RESEARCH ARTICLE

Outcomes of CAR T-cell Therapy and Bispecific Antibodies as Single-Modality and Sequential Strategies in Relapsed/Refractory Multiple Myeloma

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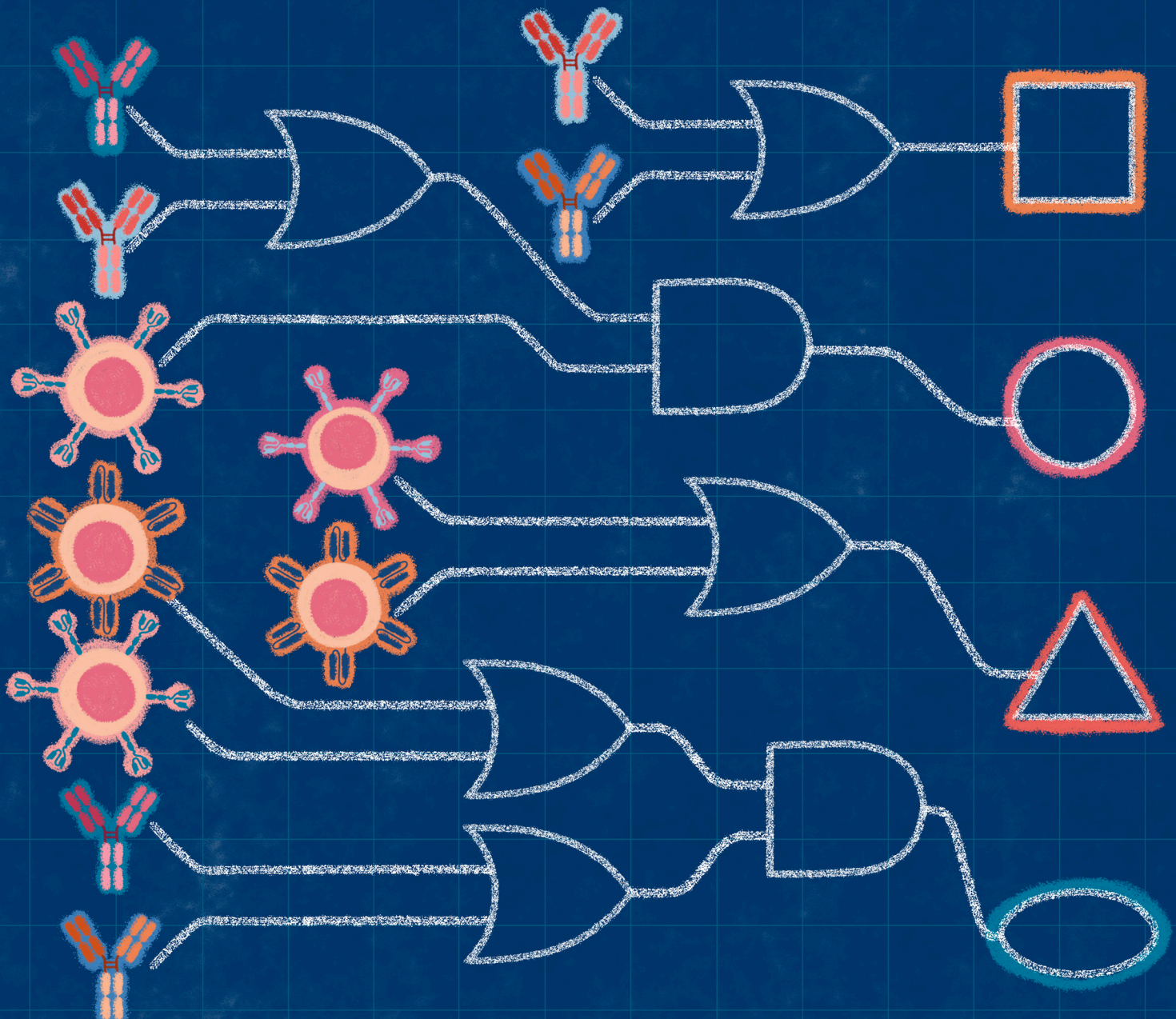

ABSTRACT We explored single or consecutive chimeric antigen receptor (CAR) T and bispecific antibody (BsAb) treatment modalities as correlates of clinical outcomes, by complementary bias-correction analysis of a retrospective multicenter study of 640 patients with relapsed/refractory multiple myeloma. The sequential use of both modalities seemed to yield the most favorable survival trajectories. Initiating treatment with CAR T [idecabtagene vicleucel (ide-cel), ciltacabtagene autoleucel (cilta-cel), cesnicabtagene autoleucel (cesni-cel)] was associated with longer remission. However, mortality from early progression was similar regardless of initial modality, suggesting that resistance may negate initial efficacy difference. On the product level, the benefit of CAR T seemed to be driven by cilta-cel and cesni-cel, whereas BsAbs showed at least comparable outcomes with ide-cel. These exploratory findings highlight the critical importance of treatment sequencing in optimizing long-term outcomes and underscore the need for equitable and timely access to both modalities across healthcare systems.

SIGNIFICANCE: In this real-world cohort, initiating treatment with CAR T was associated with longer remission, and sequential immunotherapy incorporating both modalities yielded the most favorable outcomes. However, early treatment failure negated initial efficacy differences between modalities. These findings provide a rationale for prospective sequencing trials and equitable access to both treatments.

See related commentary by Banerjee, p. 650

INTRODUCTION

Immunotherapies against B-cell maturation antigen (BCMA) or G protein–coupled receptor class C group 5 member D (GPRC5D) have revolutionized the treatment of relapsed/refractory multiple myeloma (RRMM), expanding options for patient populations characterized by poor clinical prognosis (1–3). Chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies (BsAb) have shown substantial efficacy in heavily pretreated patients, leading to regulatory approvals and rapidly evolving clinical use (4, 5). The optimal sequencing of these modalities remains an unresolved question in clinical practice. Despite promising trial outcomes, real-world access to CAR T-cell therapies is highly variable because of regulatory, logistical, and economic constraints (6–8). In contrast, BsAbs offer logistical advantages but may differ in efficacy and safety profiles. Comparative data to

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inform decision-making between these two treatments are lacking, particularly in real-world settings, where patient populations are heterogeneous and often frailer than those enrolled in pivotal trials. Directly comparing the isolated impact of both modalities on survival remains difficult, given that real-world practice commonly involves treatment crossover, and randomized studies are improbable. To address this gap, we conducted a large, retrospective multicenter European study to directly compare the clinical outcomes of CAR T-cell therapies and BsAb. Our study leverages a large bispecific-only population without CAR T access, providing a rare opportunity to evaluate the distinct effects of each modality. Using multiple modeling approaches to account for baseline imbalances and treatment dynamics, we evaluated efficacy and safety across and between both modalities. This analysis not only offers a benchmark for current clinical outcomes in routine practice but also provides critical insights into how treatment sequencing should be approached.

