French early nationwide idecabtagene vicleucel chimeric antigen receptor T-cell therapy experience in patients with relapsed/refractory multiple myeloma (FENIX): A real-world IFM study from the DESCAR-T registry

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French early nationwide idecabtagene vicleucel chimeric antigen receptor T-cell therapy experience in patients with relapsed/refractory multiple myeloma (FENIX): A real-world IFM study from the DESCAR-T registry

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Summary

Idecabtagene vicleucel (ide-cel), a chimeric antigen receptor T-cell therapy targeting B-cell maturation antigen (BCMA), received early access program (EAP) authorization in France in April 2021 for relapsed/refractory multiple myeloma (RRMM). We conducted a real-world registry-based multicentre observational study in 11 French hospitals to evaluate ide-cel outcomes. Data from 176 RRMM patients who underwent apheresis between June 2021 and November 2022 were collected from the French national DESCAR-T registry. Of these, 159 patients (90%) received ide-cel. Cytokine release syndrome occurred in 90% with 2% grade ≥3, and neurotoxicity occurred in 12% with 3% grade ≥3. Over the first 6 months, the best overall response and ≥complete response rates were 88% and 47% respectively. The median progression-free survival (PFS) from the ide-cel infusion was 12.5 months, the median overall survival (OS) was 20.8 months and the estimated OS rate at 12 months was 73.3%. Patients with extra-medullary disease (EMD) had impaired PFS (6.2 months vs. 14.8 months). On multivariable analysis, EMD and previous exposure to BCMA-targeted immunoconjugate or T-cell-redirecting GPRC5D bispecific antibody were associated with inferior PFS. Our study supports ide-cel's feasibility, safety and efficacy in real-life settings, emphasizing the importance of screening for EMD and considering prior treatments to optimize patient selection.

KEYWORDS
cellular therapies, immunotherapy, multiple myeloma, real-world experience

For affiliations refer to page 8.

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INTRODUCTION

Despite recent therapeutic advances, current options for relapsed or refractory multiple myeloma (RRMM) are limited.[1,2] Triple-class-exposed patients (having received a proteasome inhibitor [PI], an immunomodulatory drug [IMiD] and an anti-CD38 monoclonal antibody [mAb]) still exhibit a poor prognosis, and until recently, no recommended standard of care has been identified.[1]

Idecabtagene vicleucel (ide-cel), a B-cell maturation antigen (BCMA)-targeting chimeric antigen receptor T-cell therapy, was authorized in France, in an early access program (EAP), in April 2021 for patients with RRMM who have received at least three prior treatments (including IMiD, PI and an anti-CD38) and whose disease progressed during the last treatment, based on the pivotal phase II KarMMa trial.[2] While ide-cel has been available for triple-class-exposed RRMM in France for the past 2 years, real-world patients may present a broader disease and treatment profile with different clinical-biological features compared with the KarMMa patient population. Therefore, we conducted a nationwide multicentre retrospective study to evaluate the efficacy and safety of ide-cel in real-world settings.

MATERIALS AND METHODS

This registry-based multicentre observational study included all patients with RRMM included in the DESCAR-T registry[3] who underwent apheresis between June 2021 and November 2022 with the intent to manufacture ide-cel in the EAP from 11 French centres. The study protocol received approval from national ethics committees, adhering to the Declaration of Helsinki and the national data protection agency. DESCAR-T is registered under the ClinicalTrials.gov identifier NCT04328298.

Treatment and clinical assessment

Bridging treatment including chemotherapy and/or radiation were performed at the physician's discretion. All but three of the infused patients received lymphodepleting chemotherapy using cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) on Days −5, −4 and −3 before ide-cel infusion. Three patients received bendamustine-based regimen.

Haematological toxicity was graded according to the CTCAE version 5.0, whereas cytokine release syndrome (CRS) and neurotoxicity (NT) were assessed on the basis of the ASTCT criteria.[4] Treatment of CRS and NT as well as infectious disease prophylaxis were conducted according to institutional guidelines. Response was assessed according to the IMWG[5] per investigator discretion. Minimal residual disease (MRD) was assessed by clonoSEQ or flow cytometry, at a sensitivity of at least 10^{-5} nucleated cells. High-risk cytogenetic was defined by the presence of del (17p) and/or t(4;14). EMD was defined as soft-tissue plasmacytomas with no contact with bony structures[6] and was assessed by the investigator.

