL/min, N=6) (*Online Supplementary Table S3*).

Efficacy

Response

Patients with and without RI had similar response rates as shown in Figure 1 and *Online Supplementary Table S4*. At day 30, overall response rate (ORR, partial response or better) was 92% *versus* 76%; *P*=0.06 and complete response or better rate (CR rate) of 38% *versus* 28%, *P*=0.3 in patients with and without RI, respectively. When considering best response at any time, ORR was 93% *versus* 82%; *P*=0.2 and CR rate was 61% *versus* 49%; *P*=0.2.

Survival

The median follow-up of the cohort was 9.6 months. Renal function did not impact PFS or OS (Figure 2; *Online Supplementary Figure S1*). Median PFS in patients with and without RI was 9 *versus* 8 months; *P*=0.28, and median OS was not reached *versus* 15.5 months; *P*=0.25, respectively. On multivariable analysis (Table 3), RI was not an independent predictor for PFS (hazard ratio [HR] =0.82; 95% confidence interval [CI]: 0.45-1.49; *P*=0.5), while high-risk cytogenetics and prior BCMA therapy were independent adverse prognostic factors. Similarly, RI was not an independent predictor for OS (HR=0.61; 95% CI: 0.26-1.45; *P*=0.3), while prior BCMA threapy and younger age were independent adverse prognostic factors. When analyzing renal function as three groups: severe RI (CrCl <30 mL/min or dialysis dependence), moderate RI (CrCl 30-49 mL/min) and no RI (CrCl ≥50 mL/min), we observed similar results, with no difference in PFS and OS amongst the three groups, including in multivariable analysis (*Online Supplementary Table S5; Online Supplementary Figure S1*). Fludarabine dose reduction did

Table 1. Baseline and treatment characteristics in patients with relapsed/refractory multiple myeloma with and without renal impairment receiving idecabtagene vicleucel.

Characteristics	Overall N=214	CrCl <50 mL/min N=28	CrCl ≥50 mL/min N=186	*P*
	Median (range) or N (%)	Median (range) or N (%)	Median (range) or N (%)	
Age in years	64 (36-83)	69 (50-83)	63 (36-83)	0.001
Age ≥65 years	103 (48)	20 (71)	83 (45)	0.008
Sex: Female	86 (40)	19 (68)	67 (36)	0.001
Race and ethnicity				0.11
Hispanic	22 (10)	0 (0)	22 (12)	
Non-Hispanic Black	36 (17)	6 (21)	30 (16)	
Non-Hispanic White	148 (69)	20 (71)	128 (69)	
Other	8 (4)	2 (7)	6 (3)	
Extramedullary disease	96 (45)	13 (46)	83 (45)	0.9
BMPC (≥50%)	58 (30)	9 (32)	49 (29)	0.7
Marrow PC unknown	18	0	18	
ECOG PS 2-4, N=206	35 (17)	6 (23)	29 (16)	0.4
R-ISS at CAR T-cell infusion, N=163				0.03
I	36 (22)	1 (4.3)	35 (25)	
II	83 (51)	12 (52)	71 (51)	
III	44 (27)	10 (43)	34 (24)	
High-risk cytogenetics, N=187	62 (33)	12 (48)	50 (31)	0.09
Laboratory data				
ANC <1,000/uL	26 (12)	2 (7.1)	24 (13)	0.5
Hemoglobin <8 g/dL	33 (15)	6 (21)	27 (15)	0.4
Platelets <50x10^9/L	41 (19)	9 (32)	32 (17)	0.06
β-2-microglobulin, mg/L	3.0 (0.7-15.3)	4.2 (2.4-13.5)	2.9 (0.7-15.3)	0.004
Albumin, g/dL	3.6 (1.7-4.8)	3.3 (2.4-4.7)	3.7 (1.7-4.8)	0.005
Prior therapy				
Prior lines of therapy	6 (3-19)	8 (5-15)	6 (3-19)	0.03
Prior autologous SCT	180 (84)	23 (82)	157 (84)	0.8
Prior allogeneic SCT	10 (5)	2 (7)	8 (4)	0.6
Prior anti-BCMA therapy	53 (25)	7 (25)	46 (25)	>0.9
Triple refractory	178 (83)	26 (93)	152 (82)	0.2
Penta refractory	93 (43)	10 (36)	83 (45)	0.4
Bridging therapy	166 (78)	26 (93)	140 (75)	0.04
CAR T-cell dose, median (range)*	406 (154-459)	416 (156-455)	406 (154-459)	0.6
Cell dose ≥400 million CAR T-cells	120 (56)	18 (64)	102 (55)	0.4
Fludarabine dose reduction, yes	61 (29)	22 (79)	39 (21)	<0.001
Fludarabine dose reduction %				
≤20	22 (36)	3 (14)	19 (49)	
21-40	16 (26)	7 (32)	9 (23)	0.018
>40	23 (38)	12 (55)	11 (28)	