RESULTS

Patient Characteristics

A total of 640 patients with RRMM were included in the analysis (Fig. 1A and B; Supplementary Fig. S1): 399 received a BCMA-directed CAR T-cell therapy first [idecabtagene vicleucel (ide-cel): $n = 202$; ciltacabtagene autoleucel (cilta-cel): $n = 162$; cesnicabtagene autoleucel (cesni-cel): $n = 35$] and 241 received a BsAb first (teclistamab: $n = 147$; talquetamab: $n = 71$; elranatamab: $n = 23$). Among BsAb, 200 (83%) had no access to CAR T-cell therapy because of regulatory policies. At baseline, the BsAb group was older (median 66 vs. 64 years; Table 1), presented higher frequency of high-risk cytogenetics (74% vs. 55%), extramedullary disease (EMD; 32% vs. 25%), and Eastern Cooperative Oncology Group (ECOG) ≥2 (35% vs. 17%). Penta-refractoriness was similar between the groups (BsAb: 78%; CAR T: 76%). Patient characteristics are summarized in Table 1.

Overall Survival and State Occupation Probabilities from the Multistate Model

Overall survival (OS) derived from the multistate model demonstrated significantly higher survival probabilities for CAR T–first compared with BsAb-first strategy throughout the observation period ($P < 0.001$; Fig. 2A). At 6, 12, and 18 months, the multistate-derived probability of being alive was 93%, 86%, and 79% for CAR T–first strategy compared with 79%, 69%, and 63% for BsAb-first strategy, respectively. These estimates were validated against the observed Kaplan–Meier curves by initial treatment modality. At a median follow-up of 14.3 months for CAR T recipients and 9.9 months for BsAb recipients, 139 deaths were observed (69 in the CAR T group; 70 in the BsAb group). Kaplan–Meier–estimated OS at 6, 12, and 18 months was 93% [95% confidence interval (CI), 90.3–95.6], 85.5% (95% CI, 81.6–89.5), and 78.6% (95% CI, 73.3–83.8) for patients initially treated with CAR T, compared with 81.5% (95% CI, 76.7–86.3), 71% (95% CI, 64.5–77.5), and 63.8% (95% CI, 55.2–72.3) for those initially treated with BsAbs, respectively (Supplementary Fig. S2). The median OS was not reached in the BsAb group because of limited follow-up; in the CAR T group, the median OS was 34.4 months. These observed estimates were consistent with the OS derived from the multistate model (1 minus the state occupation probability of death), supporting the validity of the Monte Carlo calibration approach used for transition time estimation in the multistate framework. Differences in observed OS between groups should be interpreted with caution given the nonrandomized design, shorter follow-up in the BsAb cohort, and potential confounding by patient and disease characteristics at treatment initiation.

To characterize the clinical states underlying these survival differences, state occupation probabilities were estimated from the four-state multistate model (Fig. 2B). Among CAR T–first strategy, 63% remained in first-line remission at 6 months and 41% at 12 months, with a gradual transition into post-progression states. By 12 months, 40% of CAR T–first strategy had transitioned to second-line immunotherapy (BsAb after CAR T), reflecting the high accessibility of BsAb as subsequent therapy. In contrast, BsAb-first patients experienced a more rapid loss of remission (51% at 6 months; 31% at 12 months), consistent with the shorter progression-free survival (PFS) observed under BsAb therapy (median PFS, 1.8 months for BsAb-only progressors vs. 4.3 months for CAR T–only progressors in the reference groups). A considerably smaller proportion of BsAb-first strategy transitioned to second-line immunotherapy (16% at 12 months vs. 40% for CAR T-first), whereas a substantially larger proportion remained in the progressed-without-second-line state (22% vs. 5%).

Bias-Corrected Survival and Determinants of Post-progression Outcomes

To mitigate the immortal time and guarantee-time bias inherent in trajectory-based group classification, a landmark analysis was performed 3 and 6 (Supplementary Fig. S3) months after treatment initiation. Of 640 patients, 569 (88.9%) were alive at the landmark and included in this analysis (CAR T only, $n = 191$; CAR T→BsAb, $n = 175$; BsAb only, $n = 165$; BsAb→CAR T, $n = 38$). Royston–Parmar modeling yielded modeled 12-month OS from the 3-month landmark of 84% (95% CI, 78%–89%) for CAR T only, 87% (95% CI, 81%–91%) for CAR T→BsAb, 73% (95% CI, 6%–80%) for BsAb only, and 84% (95% CI, 59%–95%) for BsAb→CAR T (overall log-rank $P = 0.011$; Fig. 3A). However, the separation between sequential and single-modality trajectories attenuated beyond 12 months from the landmark, suggesting a diminishing benefit of treatment sequencing over time.

To identify the specific transitions driving this survival difference, transition-specific Cox regression models were fitted within the multistate framework on the full cohort (Fig. 3B). CAR T–first patients had a lower hazard of first-line progression compared with BsAb-first patients [hazard ratio (HR), 0.79; 95% CI, 0.63–0.98]. After progression, however, the hazard of death was virtually identical regardless of initial treatment modality, both in the absence of next-line immunotherapy (HR, 0.97; 95% CI, 0.57–1.65) and while receiving next-line immunotherapy (HR, 1.16; 95% CI, 0.38–3.54). These findings indicate that the OS advantage of CAR T–first strategies is primarily driven by superior initial-line disease control rather than by differential post-progression outcomes.