Refractoriness was defined as disease progression on or within 60 days after the last dose of the most recent drug given in each drug class. Triple-refractory patients were those refractory to one PI (bortezomib or carfilzomib), one IMiD (lenalidomide or pomalidomide) and one monoclonal anti-CD38 antibody (daratumumab or isatuximab). Penta-refractory patients were those refractory to both PI (Bortezomib AND Carfilzomib), both IMiD (Lenalidomide AND Pomalidomide) and at least one anti-CD38 mAb.

Statistical analyses

Quantitative data are described using median, ranges and interquartile ranges. Qualitative data are presented using frequency and percentage. Overall survival (OS) was defined as the time between CAR-T-cell infusion and death from any cause. Progression-free survival (PFS) was defined as the time between infusion to either progression or death. OS and PFS were estimated using Kaplan–Meier method and presented with their respective two-sided 95% CI. The association between baseline covariates and at least VGPR as the best overall response at 6 months was estimated using logistic regression and presented by the corresponding odds ratio (OR) with 95% CI. The association between baseline covariates and PFS or OS was estimated using Cox proportional hazard regression and is presented by the corresponding hazard ratio (HR) with 95% CI. Where more than one variable was significantly associated with an outcome, a multivariable analysis including all associated covariates ($p < 0.3$) was performed, using an Akaike information criterion stepwise algorithm for variable selection. Finally, a landmark analysis was used to assess the association between response at M1 and PFS. All statistical tests are two-sided, with a significance level set at 5%.

RESULTS

Patients and treatment

Between June 2021 and November 2022, 176 patients from 11 French centres underwent leucapheresis with the intent to manufacture ide-cel as part of the EAP. Fifty patients (28%) did not meet the KarMMa trial inclusion criteria (ClinicalTrials.gov identifier: NCT03361748). The most common reasons for trial ineligibility included cytopenias (absolute neutrophil count <1000/mL or platelet count <50 000/mL) in 22 patients (45%), renal dysfunction (creatinine clearance ≤45 mL/min) in 13 patients (33%), prior use of belantamab mafodotin, an immunoconjugate targeting BCMA in 8 patients (16%), an Eastern Cooperative Oncology Group performance status (ECOG PS) >1 in 9 patients (20%) and prior allogenic haematopoietic stem cell transplantation in 4 patients (8%).

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Among the 176 apheresed patients, 17 patients (10%) were not infused: six died before administration, three experienced significant clinical deterioration after apheresis, five underwent manufacturing failure, two patients refused infusion and one patient was not infused based on the decision of the physician. Finally, 159 patients were infused (Figure 1).

Patient characteristics are shown in Table 1. The median age was 61 years (range, 34–82 years), and 59% of patients were male. The median number of prior lines of therapy was 4 (range, 2–12); 91% of patients had received a prior autologous stem cell transplant; 79% and 28% of patients had triple-refractory and penta-refractory disease respectively. Seven patients (4%) had previously received belantamab mafodotin, and six patients (4%) had received talquetamab, a T-cell-redirecting GPRC5D bispecific antibody. Forty-four patients (42%) had high-risk cytogenetics, and 27 patients (17%) had EMD at lymphodepletion.

One hundred and thirty-seven patients (86%) received bridging therapy during the manufacturing period, at investigator discretion (drug classes are reported in Table 1). Responses to bridging therapy were observed in 33% of patients with CR, VGPR, PR and MR in 4%, 7%, 19% and 3% of patients respectively. Stable disease was observed in 21% of patients and progressive disease in 46% of patients (Table 1).

In seven patients, manufacturing failure occurred at the first leucapheresis; two of them were infused after a second leucapheresis. The median time from leucapheresis to infusion was 62 days (range, 50–131 days). The median number of cells infused was 420×10^6 (range, 96×10^6–509×10^6 cells), and the median cell viability rate was 95% (range, 84%–99%).

Safety

Toxicities associated with ide-cel infusion are reported in Table 2. CRS occurred in 90% of patients, mostly of grade 1 or 2, with three patients (2%) experiencing grade ≥3 CRS. The median time to the onset of CRS was within 24 h after infusion (range, 0–16 days). Early NT (within 10 days after infusion) occurred in 20 patients (13%), with six patients (4%) having grade ≥3 NT. The median time to the onset of NT was 1.5 days (range, 0–7 days). Management of CRS and/or NT included tocilizumab in 61% of patients and steroids in 23% of patients. One patient experienced a spontaneously resolving grade 1 NT 3 months after infusion.