CrCL: creatinine clearance; BMPC: bone marrow plasma cells; PC: plasma cells; ECOG PS: Eastern Cooperative Oncology Group performance status; R-ISS: Revised International Staging System; CAR: chimeric antigen receptor; high-risk cytogenetics: includes del(17p), t(4;14) and t(14;16); SCT: stem cell transplantation; ANC: absolute neutrophil count; BCMA: B-cell maturation antigen; triple-refractory disease: refractory to an immunomulatory drug, proteosome inhibitor, and an anti-CD38 monoclonal antibody; penta-refractory disease: refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab or isatuximab. *CAR T-cell dose was not known in 1 patient with CrCl ≥50 mL/min.

not impact PFS or OS, as shown in Figure 3. Median PFS for patients with no dose reduction, up to 40% dose reduction and more than 40% dose reduction was 7.7 *versus* 9.3 *versus* 8.1 months; *P*=0.81 respectively.

Sub-group analysis for creatinine clearance cutoff of 45 mL/min

As patients with CrCl <45 mL/min were excluded from the KarMMa clinical trial, we conducted a sub-group analysis of safety and efficacy of ide-cel using this CrCL cutoff. Results were similar. Differences in baseline characteristics and safety were comparable to the analysis using the 50 mL/min CrCL clearance cutoff (*Online Supplementary Tables S6* and *S7*). Response rates, PFS and OS were also similar between groups (*Online Supplementary Figures S2* and *S3*).

Discussion

This large retrospective study is the first cohort study to report on outcomes of RRMM patients with renal dysfunction treated with BCMA-directed CAR T-cell therapy. Such patients have been historically excluded from clinical trials of CAR T-cell therapy in RRMM, and the safety and efficacy of CAR T-cell therapy has not been previously described in this population. We observed that ide-cel CAR T-cell therapy is feasible in patients with RI, with efficacy comparable to

Table 2. Toxicities in patients with relapsed/refractory multiple myeloma with and without renal impairment (creatinine clearance of <50 mL/min) receiving idecabtagene vicleucel.

	Overall N=214	CrCl <50 mL/min N=28	CrCl ≥50 mL/min N=186	*P*
	Median (range) or N (%)	Median (range) or N (%)	Median (range) or N (%)	
Cytokine release syndrome				
Any	82 (85)	25 (89)	157 (84)	0.8
Grade ≥3	6 (3)	2 (7)	4 (2)	0.2
ICANS[a]				
Any	41 (20)	6 (23)	35 (20)	0.7
Grade ≥3	13 (6)	3 (12)	10 (6)	0.2
Resource utilization				
Median hospital stay, days	9 (5-69)	13.5 (6-69)	9 (5-68)	0.03
Intensive care unit stay, yes	19 (9)	5 (18)	14 (8)	0.08
Tocilizumab use	149 (70)	22 (79)	127 (68)	0.3
Corticosteroid use	61 (29)	12 (43)	49 (26)	0.07
Anakinra use	10 (5)	1 (4)	9 (5)	>0.9
Infection	69 (32)	12 (43)	57 (31)	0.2
Hematologic toxicity in 90 days[b]				
Day 7: grade ≥ 3 cytopenia				
Grade ≥3 anemia	58 (27)	12 (43)	46 (25)	0.046
Grade ≥3 neutropenia	143 (70)	22 (79)	121 (68)	0.7
Grade ≥3 thrombocytopenia	105 (49)	21 (75)	84 (45)	0.004
Day 30: grade ≥3 cytopenia				
Grade ≥3 anemia	39 (19)	8 (29)	31 (17)	0.2
Grade ≥3 neutropenia	76 (37)	15 (54)	61 (34)	0.047
Grade ≥3 thrombocytopenia	94 (45)	21 (75)	73 (41)	<0.001
Day 60: grade ≥3 cytopenia				
Grade ≥3 anemia	32 (19)	9 (39)	23 (16)	0.02
Grade ≥3 neutropenia	44 (26)	7 (30)	37 (26)	0.6
Grade ≥3 thrombocytopenia	58 (35)	10 (43)	48 (33)	0.3
Day 90: grade≥3 cytopenia				
Grade ≥3 anemia	16 (9)	2 (8)	14 (9)	>0.9
Grade ≥3 neutropenia	24 (13)	3 (12)	21 (14)	>0.9
Grade ≥3 thrombocytopenia	41 (23)	5 (20)	36 (23)	0.7
Supportive care for cytopenias				
G-CSF	162 (76)	25 (89)	137 (74)	0.09
TPO agonist	35 (17)	10 (36)	25 (14)	0.01
Stem cell boost	8 (4)	1 (5)	7 (4)	>0.9