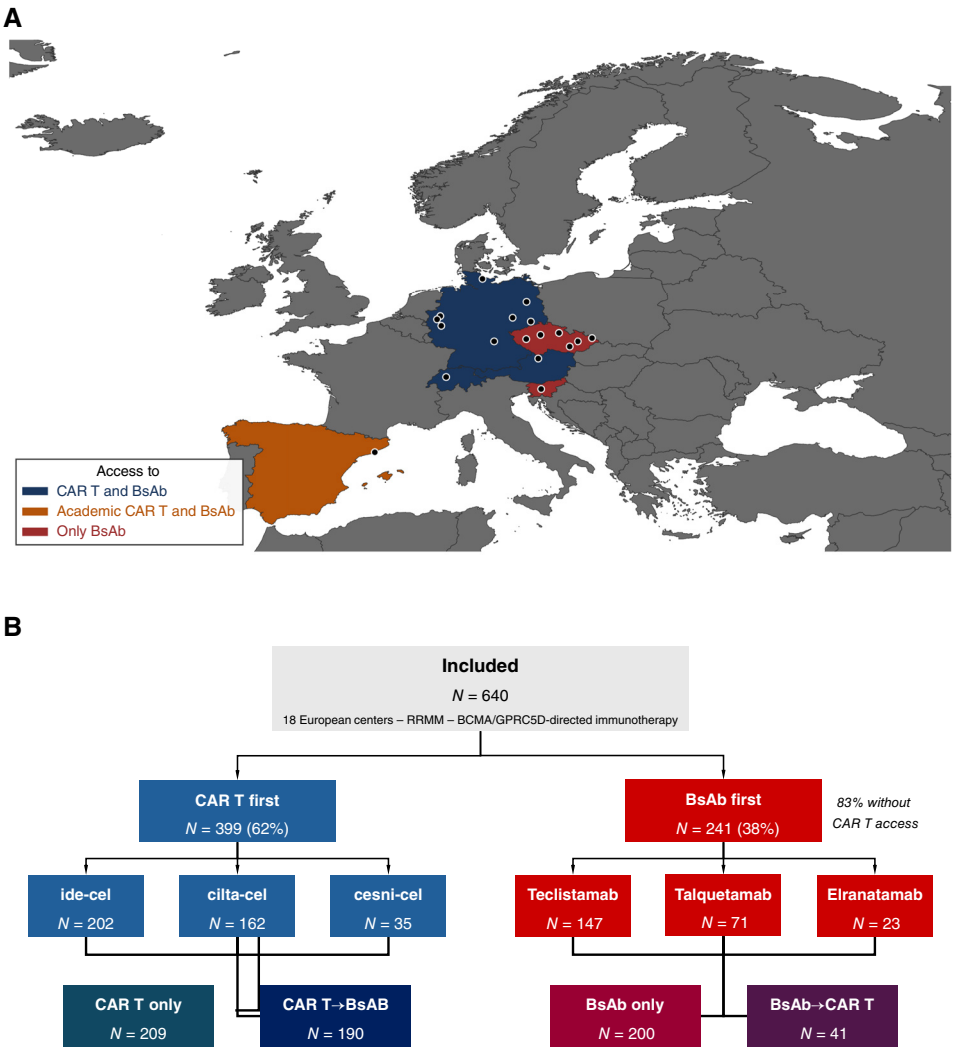

Figure 1. Participating centers and patient flow. **A,** Geographic distribution of the 18 participating European centers. Participating countries are color-coded by treatment access. Countries in gray did not participate in the study and coloring does not reflect treatment access in these countries. **B,** Flow diagram of the study cohort.

To evaluate the potential impact of resistance development on sequential BCMA-directed therapy, initial-line PFS duration was assessed as a clinically interpretable proxy for antigen escape within the same multistate framework. Patients with early first-line failure (≤3 months) had a significantly higher hazard of post-progression death (HR, 2.30; 95% CI, 1.24–4.27) and increased hazard of death while receiving second-line immunotherapy (HR, 4.15; 95% CI, 1.97–8.72; Fig. 3B). These findings support the hypothesis that rapid treatment failure—potentially reflecting primary resistance mechanisms including BCMA loss—substantially compromises the efficacy of subsequent immunotherapy and may provide a rationale for considering non–BCMA-directed alternatives in patients experiencing very early relapse.

Product-Level Outcomes

Among CAR T products, cilta-cel and cesni-cel achieved the highest complete response (CR) rate (69% and 60%), followed by ide-cel (48%). Bispecific antibody agents showed the following CR rates: elranatamab (22%), teclistamab (17%), and talquetamab (9%; Fig. 4A). Unadjusted 12-month PFS was 86% (95% CI, 80%–93%) for cilta-cel, 69% (95% CI, 53%–85%) for cesni-cel, and 52% (95% CI, 44%–59%) for ide-cel. For BsAb products, the 12-month PFS was 46% (95% CI, 23%–69%) for elranatamab, 52% (95% CI, 38%–65%) for talquetamab, and 44% (95% CI, 34%–54%) for teclistamab, with the median PFS of 9, 13, and 11 months, respectively.

Unadjusted frequencies of treatment-related adverse events including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) seemed higher in patients treated with CAR T, except for cesni-cel, which showed a more favorable toxicity profile (Table 2). Unadjusted product-level non-relapse mortality (NRM) was 5% for ide-cel, 6% for cilta-cel, and cesni-cel, respectively; 12% for teclistamab, 11% for talquetamab, and 20% for elranatamab. Deaths were attributable to infection in all NRM cases in the BsAb cohort and 68% in the CAR T cohort [other causes: organ failure (21%) and unknown (11%)].

Table 1. Characteristics of CAR T and BsAb groups.

Characteristic	CAR T (*n* = 399)	BsAb (*n* = 241)	*P*
Age, median (range)	64 (28–84)	66 (34–85)	0.02
Sex, *n* (%)			0.01
Male	246 (62)	121 (50)	
Female	153 (38)	120 (50)	
ECOG, *n* (%)			<0.001
0	160 (40)	30 (12)	
1	161 (40)	128 (53)	
2	56 (14)	67 (28)	
3	12 (3)	16 (7)	
Unknown	10 (3)	0	
R-ISS, *n* (%)			<0.001
I	71 (18)	65 (27)	
II	196 (49)	82 (34)	
III	105 (26)	94 (39)	
Unknown	27 (7)	0	
EMD, *n* (%)	98 (25)	78 (32)	0.04
High-risk cytogenetics, *n* (%)	216 (54)	137 (57)	0.34
Penta-refractory, *n* (%)	149 (37)	114 (47)	0.02
Anti-BCMA exposure, *n* (%)	41 (10)	35 (14)	0.13
Years from diagnosis to treatment, median (range)	6.6 (0.2–29.1)	6 (0.5–26.1)	0.20

Abbreviations: *n*, number; R-ISS, Revised International Staging System.

Inverse Probability of Treatment Weighting: Adjusted Analysis and Prognostic Factors

To corroborate the multistate and landmark findings using an independent analytic framework, inverse probability of treatment weighting (IPTW) was applied to adjust for measured baseline confounders (EMD, ECOG, cytogenetics, time from diagnosis to treatment, and age; $n = 630$ with complete covariate data; Supplementary Fig. S1). Adequate covariate balance was achieved across all three treatment groups (all standardized mean differences <0.03 after weighting; Supplementary Table S1). In the IPTW-adjusted univariable analysis, cilta-cel/cesni-cel was associated with a markedly reduced risk of progression or death compared with ide-cel (Fig. 4B), which was confirmed in multivariable modeling (PFS: HR, 0.27; 95% CI, 0.19–0.40; OS: HR, 0.30; 95% CI, 0.16–0.56), whereas outcomes with BsAb were not significantly different from ide-cel (PFS: HR, 0.72; 95% CI, 0.52–1.01; OS: HR, 0.77; 95% CI, 0.51–1.17; Table 3; Supplementary Tables S2 and S3). These product-level findings are consistent with the multistate-derived results, in which the OS advantage of CAR T–first strategies was attributed primarily to lower first-line progression risk, and corroborate the observed treatment hierarchy through an independent analytic approach. The presence of EMD and ECOG performance status 1 through ECOG 3 were associated with inferior outcome (Table 3). Longer time from diagnosis to immunotherapy initiation was associated with improved outcomes, likely reflecting a surrogate for more indolent disease biology, whereas age did not seem to be associated with either endpoint, in line with previous reports (9).