Haematological toxicities were the most common grade ≥3 adverse effects arising from treatment. By 1 month after infusion (M1), grade ≥3 thrombocytopenia, neutropenia and anaemia were reported in 35%, 59% and 13% of patients respectively. Persistence of grade ≥3 cytopenias to M3 and M6 was, respectively, observed for 21% and 11% of patients with thrombocytopenia, 25% and 9% of patients with neutropenia and 7% and 4% of patients with anaemia. Management of cytopenias included granulocyte colony-stimulating factor injection in 56% of patients, recombinant erythropoietin substitution in 21% of patients and

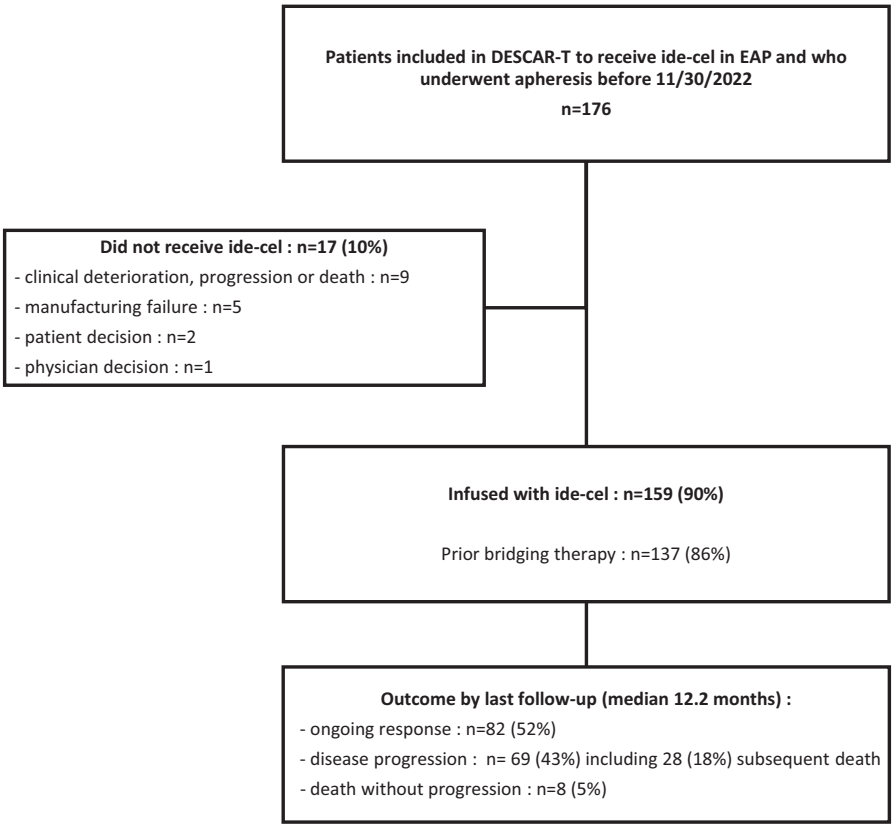

FIGURE 1 Study flowchart. EAP, early access program.

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TABLE 1 Baseline characteristics of infused patients. Alkylating agents include melphalan, cyclophosphamide and bendamustine.

Parameters	*N*	Median [IQR] (range)/percentage	Parameters	*N*	Median [IQR] (range)/percentage
Age	159	61 [54;69] (34;82)	Refractory status		
<60 years	71	45%	Proteasome inhibitor	149	94%
Female gender	65	41%	Bortezomib	94	59%
ECOG			Carfilzomib	121	76%
0–1	137	94%	IMiD	147	92%
2–4	8	6%	Lenalidomide	113	71%
Unknown	14		Pomalidomide	126	79%
Cytogenetics			Anti-CD38	142	89%
High-risk cytogenetics: del(17p) or t(4;14) present	44	42%	Daratumumab	117	74%
del(17p) or t(4;14) unknown	53		Isatuximab	41	26%
del(17p) present	31	29%	Triple-refractory	126	79%
del(17p) unknown	52		Penta-refractory	45	28%
t(4;14) present	19	17%	Bridging therapy	137	86%
t(4;14) unknown	48		IMiD based	45	33%
Extra-medullar involvement at lymphodepletion	27	17%	PI based	68	50%
			Anti-CD38 based	32	23%
			Alkylating agents based	62	45%
Prior therapies			Non-alkylating chemotherapy based	27	20%
Number of treatment lines before enrolment	159	4 [3;6] (2;12)	Radiotherapy based	8	6%
≥5 prior treatment lines	75	47%	Best response to bridging		
Prior autologous transplant	144	91%	CR	5	4%
Prior allogenic transplant	4	3%	VGPR	8	7%
Prior belantamab mafodotin	7	4%	PR	23	19%
Prior talquetamab	6	4%	MR/SD	29	24%
Prior radiotherapy	42	26%	PD	55	46%
			Unknown	17	

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

transfusion with red blood cell or platelet concentrates in 23% and 25% of patients respectively. No autologous stem cell boost was used.