CrCL: creatinine clearance; G-CSF: granulocyte colony-stimulating factor; ICANS: immune effector cell-associated neurotoxicity; TPO: thrombopoietin. [a]Data on ICANS was missing in 10 patients (2 in CrCl <50 mL/min cohort and 8 in CrCL ≥50 mL/min cohort. [b]For hematology labs, at day 7, 1 patient missing anemia and thrombocytopenia data and 9 patients missing neutropenia data; day 30: 6 patients missing anemia and thrombocytopenia data and 7 missing neutropenia data; day 60: 46 missing anemia and thrombocytopenia data and 47 missing neutropenia data; day 90: 33 patients missing anemia and thrombocytopenia data and 34 missing neutropenia.

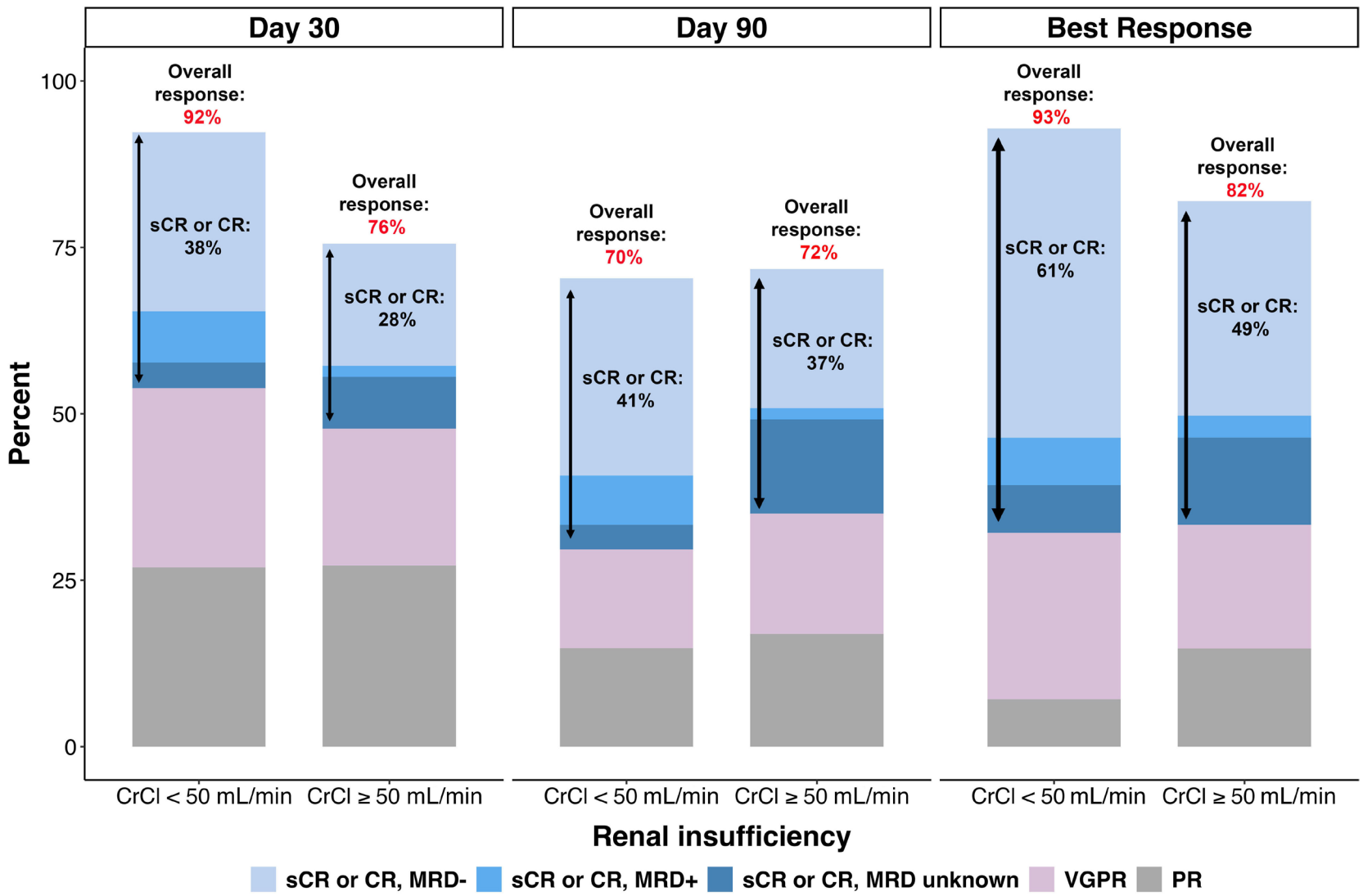
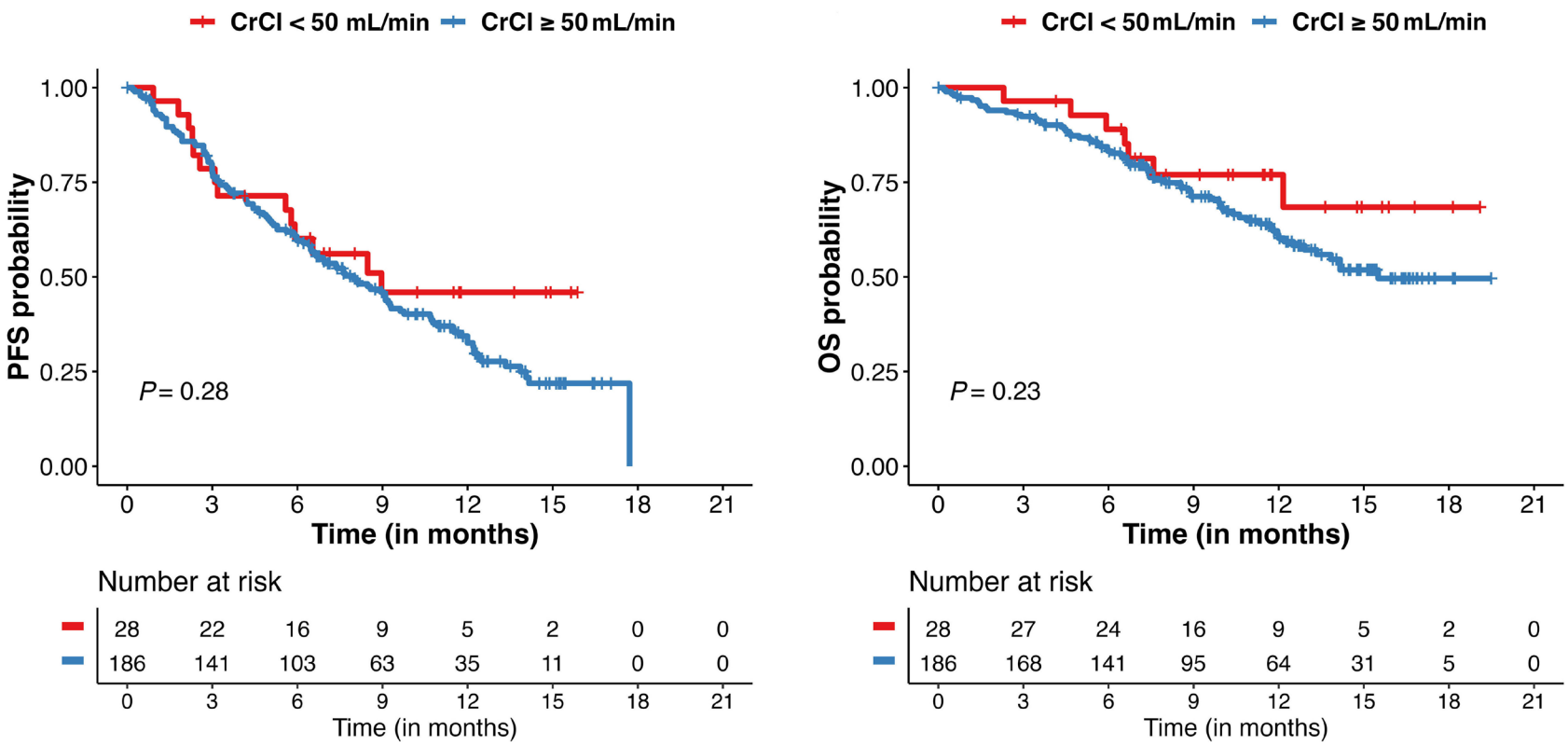