Observed versus Multistate Survival: Rank-Preserving Structural Failure Time Model

To further account for the impact of treatment switching on the comparison of initial treatment modalities, a rank-preserving structural failure time model (RPSFTM) was applied as a sensitivity analysis. Among 241 patients initiating BsAbs, 41 (17%) subsequently switched to CAR T-cell therapy; among 399 patients initiating CAR T, 190 (47.6%) subsequently received BsAbs. G-estimation yielded an acceleration factor (AF) of 0.26 (95% CI, 0.07–0.57), corresponding to $\psi = -1.33$ (95% CI, −2.61 to −0.56). This indicates that exposure to CAR T-cell therapy decelerated the failure time by a factor of approximately 3.8 (1/0.26), meaning that each month of CAR T–associated time corresponds to approximately 3.8 months of disease-free equivalent time without CAR T exposure.

The RPSFTM-adjusted Kaplan–Meier curves are shown in Supplementary Fig. S4. After adjusting for treatment switching using counterfactual survival times, the 12-month OS of the BsAb-first arm decreased from 71% (observed) to 68% (RPSFTM adjusted), reflecting the removal of the survival benefit attributable to subsequent CAR T exposure among switchers. The observed 12-month OS of the CAR T–first arm was 85% (95% CI, 80%–88%). The unadjusted HR (BsAb first vs. CAR T first) was 1.90 (95% CI, 1.36–2.66); after RPSFTM adjustment, the HR was 1 (95% CI, 0.71–1.41).

The convergence of the RPSFTM-adjusted HR toward 1 after removing the CAR T switching effect from the BsAb arm is consistent with the interpretation that the observed survival advantage of CAR T–first strategies is attributable to the direct effect of CAR T-cell therapy rather than unmeasured confounders favoring the CAR T arm. However, the wide CI of the AF reflects uncertainty inherent in the limited number of switchers ($n = 41$ in the BsAb arm) and the observational study design. The common treatment effect assumption (that CAR T has the same relative effect regardless of treatment line) is a recognized limitation, as the efficacy of CAR T may differ when administered as second-line immunotherapy after BsAb failure. These results should therefore be interpreted as supportive evidence within the triangulation of multistate, landmark, IPTW, and RPSFTM analyses, rather than as definitive causal estimates.

DISCUSSION

In this large, multicenter, real-world European cohort study, we present the first analysis of sequencing CAR T-cell therapies and BsAbs in patients with RRMM. Our findings indicate that administering CAR T therapies (particularly cilta-cel and cesni-cel) prior to BsAbs is associated with improved outcomes compared with initiating treatment with BsAbs first.

The rapid expansion of targeted therapies has fundamentally altered the therapeutic landscape of RRMM. Both CAR T cells and BsAbs have demonstrated unprecedented activity

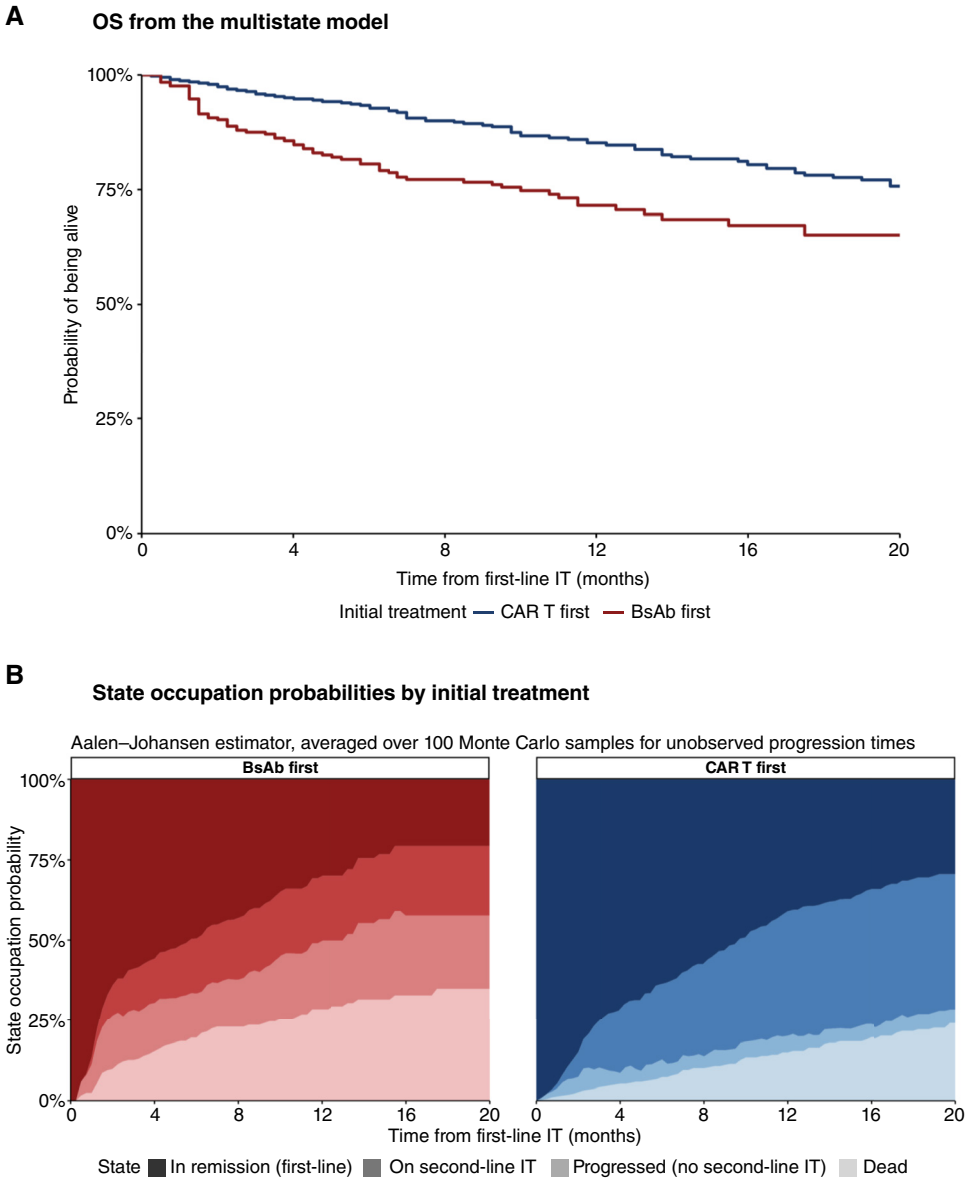

Figure 2. Multistate model for comparison of first-line immunotherapy strategies. **A,** OS derived from the multistate model [1 – P(dead)] by initial treatment modality. Step functions represent the averaged Aalen–Johansen estimate across 100 Monte Carlo iterations. These model-based estimates account for the time-dependent nature of treatment transitions. All curves are descriptive and should be interpreted in the context of nonrandomized treatment allocation. **B,** State occupation probabilities by initial immunotherapy (IT) treatment modality from the four-state multistate model. Probabilities were estimated using the Aalen–Johansen estimator, averaged across 100 Monte Carlo iterations to account for unobserved progression times in sequencing patients. States from bottom to top: dead, progressed without second-line immunotherapy, receiving second-line immunotherapy, and in first-line remission. Left, BsAb first ($n = 241$); right, CAR T first ($n = 399$). All curves were derived from the multistate model and should be interpreted in the context of nonrandomized treatment allocation.