In the first 6 months, 42 patients (26%) presented grade ≥3 infection (58 events): 28 bacterial infections (mostly catheter-related bloodstream infections), 11 viral infections, 5 fungal infections and 14 undocumented infections.

Efficacy

Depth of response

M1, M3, M6 and M12 responses were assessed in 146, 153, 141 and 101 patients respectively. Dead patients (any cause) were considered non-responders. Over the first 6 months, the best overall response ≥PR rate was 88%, ≥VGPR rate was 73% and (s) CR rate was 47%. Responses at each time point among evaluable patients are reported in Figure 2: M1, M3 and M6 overall response rates (ORR) were 80%, 78% and 68%, with corresponding ≥VGPR rates being 43%, 60% and 63% respectively. During the first 6 months, MRD status was evaluated at least once in 47 patients (30%), of whom 37 (79%) achieved MRD negativity.

No baseline characteristic was found to be significantly associated with a best response of ≥VGPR in the first 6 months (Table S1). In particular, neither EMD (OR = 0.69 [0.28–1.69]; $p = 0.42$), nor high-risk cytogenetics (OR = 1.04 [0.43–2.54]; $p = 0.93$), nor prior use of belantamab mafodotin (OR = 0.73 [0.13–4.15]; $p = 0.93$) were significantly associated with a different response.

PFS and OS

The median follow-up time after infusion was 12.2 months [95% CI, 11.5–12.3]. The median PFS from ide-cel infusion

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TABLE 2 Ide-cel-associated adverse events.

Parameters	*N* patients	Median [IQR] (range)/percentage
Early toxicity (infusion D1 to D10) (*N* = 159)		
Cytokine release syndrome (CRS)	143	90%
CRS within the first 2 days	132	83%
CRS grade ≥3	3	2%
Time between reinjection and CRS (days)	143	0 [0;1] (0;16)
Neurotoxicity	20	13%
Neurotoxicity grade ≥3	6	4%
Time between reinjection and neurotoxicity (days)	20	1.5 [1;4] (0;7)
Tocilizumab use	97	61%
Corticosteroids use	37	23%
Infections in the first 6 months (*N* = 159)		
Any grade	54	34%
Grade ≥3	42	26%
Haematological toxicity		
Anaemia grade ≥3		
M1 (*N* = 158)	21	13%
M3 (*N* = 154)	11	7%
M6 (*N* = 151)	6	4%
M12 (*N* = 119)	1	1%
M18 (*N* = 56)	0	0%
Thrombocytopenia grade ≥3		
M1 (*N* = 158)	56	35%
M3 (*N* = 154)	32	21%
M6 (*N* = 151)	16	11%
M12 (*N* = 119)	6	5%
M18 (*N* = 56)	5	9%
Neutropenia grade ≥3		
M1 (*N* = 158)	93	59%
M3 (*N* = 154)	38	25%
M6 (*N* = 151)	13	9%
M12 (*N* = 119)	8	7%
M18 (*N* = 56)	3	5%
Growth factors/transfusion		
Red blood cell concentrates transfusion	37	23%
Platelets concentrates transfusion	40	25%
Recombinant erythropoietin injection	33	21%
Granulocyte colony-stimulating factor injection	89	56%

was 12.5 months [95% CI, 8.8–16.3], the median OS was 20.8 months [95% CI, 19.4–NA] and the estimated OS rate at 12 months was 73.3% [95% CI, 65.5–81.9] (Figure 3). Patients with EMD ($n = 27$) had a significantly decreased PFS compared with those without EMD ($n = 132$): median PFS was 6.21 months (95% CI [4.01–NA]) vs. 14.82 months (95% CI [11.3–18.37]). Of interest, patients with EMD had a significantly lower rate of infusion compared with patients without EMD: 8/35 not infused versus 9/141 ($p = 0.007$). Penta-refractory status was associated with a trend towards shorter PFS ($p = 0.063$) (Figure S1). Neither high-risk cytogenetics ($p = 0.63$), nor the number of previous lines of treatment ≥5 ($p = 0.51$), nor progression after bridging therapy ($p = 0.95$) were significantly associated with shorter PFS (Figure S1).

A multivariate analysis using the Cox model was performed to determine factors independently associated with shorter PFS (Table S2). From this analysis, EMD (HR = 3.15; 95% CI [1.82–5.47]; $p < 0.0001$), prior use of belantamab mafodotin (HR = 4.49; 95% CI [1.89–10.67], $p = 0.007$) and talquetamab (HR = 7.4; 95% CI [3.11–17.64]; $p < 0.0001$) were associated with shorter PFS (Figure 4). Among patients without progression during the first month, response <VGPR at M1 was associated with a trend towards shorter PFS ($p = 0.049$) (Figure S1).