Figure 1. Efficacy of idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma with and without renal impairment. Patients who died or progressed before the time point of interest were considered non-responders. Patients who were not evaluable by International Myeloma Working Group response criteria, or when data was not provided or time point not reached were excluded from the denominator. CrCL: creatinine clearance; CR: complete response; sCR: stringent complete response; MRD: minimal residual disease; VGPR: very good partial response; PR: partial response.

patients with normal renal function. Safety was also similar, although there were notable differences of short-term high grade cytopenias and longer hospital stay.

In terms of safety, the incidence and severity of CRS and neurotoxicity were comparable in patients with and without RI, including in patients with severe RI (defined as CrCl <30 mL/min or dialysis dependence). There was no difference in the timing of such toxicities. Management of CRS and neurotoxcity was generally similar with no difference in rates of tocilizumab or anakinra use, although we observed a trend towards higher use of steroids in patients with RI. It is possible that investigators used a more aggressive toxicity management approach in such patients, given lack of prior safety data in this population. Compared to patients without RI, patients with RI had longer hospital stay, and while not statistically significant, a higher incidence of intensive care unit stay. The reasons for higher incidence of intensive care unit stay is unclear given similar severity of CRS and neurotoxicty. The rates of infectious complications were not significantly different amongst the two groups, though were numerically higher in patients with RI. However, we did not capture all adverse events or analyze the time trends in infectious complications, and it is unknown whether patients with RI had more infections in the first few weeks after CAR T-cell therapy, especially in context of higher rates of severe neutropenia in the short-term in this group. Patients with RI were more likely to have ongoing grade ≥3 neutropenia and thrombocytopenia at 1 month following CAR T-cell therapy, though rates were comparable by 2 months following CAR T-cell infusion. Therefore, it was not surprising to see higher use of TPO agonists and a trend towards higher use of G-CSF in patients with RI. Given renal clearance of fludarabine, fludarabine-associated toxicities are of concern in this population. It is important to note that we did not observe any occurrence of fludarabine-related cerebellar toxicity. It was reassuring to see that renal function did not deteriorate following CAR T-cell therapy in patients with RI, and some patients actually had an improvement in renal function. There was no new need for dialysis in patients with RI following CAR T-cell infusion. Importantly, efficacy including response rates and survival outcomes following ide-cel were similar in patients with and without RI, including in patients with severe RI. There was no difference in PFS and OS, even after accounting for other known prognostic factors in a multivariable model. Consistent with previous data reported by our group in



	Median PFS in months	95% CI (PFS) in months	Median OS in months	95% CI (OS) in months
CrCl <50 mL/min	9	5.8-NR	NR	NR-NR
CrCl ≥50 mL/min	8	6.5-9.3	15.5	12.9-NR
Median follow-up in months: 9.6				

Figure 2. Survival outcomes with idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma with and without renal impairment. PFS: progression-free survival; CI: confidence interval; OS: overall survival; CrCL: creatinine clearance; min: minutes; NR: not reached.