in heavily pretreated patient populations, leading to accelerated approvals. More recently, CAR T-cell therapies and BsAbs have demonstrated excellent outcomes after first-line treatment, prompting the question of which therapy should be administered first and which sequencing strategy achieves the most durable disease control (10, 11). However, head-to-head comparisons have been lacking, and clinical decisions are often driven by availability, toxicity profiles, and physician experience rather than comparative efficacy data. Our study addresses this gap by providing real-world evidence from a diverse European population, using rigorous statistical adjustment to minimize confounding from treatment selection bias. A major strength of this analysis was the inclusion of a large cohort of patients who received BsAbs but had no access to CAR T-cell therapies because of treatment barriers, offering a unique opportunity to investigate the effects of BsAbs without cross-over to CAR T-cell therapy and providing a distinctive perspective on real-world practice patterns.

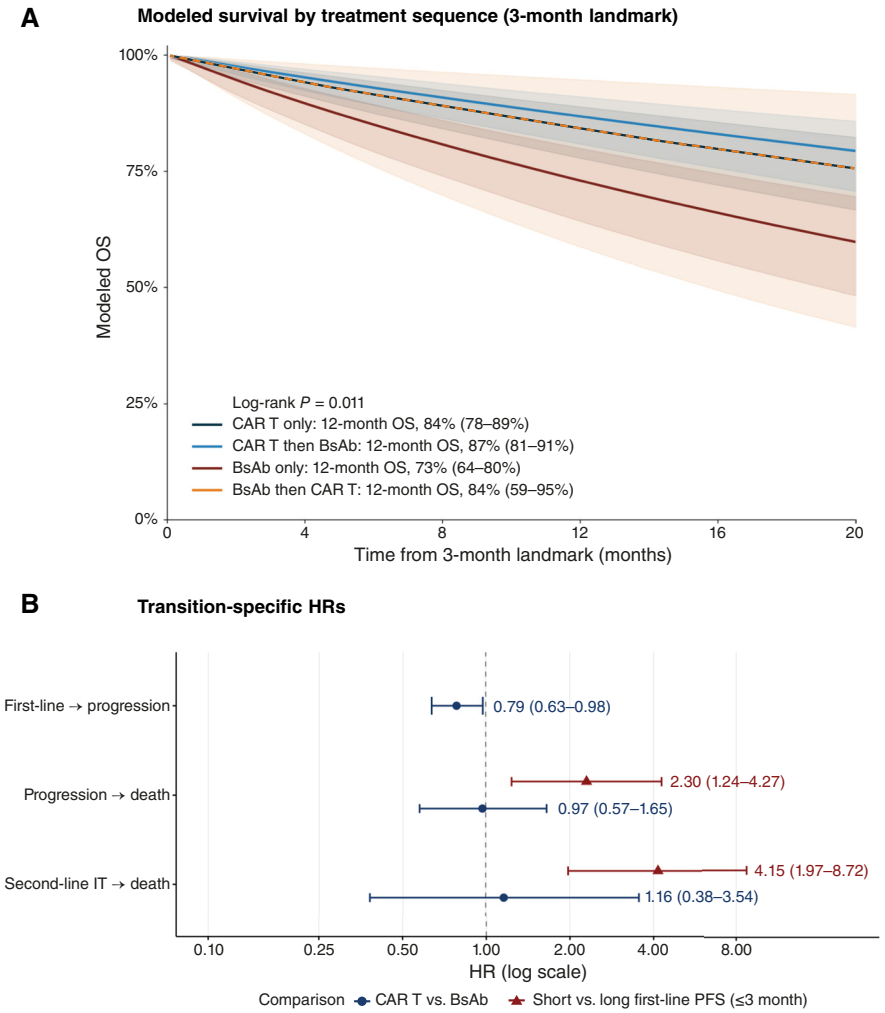

Figure 3. Treatment sequencing and importance of remission duration. **A,** Modeled OS by treatment sequence from the 3-month landmark. A Royston–Parmar flexible parametric model (k = 3) was fitted to 569 patients alive at 3 months after initial immunotherapy. Shaded areas represent 95% CIs. All modeled curves are descriptive and should be interpreted in the context of nonrandomized treatment allocation. **B,** Transition-specific HRs from Cox regression models fitted within the multistate framework (full cohort, *n* = 640). Blue circles indicate HRs for CAR T vs. BsAb as initial treatment; red triangles indicate HRs for short (≤3 months) vs. long (>3 months) first-line PFS as a proxy for resistance development. Error bars represent 95% CIs; the dashed line indicates HR = 1. All estimates are descriptive and should be interpreted in the context of nonrandomized treatment allocation. IT, immunotherapy.

The superior efficacy of CAR T-cell therapy observed in our cohort is consistent with findings from pivotal clinical trials. In CARTITUDE-1, cilta-cel achieved a CR or better in 82% of patients, with an exceptional long-term survival outcome (1). Similarly, ide-cel demonstrated overall response rates (ORR) around 70% to 75% (12). Our real-world data align with these values, particularly for cilta-cel, which showed the highest CR rate (69%) and longest PFS (86% at 12 months), as has been previously shown in other real-world studies (13, 14). The academic CAR T construct cesni-cel also performed favorably, with a CR rate of 60% and 12-month PFS of 69% (15), suggesting that well-engineered, locally manufactured products can deliver competitive outcomes in settings with limited access to commercial CAR T cells.

In contrast, BsAbs demonstrated lower CR rates and shorter PFS, most likely reflecting their administration in a more clinically older and frail population. Furthermore, confirmation of CR by bone marrow (BM) assessment is less frequently pursued in clinical practice than in clinical trials, largely because such confirmation rarely alters management; BsAb therapy is typically continued until disease progression, rendering routine invasive reassessment clinically discretionary. Importantly, our IPTW-adjusted Cox model results are in line with previous real-world data of BsAb (16, 17), and it confirmed that BsAb therapy remained independently associated with inferior PFS compared with CAR T, even after accounting for age, EMD, ECOG status, cytogenetics, penta-refractoriness, and time from primary diagnosis to start of either CAR T or BsAb.