Out of 69 (43%) patients who progressed, 59 (86%) of them received subsequent anti-myeloma therapy at the discretion of the physician.

Deaths

A total of 36 patients (23%) have died after commercial ide-cel infusion by last follow-up. Eight patients (5%) died without progression, including four who died within 30 days after infusion (one grade 5 CRS, one cerebral haemorrhage, one sepsis and one unknown cause). Causes of death without progression after M1 were cardiovascular events ($n = 2$), COVID-19 ($n = 1$) and unknown ($n = 1$).

DISCUSSION

In this real-world study, we report clinical outcomes in an observational cohort of 176 patients with RRMM from 11 French hospitals who underwent leucapheresis with the intent to administer ide-cel in the EAP. To the best of our knowledge, this is the largest European cohort studied to date. This study shows that in the real-world setting, anti-BCMA CAR-T-cell therapy with ide-cel is safe and effective for RRMM patients who have received at least three prior treatments.

In our cohort, 90% of the patients who underwent leucapheresis were successfully infused with ide-cel, and manufacture failure at the first attempt occurred in seven patients (4%). The median time from leucapheresis to infusion was 62 days. These results are consistent with both the KarMMa trial[2] (91% infusion rate, 1% manufacture failure) and the US real-world experience[7] (90% infusion rate, 6% manufacture failure at first attempt, median time from leucapheresis to infusion 47 days).

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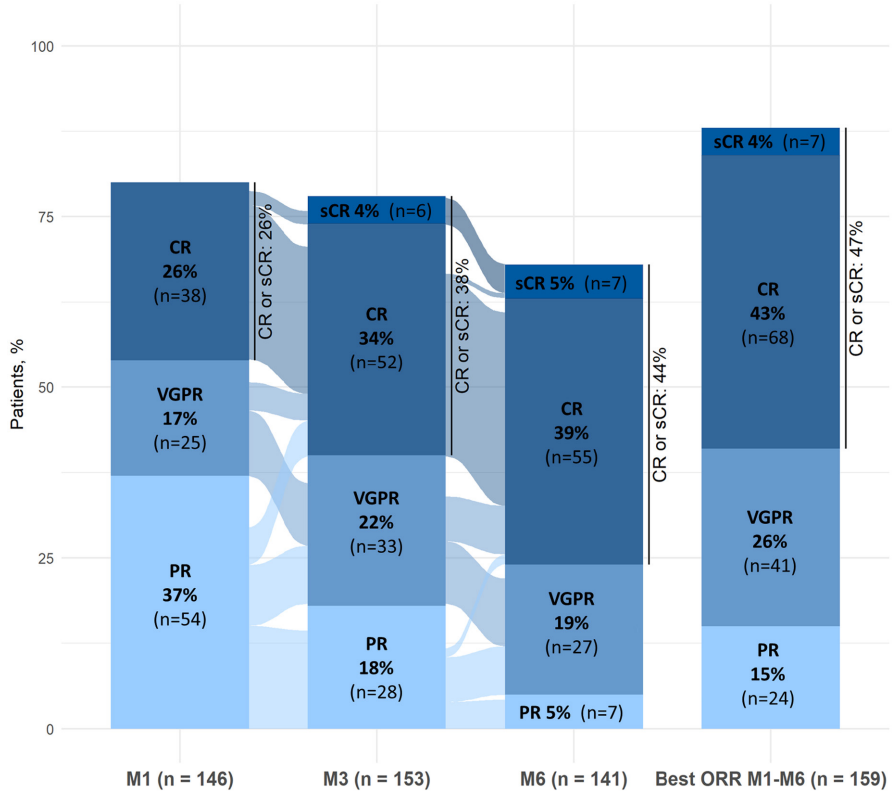

FIGURE 2 Response rates at 1 month after infusion (M1), 3 months (M3) and 6 months (M6), with evolution between time points and the best overall response rate (Best ORR): partial response (PR), very good partial response (VGPR), complete response (CR) or stringent complete response (sCR).

Overall, these data demonstrate the feasibility of ide-cel in the real-world setting in Europe.