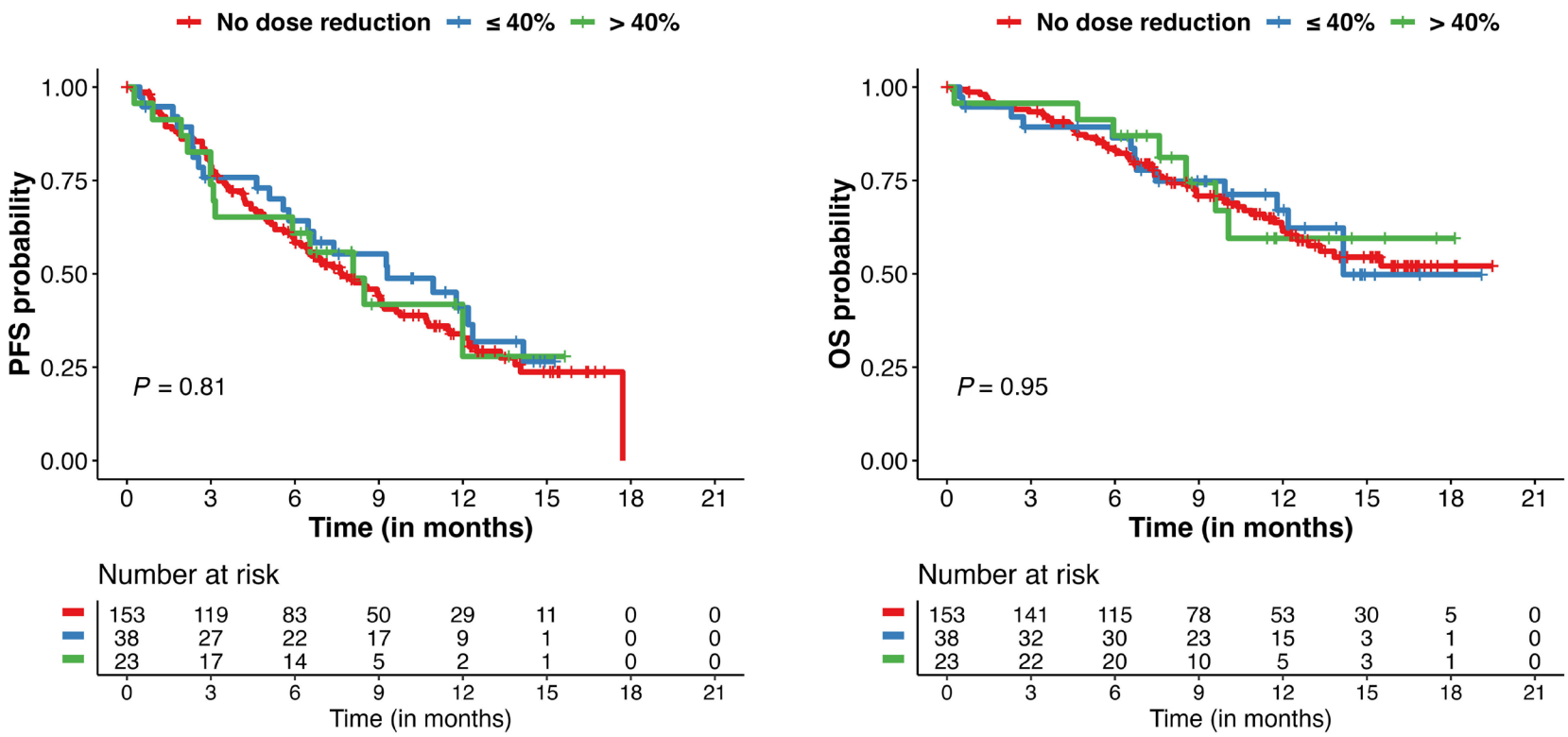
Table 3. Multivariable models of the association of selected patient characteristics with progression-free survival and overall survival in patients with and without renal impairment treated with idecabtagene vicleucel.