A critical aspect of our findings relates to the effect of EMD and ECOG performance status on treatment outcomes. EMD remains a major adverse prognostic factor in RRMM (9, 18, 19), and both CAR T and BsAbs show reduced efficacy in this subgroup. Nonetheless, the relative benefit of CAR T

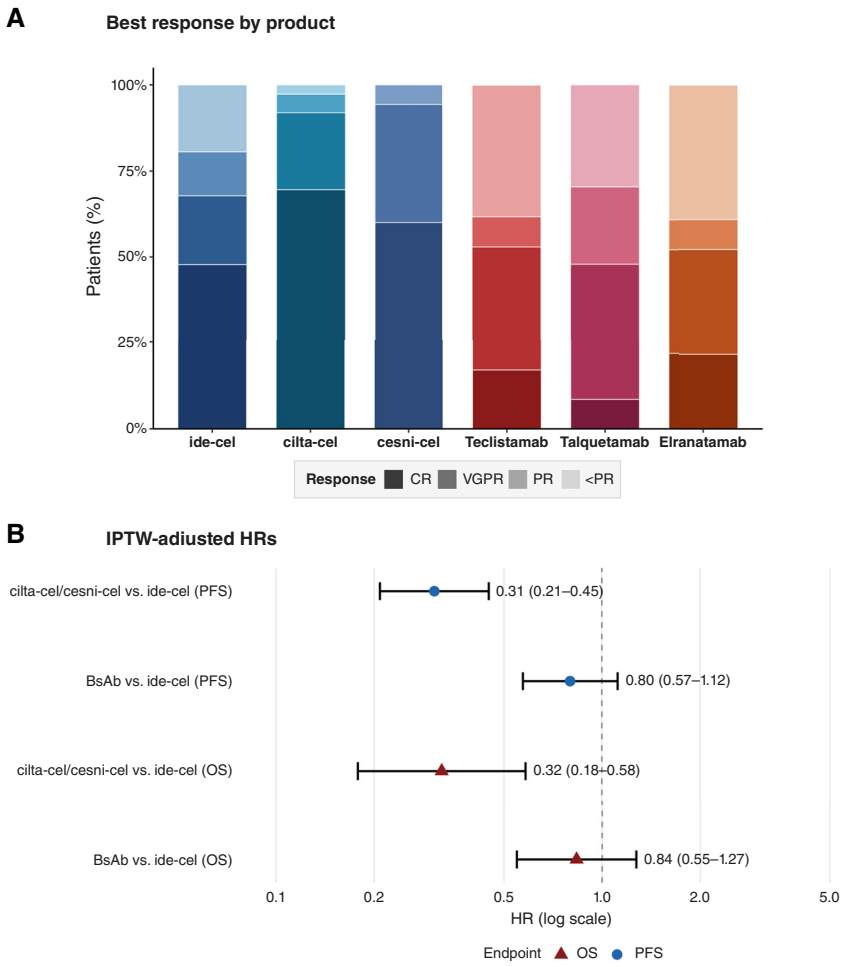

Figure 4. Best overall response and IPTW-adjusted HRs by treatment group. **A,** Stacked bar chart depicting the distribution of best overall response categories across six therapies. Blue shades represent CAR T-cell therapies (ide-cel, cilta-cel, and cesni-cel), and red shades represent BsAb (teclistamab, talquetamab, and elranatamab). **B,** Forest plot of IPTW-adjusted HRs with 95% CIs from Cox proportional hazards models with robust standard errors, comparing cilta-cel/cesni-cel and BsAb against ide-cel as the reference group. PR, partial response; VGPR, very good partial response.

over BsAbs was maintained in patients with EMD, suggesting greater disease control even in this high-risk population. Similarly, patients with ECOG ≥2 had worse outcomes across both modalities, but CAR T therapy still conferred a significant PFS advantage, even in this frail patient population. These observations emphasize the importance of timely referral for CAR T-cell therapy, as delays may result in deterioration of performance status and loss of eligibility. Although ECOG may be confounded by treatment selection bias in centers offering both CAR T and BsAbs, it remained a strong predictor of poor prognosis in the Eastern European cohort, where such bias is minimal. Outcomes were substantially worse than in CAR T recipients with similarly impaired ECOG.

Although CAR T-cell therapies offer superior disease control, they are associated with unique logistical and safety challenges. The requirement for leukapheresis, manufacturing delays, terminations, and bridging therapy can be prohibitive in rapidly progressing patients. Moreover, toxicities such as CRS, ICANS, and delayed neuro- and gastrointestinal toxicities remain concerns, particularly with cilta-cel. In our study, BsAbs were generally better tolerated, with lower rates of CRS and ICANS. cesni-cel demonstrated a more favorable toxicity profile, with rates comparable with BsAbs, possibly due to differences in T-cell composition, fractionated administration, or manufacturing protocols.

Remarkably, despite lower acute toxicity, BsAb therapy did not seem to be associated with lower nonrelapse mortality. However, this finding should be interpreted with caution and could be confounded by still relatively small sample sizes. Other potential explanations include prolonged immunosuppression with continuous BsAb exposure as well as disease-related rather than therapy-related complications associated with heavily pretreated patients.

Our study also raises broader policy and access considerations. The disparity in CAR T availability across Europe remains a major barrier to equitable care. In our cohort, we included more than 80% of BsAb-treated patients with no access to CAR T due to systemic limitations, rather than clinical ineligibility. This underscores the urgent need for harmonized regulatory pathways, cross-border treatment networks,

Table 2. Safety.

Outcome/grade	ide-cel	cilta-cel	cesni-cel	Teclistamab	Talquetamab	Elranatamab
CRS						
1	57%	49%	34%	37%	42%	35%
2	28%	29%	26%	6%	6%	0%
3	3%	6%	0%	0%	0%	0%
4	1%	1%	0%	1%	0%	4%
ICANS						
1	14%	6%	0%	3%	4%	4%
2	0%	2%	0%	3%	1%	0%
3	1%	3%	0%	1%	0%	0%
4	1%	2%	0%	0%	0%	0%

and investment in academic manufacturing capabilities to expand CAR T access. Without such measures, therapeutic decisions will continue to be shaped more by geography than by evidence, perpetuating inequities in outcomes. Importantly, access to BsAbs also improved long-term outcomes after CAR T-cell therapy, whereas patients treated with CAR T cells alone had adverse outcomes.