Safety was also comparable to that reported in the KarMMa trial[2] and the US real-world experience.[7] Indeed, we observed similar rates of CRS (90% including 2% of grade ≥3 vs. 84% including 5% of grade ≥3 vs. 82% including 3% of grade ≥3), NT (13% including 3% of grade ≥3 vs. 18% including 3% of grade ≥3 vs. 18% including 6% of grade ≥3), infections (34% including 25% of grade ≥3 vs. 69% including 22% of grade ≥3 vs. 34% all grades included) and grade ≥3 cytopenias persistent to M1 (anaemia 13%, thrombocytopenia 35% and neutropenia 59% vs. thrombocytopenia 48% and neutropenia 41% vs. anaemia 38%, thrombocytopenia 59% and neutropenia 60%). Only one case of delayed NT was reported, which was transient and low grade.

Efficacy was consistent with previously reported data, both in terms of depth of response and PFS. In our cohort, the ORR was 88%, with 73% achieving ≥VGPR and 47% (s)CR (KarMMA trial: ORR 73%, CR 33%; US real-world experience: ORR 84%, 42% CR).[1,7] In our series, the median PFS was 12.5 months, similar to the KarMMa study (8.8 months) and US real-world experience (8.5 months). Due to comorbidities, at least 28% of patients in our cohort would not have been eligible for the pivotal KarMMa trial that resulted in the approval of ide-cel, which suggests that this therapy is tolerable and effective in patients with comorbidities and some degree of organ dysfunction. In the previously reported US real-world experience of ide-cel, 77% of patients had KarMMa exclusion criteria. In our study, the relatively low percentage of patients who would not have been eligible for KarMMa may explain the slightly superior result regarding ORR and PFS. The median OS was 20.8 months, with an OS rate of 73.3% at 1 year.

Multivariate analysis revealed that EMD was associated with significantly shorter PFS: median PFS was 6.2 months in patients with EMD versus 14.8 months in patients without EMD. Moreover, patients with EMD had a significantly lower rate of infusion. Together, these results suggest that EMD is a major risk factor for a poorer response to ide-cel, and so screening for EMD should be carefully performed to allow a better selection of patients for ide-cel. Although based on only a small number of patients, our data suggest that prior treatment with an anti-BCMA immunoconjugate, belantamab mafodotin and T-cell-redirecting GPRC5D bispecific antibody talquetamab could be associated with shorter PFS, and that treatment sequence should be considered prior to enrolment in anti-BCMA CAR-T therapy. However, these results require confirmation in a larger cohort of patients.

The strengths of this study include a large nationwide multicentre cohort of patients treated with ide-cel in a real-world setting over the 2-year period after approval. We also note several limitations of our study including its retrospective nature and some missing data, as well as its limited

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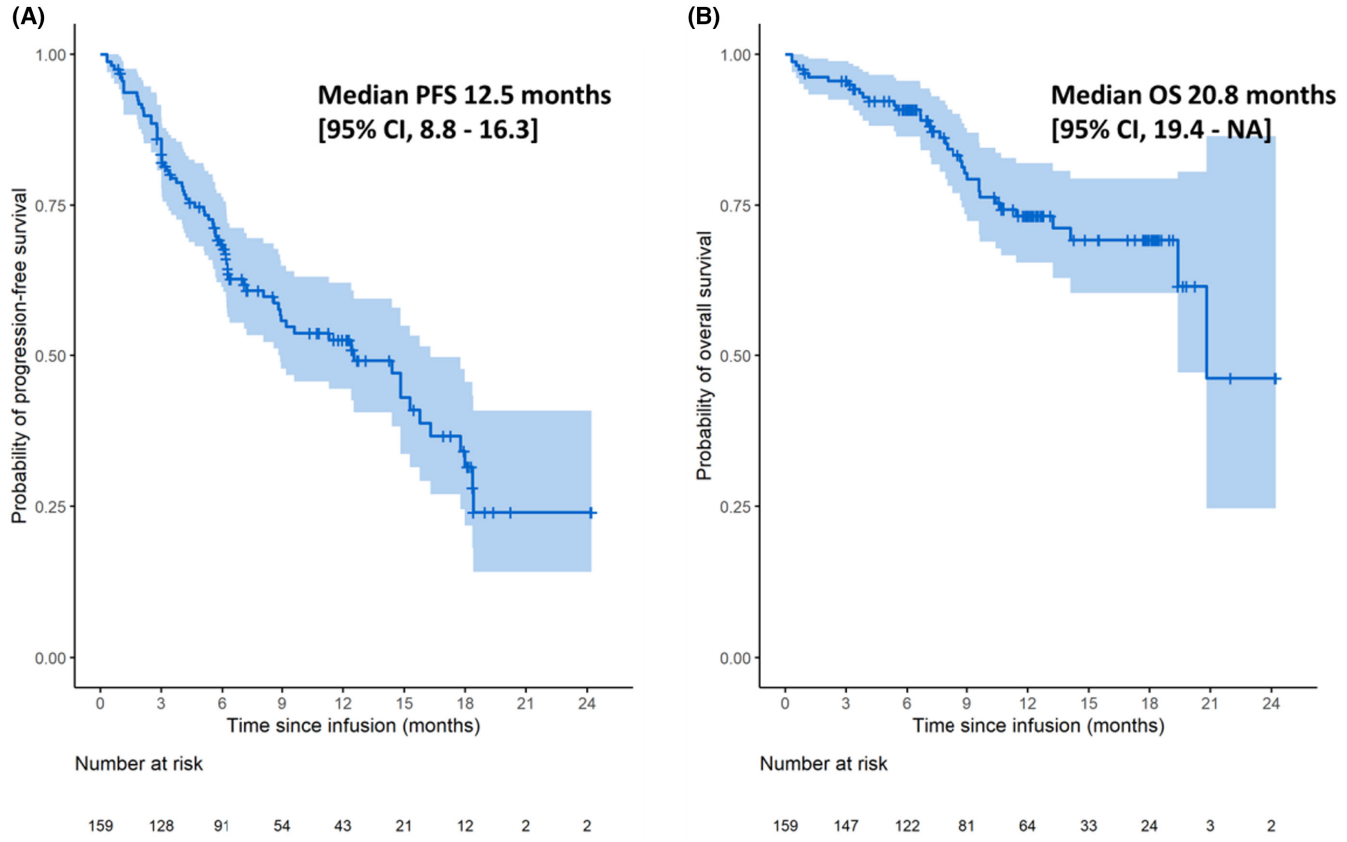