Characteristic	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Renal function CrCl ≥50 mL/min CrCl <50 mL/min	 1.00 (Referent) 0.82 (0.45-1.49)	0.5	 1.00 (Referent) 0.61 (0.26-1.45)	0.3
Prior BCMA-TT No Yes	 1.00 (Referent) 1.81 (1.22, 2.67)	0.003	 1.00 (Referent) 1.65 (0.99-2.74)	0.05
High-risk cytogenetics No Yes	 1.00 (Referent) 1.61 (1.10-2.36)	0.02	 1.00 (Referent) 1.43 (0.87-2.36)	0.2
Patient age	0.98 (0.96-1.00)	0.08	0.97 (0.95-1.00)	0.06

Full data on all variables available in 187 patients. Missing data in 27 patients is due to missing cytogenetic data. PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; CrCl: creatinine clearance; HR: hazard ratio; BCMA-TT: B-cell maturation antigen-targeted therapy; min: minutes. High-risk cytogenetics: includes del(17p), t(4;14) and t(14;16).

patients receiving standard of care ide-cel,[25] high-risk cytogenetics and prior use of BCMA-targeted therapy were independent adverse prognostic factors. Interestingly, there was no difference in survival based on fludarabine dose reduction, likely reflecting similar exposure to fludarabine with reduced dose fludarabine in patients with RI due to decreased clearance of fludarabine.

While data on use of CAR T-cell therapy in RRMM patients with RI is sparse and limited to case reports,[26] a few recent studies have reported on outcomes with CD19-directed CAR T-cell therapy for large cell lymphoma in patients with RI.[21,27] It has been reported that CD19 CAR T-cell therapy is feasible in patients with RI, including patients on dialysis. Safety and efficacy of CD19 CAR T-cell therapy in patients



Fludarabine dose reduction	Median PFS in months	95% CI (PFS) in months	Median OS in months	95% CI (OS) in months
No dose reduction	7.7	6.4-9.2	NR	12.9-NR
Up to 40% reduction	9.3	6.5-NR	14.2	NR
>40% reduction	8.1	3.2-NR	NR	9.6-NR
Median follow-up: 9.6 months				

Figure 3. Survival outcomes with idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma based on fludarabine dose reduction. PFS: progression-free survival; CI: confidence interval; OS: overall survival; NR: not reached.

with RI was comparable to patients with normal renal function. In these two studies, RI was defined as having a CrCl <60 mL/min, while we defined RI as having a CrCl <50 mL/min. We selected the latter threshold as CrCl of <50 mL/min for two reasons. First, this is a common cutoff for change in fludarabine dose in several institutional protocols and second, this cutoff was more closely aligned with exclusion criteria of the pivotal KarMMa clinical trial.[6] We also conducted a sub-group analysis for CrCL cutoff of <45 mL/min as that was the cutoff used in the KarMMa clinical trial. Our findings investigating differences in safety and efficacy by renal insufficiency were comparable using a CrCL cutoff of 45 or 50 mL/min.

Strengths of this study include multi-institutional cohort of patients treated with ide-cel, with this being the largest cohort of patients with RI undergoing CAR T-cell therapy to best of our knowledge. Limitations of our study include its retrospective design, and heterogeneity in institutional standards for fludarabine dose reduction and toxicity management across different centers. Data on etiology of RI was not available. This data provides the foundation to further investigate CAR T-cell therapy in patients with RRMM, and a future clinical trial is planned in this population with uniform fludarabine dose reduction and toxicity management. Cast nephropathy is a hallmark feature of MM and many patients never completely recover renal function. Additionally, adverse effects of treatment can also lead to worsening renal function in patients over time. Excluding patients with RI in clinical trials of CAR T-cell therapy limits access of these novel therapies to a large proportion of patients with RRMM. Given our findings showing that CAR T-cell therapy is feasible, safe and effective in this population, future clinical trials of CAR T-cell therapy should include patients with RI. This can be done as part of the main population under study or in unique cohorts carved out for patients with RI. In summary, it is feasible to treat patients with MM who have RI with CAR T-cell therapy. The efficacy and safety profile with SOC ide-cel in patients with RI is comparable to patients without RI, with some notable differences. Such patients should not be excluded from future clinical trials of CAR T-cell therapy in MM.

Disclosures

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Contributions

SS, LCP and DKH developed the concept and designed the study. SS, LCP, HH, HH, CF, JK, DD, SA, PV, GS, NK, VH, SB, DM, DWS, CW, CF, MA, FL, RG, MHK, GK, AA, JMG, LS, KKP and DKH provided study materials and patients. HH, HH, CF, JKi, DDa, SA, PV, GS, NK, VH, SB, DM, DWS, CW, CF, MA, FL, RG, MHK, GK, AA, JMG, LS, KKP and DKH collected and assembled data. SS, LCP, KKP and DKH analzed and interpreted data. All authors wrote the manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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