An important nuance emerging from the transition-specific analysis is that the OS advantage of CAR T–first strategies is primarily driven by superior first-line disease control (HR, 0.79 for progression) rather than differential post-progression outcomes—once patients progressed, the hazard of death was virtually identical regardless of initial modality. This finding has two critical implications. First, it suggests that the apparent benefit of treatment sequencing observed in unadjusted analyses largely reflects the longer first-line remission achieved by CAR T, which in turn provides a wider window for accessing subsequent therapy. Indeed, the asymmetry in second-line access is striking; 48% of CAR T–first patients received subsequent BsAb after progression, whereas only 17% of BsAb-first patients transitioned to CAR T, with 22% remaining in a progressed state without second-line immunotherapy compared with only 5% in the CAR T–first arm. This differential attrition (driven by the logistic barriers inherent to CAR T manufacturing, leukapheresis, and bridging) means that BsAb-first patients who progress face a substantially higher risk of clinical deterioration before salvage therapy can be initiated. Second, the landmark analysis did not confirm a statistically significant sequential benefit (HR, 0.82 for CAR T→BsAb vs. CAR T only), and the RPSFTM sensitivity analysis (AF, 0.26) indicates that the observed survival differences are attributable to CAR T exposure itself rather than the specific treatment sequence (Supplementary Fig. S4). Taken together, these findings suggest that timely access to potent CAR T constructs (particularly cilta-cel and cesni-cel) at any point during the disease course is the primary determinant of outcome and that the sequential benefit, although plausible, requires prospective validation in dedicated trials.

This study has several limitations that warrant consideration. Its retrospective, nonrandomized design introduces potential selection bias. Although IPTW adjustment, multistate modeling, and landmark analyses were employed as complementary bias-correction approaches, residual confounding from unmeasured variables (including prior treatment history, disease biology, and physician preference) cannot be excluded. To further interrogate the impact of treatment switching, a RPSFTM was applied as an additional sensitivity analysis, estimating counterfactual survival times in the absence of CAR T exposure. The RPSFTM and the multistate model address treatment cross-over from complementary angles; the former estimates a causal AF on the failure time scale, whereas the latter decomposes the survival difference into transition-specific hazards while modeling cross-over as a time-dependent event. Both converge on the same conclusion—that the survival advantage of CAR T–first strategies is attributable to the direct therapeutic effect rather than confounding—despite differing assumptions, thereby strengthening the robustness of our findings. Second, treatment allocation was largely access driven rather than clinically determined. Furthermore, although Monte Carlo calibration was used to enhance robustness, immortal time bias cannot be ruled out completely. Additionally, first-line PFS duration was used as a clinical proxy for resistance development in the absence of granular molecular data like BCMA expression and T-cell functionality, which limits mechanistic interpretation. Product-level comparisons should be interpreted cautiously given differences in patient profiles, dosing schedules, and institutional experience across products. The lower CR rates observed with BsAbs may partly reflect less frequent confirmatory BM assessment in routine clinical practice, and the relatively small BsAb→CAR T subgroup (n = 41) limits estimates for this trajectory. Finally, the follow-up period may be insufficient to capture long-term outcomes or late toxicities.

Our analysis focused on BsAb monotherapy or CAR T cells in later lines of therapy, reflecting the treatment landscape during the study period. Notably, the high proportion of infection-related nonrelapse mortality observed in the BsAb cohort should be interpreted in the context of the enrollment period, which overlapped with the later phases of the COVID-19 pandemic; early real-world BsAb experience (including the initial teclistamab cohorts) reported COVID-19–related deaths accounting for up to 50% of early

Table 3. IPTW-adjusted multivariable Cox regression.

	PFS		OS	
Variable	HR	95% CI	HR	95% CI
Treatment (vs. ide-cel)				
cilta-cel/cesni-cel	0.27	0.19–0.40	0.30	0.16–0.56
BsAb	0.72	0.52–1.01	0.77	0.51–1.17
EMD (vs. no EMD)	2.12	1.54–2.91	1.80	1.19–2.74
ECOG (vs. ECOG 0)				
ECOG 1	1.63	1.09–2.45	2.16	1.27–3.68
ECOG 2	2.09	1.36–3.21	2.76	1.56–4.88
ECOG 3	2.04	0.90–4.65	5	2.02–12.39
High-risk cytogenetics	1.39	1–1.93	1.40	0.92–2.13
Time to treatment (per month)	0.95	0.91–0.99	0.91	0.86–0.96
Age (per year)	1	0.98–1.01	1.01	0.99–1.04

infectious mortality, a risk that has since diminished with effective prophylactic strategies and broader population immunity. This temporal confounder may have disproportionately affected OS in the BsAb arm and warrants consideration when interpreting the observed survival differences by initial treatment modality. However, emerging data from trials such as MajesTEC-3 (10) and MajesTEC-9 (20) demonstrate excellent efficacy for teclistamab in earlier lines, which will likely lead to regulatory approval for use after 1 to 3 prior lines of therapy. As both CAR T-cell therapies and BsAb combinations move into earlier treatment lines, future comparative studies will be essential to define optimal sequencing strategies in this evolving landscape.

In summary, we report a large, multicenter real-world analysis evaluating clinical outcomes associated with CAR T-cell therapies and BsAbs in RRMM. Our findings suggest that access to potent CAR T constructs (particularly cilta-cel and cesni-cel) at any point during the treatment course is a key determinant of favorable outcomes, although the independent benefit of specific sequencing strategies remains to be established in prospective trials. These data support a treatment paradigm that prioritizes timely and equitable access to both modalities, recognizing that logistic barriers to CAR T availability may themselves contribute to outcome disparities.

METHODS

Data Collection and Outcomes

We conducted a retrospective, multicenter cohort study across 18 European academic and community-based centers (Fig. 1A). Eligible patients were adults (≥18 years) with RRMM who had received treatment with either a BCMA-targeted CAR T-cell therapy [commercial: ide-cel or cilta-cel; academic: cesni-cel; refs. 9, 15] or BsAb against BCMA (teclistamab or elranatamab) or GPRC5D (talquetamab) between January 2021 and March 2025. Patients were required to have received ≥3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Clinical and demographic characteristics were extracted from electronic health records, and baseline was defined as the timepoint preceding the first T-cell immunotherapy treatment. EMD was defined as true extramedullary involvement without connection to bone, excluding paraskeletal disease. Staging was determined at the time of initial diagnosis per Revised International Staging System. The study was conducted in accordance with the Declaration of Helsinki and was approved by local institutional review boards or ethics committees at each participating center. Investigators obtained written informed consent from patients.

The main endpoint for the analysis was OS, defined as the time from treatment initiation to death from any cause. Other endpoints included PFS, ORR, CR, NRM, and treatment-related adverse events including CRS and ICANS, graded per American Society for Transplantation and Cellular Therapy consensus criteria (21).

Statistical Analysis

Treatment Comparison. Patients were classified by initial immunotherapy modality (CAR T or BsAb). Given the nonrandomized, access-driven treatment allocation, main analyses are descriptive and exploratory. Results are reported as HRs with 95% CIs. No formal hypothesis testing was performed, and CIs were not adjusted for multiplicity. The complete methodologic approach is outlined in the Supplementary Methods.