FIGURE 3 Progression-free survival (PFS) (A) and overall survival (OS) (B) of patients after ide-cel infusion.

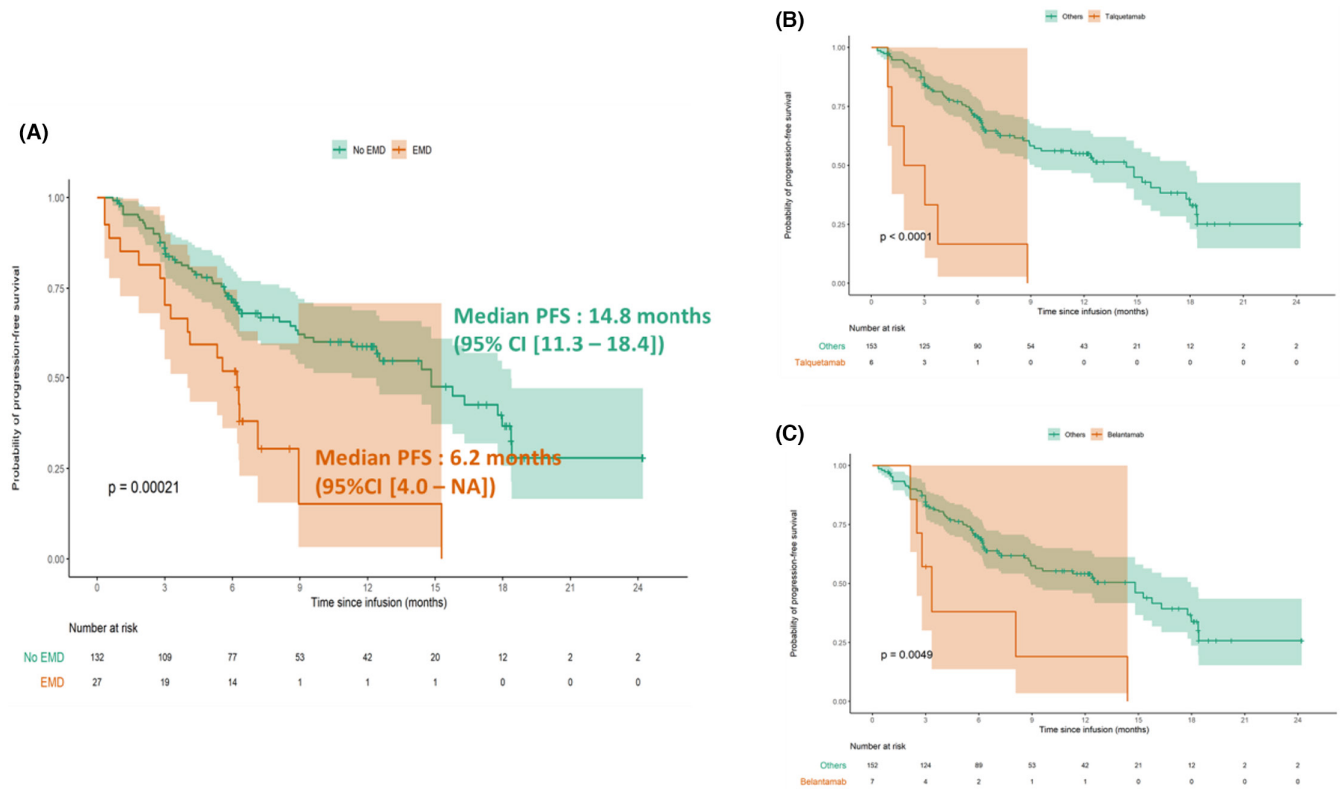

FIGURE 4 Progression-free survival (PFS) subgroup analysis according to the presence of extra-medullary disease (EMD) (A), prior immunotherapy: BCMA-directed immunoconjugate belantamab mafodotin (B) or T-cell-redirecting GPRC5D bispecific antibody talquetamab (C).

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follow-up, due to the availability of ide-cel in France for only 2 years. Finally, management of toxicities and response assessment were per investigator discretion.

In conclusion, our study shows that anti-BCMA CAR-T therapy with ide-cel is a safe and effective therapy for RRMM in Europe and that screening for EMD should be performed prior to enrolment in the ide-cel therapy process to ensure the best selection of patients.

AUTHOR CONTRIBUTIONS

BF, JL, NB and BA performed research; JL and NB performed data analysis; BF and BA wrote the manuscript; BA supervised the study; BF, DC, IL, LK, AL, CT, XL, NM, SH, AP, PB, LV, SL, MM, FM, SM, IY, JMSC, GB, AT, OD, RH, SLG, TF, JC, PM and BA enrolled and treated patients.

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CONFLICT OF INTEREST STATEMENT

LK served on advisory board, received honoraria and travel support from Amgen, *BMS/Celgene*, Janssen, AbbVie, Takeda, SANOFI, Pfizer; XL received honoraria from Janssen, *Kite/Gilead*, *BMS/Celgene*, Takeda, Sanofi, Novartis, Pfizer, GlaxoSmithKline, AbbVie; AP received honoraria from AbbVie, Amgen, *BMS/Celgene*, Janssen, Pfizer, Sanofi, Takeda; PB received honoraria from Kite Gilead, Novartis, BMS/Celgene and AbbVie; LV served on advisory boards and received travel support from *BMS/Celgene*; SL received miscellaneous support from Janssen, Gilead, Roche, AbbVie, Sanofi, Novartis, Actelion, Pfizer, received honorarium from Gilead and research funding from Janssen; MM received lectures honoraria from Adaptive