Treatment Sequencing Analysis. To evaluate sequential immunotherapy strategies, patients were categorized into four trajectory groups based on treatment received: CAR T only, CAR T→BsAb, BsAb only, and BsAb→CAR T. Because trajectory group assignment conditions on future events (receipt of second-line therapy requires surviving long enough to receive it), naïve comparison of these groups introduces immortal time bias. Therefore, two complementary bias-correction approaches were employed:

Multistate Model. A four-state illness-death model was constructed with states: (i) first-line immunotherapy, (ii) progressed, (iii) second-line immunotherapy, and (iv) dead (22). Receipt of second-line therapy was modeled as a time-dependent transition rather than a baseline group assignment. State occupation probabilities were estimated using the Aalen–Johansen estimator, stratified by initial treatment modality (23). To enhance robustness, progression times were calibrated against the empirically observed PFS distribution of the corresponding single-modality group (group 0 for CAR T starters and group 2 for BsAb starters) using a Monte Carlo resampling framework across 100 iterations, with state occupation probabilities averaged to obtain stable estimates (24). As an additional

sensitivity analysis to account for treatment switching, a RPSFTM was applied using g-estimation to estimate the causal AF of CAR T exposure on the failure time scale, with counterfactual survival times derived under the assumption of a common treatment effect (Supplementary Methods).

Transition-Specific Hazard Analysis. To decompose the OS difference into its component processes, transition-specific Cox proportional hazards models were fitted on the full cohort within the multistate framework (25). Three clinically informative transitions were analyzed: first-line progression, post-progression mortality, and mortality while receiving second-line immunotherapy. For each transition, initial treatment modality (CAR T vs. BsAb) was modeled as the primary covariate.

First-line Remission Duration as Proxy for Resistance Development. To address potential impact of resistance mechanisms in the absence of molecular BCMA expression data, first-line PFS duration was evaluated as a clinically interpretable proxy for resistance development. A 3-month cutpoint was selected based on clinical convention, in which very early treatment failure is an established indicator of primary resistance and poor prognosis. First-line PFS duration (≤3 vs. >3 months) was included as an additional covariate in the transition-specific Cox models.

Landmark Analysis. Landmark analyses were performed at 3 and 6 months. Only patients alive at the landmark were included, classified by their known treatment trajectory, and OS was measured from the landmark forward. Flexible parametric survival models (Royston–Parmar) with restricted cubic splines on the log cumulative hazard scale were fitted to the 3-month landmark cohort to estimate smooth survival curves (26). Knot placement (k = 1–3) was selected by the Akaike information criterion. The 3-month landmark served as the primary analysis.

IPTW. To corroborate the findings from the multistate and landmark analyses, IPTW was applied as an independent sensitivity analysis (Supplementary Methods; ref. 27). Propensity scores were estimated using multinomial logistic regression adjusting for EMD, ECOG, cytogenetic risk, time from diagnosis to treatment, and age. Patients with missing data were excluded from this analysis. IPTW-weighted Cox proportional hazards models with robust sandwich standard errors were fitted for both PFS and OS. Additionally, doubly robust multivariable models including all propensity score covariates were fitted to assess prognostic factors.

RPSFTM

To address potential concern about treatment switching and its potential impact on the comparison of initial treatment modalities, we applied a RPSFTM as an additional sensitivity analysis (28, 29). The RPSFTM is a causal inference method specifically designed to adjust for treatment cross-over in survival analyses by estimating counterfactual survival times (i.e., the survival each patient would have experienced had they never received the experimental treatment; refs. 30, 31). Unlike the multistate model and landmark analyses, which model treatment transitions as time-dependent events, the RPSFTM directly estimates the causal AF of the experimental treatment (here, CAR T-cell therapy) on the failure time scale.

The structural model specifies that the counterfactual failure time U_i for patient i in the absence of CAR T exposure is given by $U_i = T_{on,i} \times \exp(\psi) + T_{off,i}$, where T_{on} denotes the time spent receiving or having received CAR T-cell therapy, T_{off} denotes the time not on CAR T-cell therapy, and ψ is the AF parameter. An AF $\exp(\psi) < 1$ indicates that CAR T exposure decelerates the disease process (i.e., prolongs survival), whereas $\exp(\psi) > 1$ would indicate acceleration of failure.

For patients initiating CAR T-cell therapy (n = 399), T_{on} was defined as the entire observed survival time for patients receiving CAR T only (group 0, n = 209) and as the first-line PFS time for patients who subsequently received BsAb (group 1, n = 190), with T_{off} comprising the remaining time on BsAb. For patients initiating BsAb (n = 241), T_{on} was zero for patients who never received CAR T (group 2, n = 200) and was defined as the time from CAR T initiation to event or censoring for patients who subsequently switched to CAR T (group 3, n = 41), with T_{off} equal to the first-line BsAb PFS duration prior to switching.

The parameter ψ was estimated using g-estimation, which identifies the value of ψ for which the counterfactual survival times $U_i(\psi)$ are independent of initial treatment assignment. This independence was assessed via the log-rank test statistic comparing counterfactual survival between the CAR T–first and BsAb-first arms. The point estimate $\hat{\psi}$ was obtained as the root of the signed log-rank Z-statistic as a function of ψ, solved using the Brent method. A 95% CI was derived by grid inversion, identifying the values of ψ at which the Z-statistic equals ±1.96. Re-censoring was applied following the method of White and colleagues (32) to ensure validity of the counterfactual survival estimates.

The RPSFTM rests on three key assumptions: (i) a common treatment effect (i.e., CAR T has the same relative effect on the failure time regardless of when it is received during the disease course); (ii) no unmeasured confounding of the switching decision, conditional on the model structure; and (iii) rank preservation (i.e., the ordering of patients' failure times is preserved under the counterfactual). The common treatment effect assumption is a recognized limitation, as the efficacy of CAR T-cell therapy may differ depending on disease stage, prior treatment exposure, and timing of administration. In a setting where treatment cross-over occurs in both directions (CAR T→BsAb and BsAb→CAR T), the model adjusts for the total time on CAR T across both treatment lines. Furthermore, the RPSFTM was originally developed for randomized trials with treatment switching. Therefore, its application to this observational cohort with access-driven treatment allocation requires cautious interpretation, and results should be viewed as a complementary sensitivity analysis rather than definitive causal estimates.

Adjusted OS was visualized using Kaplan–Meier curves of the counterfactual survival times, and an RPSFTM-adjusted HR was estimated from a Cox proportional hazards model fitted to the counterfactual data.

Software

All analyses were performed in R version 4.4.2 (R Foundation for Statistical Computing). Key packages: *survival* (version 3.7) for Cox regression and Kaplan–Meier estimation, *mstate* (version 0.3.3) for multistate model construction and Aalen–Johansen estimation, *flexsurv* (version 2.3) for Royston–Parmar flexible parametric models, *WeightIt* for propensity score estimation and IPTW weight construction, *cobalt* for covariate balance assessment, *survey* for weighted Kaplan–Meier estimation, and *survminer* (version 0.5.0) for visualization.

Data Availability

Data will be made available to qualified experts adhering to privacy protection rules of participating sites upon request to the corresponding author.

Authors' Disclosures

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