Biotechnologies, Amgen, BMS/Celgene, Janssen, Takeda, Novartis, Sanofi, Stemline; FM received honoraria from Therakos/Mallinckrodt, BMS/Celgene, MSD, AstraZeneca, Sanofi, JAZZ Pharmaceuticals, Kite/Gilead and Novartis; SM provided consultancy for AbbVie, Amgen, BMS/Celgene, GlaxoSmithKline, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda; IYA received honoraria from *Kite/Gilead*, *BMS/Celgene*, Janssen, Miltenyi biomedicine; GB *received travel support from Novartis, Kite/Gilead*, *Incyte and BMS/Celgene*; AT served on advisory boards for Sanofi and *received travel support from* Pfizer; RH received honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, AbbVie and Roche; and provided consultancy for Kite/Gilead, Novartis, BMS/Celgene, ADC Therapeutics, Incyte, Miltenyi; JC served on advisory boards for Sanofi, *BMS/Celgene*, and provided consultancy for Janssen, Sanofi, *BMS/Celgene*, Pfizer, Adaptive, received research funding from Sanofi, *BMS/Celgene and received travel support from* Janssen, Sanofi, Bristol Myers Squibb, Pfizer; PM served on advisory boards and received honoraria from Janssen, Celgene/BMS, Takeda, Amgen, Sanofi, Pfizer; BA served on advisory boards for BMS/Celgene, Janssen, Takeda, Sanofi, Amgen, GSK, conducted educational activities for BMS/Celgene, Janssen and received research funding from Janssen, BMS/Celgene. Other authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data were extracted from the French DESCAR-T registry, which is not freely accessible.

ETHICS STATEMENT

The DESCAR-T registry was approved by the French authorities in June 2019. DESCAR-T clinical trial number (not specific to our study): NCT04328298.

PATIENT CONSENT STATEMENT

This research reuses data that have already been collected and enters the French MR-004 framework.

CLINICAL TRIAL REGISTRATION

DESCAR-T clinical trial number (not specific to our study): NCT04328298.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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