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Second time's the charm: B-cell maturation antigen CAR-T after GPRC5D CAR-T cells

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The rapidly expanding landscape of immunotherapies in multiple myeloma (MM) has made treatment sequencing increasingly complex. Two B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapies are currently FDA-approved for MM[1,2], while several CAR-T products targeting G protein-coupled receptor, class C, group 5, member D (GPRC5D) are under clinical investigation[3-5]. Although CAR-T therapy has transformed the treatment of relapsed/refractory multiple myeloma (RRMM), relapse is common, and the optimal strategy after CAR-T failure remains uncertain.

Current European Myeloma Network (EMN) recommendations on sequencing BCMA- and GPRC5D-targeted immunotherapies generally favor CAR-T therapy before bispecific antibodies or antibody-drug conjugates, although these recommendations are largely based on non-randomized data. As BCMA-directed therapies are increasingly used earlier in the disease course, understanding how prior antigen-directed therapy affects the subsequent treatment becomes particularly important. Emerging retrospective data support the feasibility of BCMA-directed CAR-T therapy after GPRC5D-directed bispecific antibodies, as well as after prior BCMA-directed bispecific therapy. More recently, the results of the phase 1 study of arlocabtagene autoleucel (arlo-cel), a GPRC5D direct CAR-T, were published. The study included 84 patients with RRMM, 49% of whom had previously received BCMA-targeted therapy. Among patients exposed to prior BCMA-directed therapy, the overall response rate (ORR) was 100%, with 78% achieving complete response or better[5]. However, evidence regarding sequential CAR-T therapy, particularly the use of a second CAR-T product following relapse after the first one, remains limited, with available data primarily derived from small real-world studies and expert consensus recommendations[6,7].

In this context, the study by Zhang et al. provides important evidence that progression after GPRC5D-directed CAR-T therapy does not necessarily preclude a meaningful response to subsequent BCMA-directed CAR-T therapy[8]. This retrospective study included 20 heavily pretreated patients with RRMM

who received BCMA-directed CAR-T therapy after GPRC5D-directed CAR-T therapy. Patients had received a median of six prior lines of therapy, and 50% were triple-class refractory. The median interval between the two CAR-T therapies was 14.4 months. The infused cells were isolated BCMA (55%), bispecific BCMA+CD19 (35%) and bispecific BCMA+GPRC5D (10%). Despite prior cellular therapy, the ORR following BCMA-directed CAR-T was 65%, including a stringent complete response rate of 45%. These outcomes are particularly informative when viewed alongside a previously reported cohort from the same center, in which 37 patients received the reverse sequence, i.e., GPRC5D-directed CAR-T after BCMA-directed CAR-T, with no statistically significant differences in ORR or PFS between the two sequencing strategies (Figure 1A).

When considering treatment sequencing, however, efficacy is only part of the equation. Toxicity is equally important, and not all CAR-T products have identical toxicity profiles. Reassuringly, in the current study, rates of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenias, and infections did not appear greater than those generally observed with CAR-T therapy. There was one grade 3 CRS event, one grade ≥3 infection and no ICANS.

These findings introduce a broader biological question that may ultimately be more important than the sequence itself: what exactly has failed in case of an unsuccessful outcome: the target, the CAR-T cells, or both? At present, treatment selection is not routinely guided by validated assays quantifying the BCMA or GPRC5D expression on plasma cells. Yet, understanding the mechanisms of resistance will be critical to rational sequencing. Failure after CAR-T therapy may result from the loss or downregulation of the target antigen, antigen heterogeneity, inadequate CAR-T expansion or persistence, impaired T-cell fitness, immunosuppressive tumor microenvironment, or combinations of these mechanisms. These possibilities have very different implications for the choice of subsequent therapy. If resistance is predominantly antigen-specific, switching from GPRC5D to BCMA, or vice

versa, may restore sensitivity. In contrast, if a failure reflects poor T-cell fitness or unfavorable microenvironment, a simple change of the target may be insufficient (Figure 1B).

The study by Zhang et al. provides some evidence supporting the feasibility of the GPRC5D→BCMA sequence[8]. Together with emerging data on the reverse BCMA→GPRC5D sequence, it suggests that sequential CAR-T therapy directed against different antigens may remain effective after a failure of the first cellular therapy. However, the field is already moving beyond a binary choice between BCMA and GPRC5D. Additional targets, including FcRH5, CD38, SLAMF7, and CD138, are under investigation, while dual- and multi-antigen approaches are being developed to mitigate the risk of antigen escape. A recent phase 2 trial of bispecific BCMA/GPRC5D CAR-T illustrates this approach in patients with high-risk extraosseous extramedullary disease: 36 of 37 patients (97%) achieved an overall response, including 43% with stringent complete response, and toxicity was comparable to that of single-target products. However, despite the high overall response rate, the median PFS was only 5.8 months, highlighting the limited durability of responses in this high-risk population. Whether bispecific CAR-T offers more durable disease control than sequential single-target CAR-T remains to be determined[9].

The central question may therefore evolve from "Which CAR-T to use next?" to "Could the mechanism of failure be predicted and the next target selected accordingly?" Future sequencing strategies should account for the tumor antigen biology, i.e., its expression, heterogeneity, and mechanisms of loss or shedding, alongside CAR-T suitability and persistence and the depth and durability of the prior response. A recently developed quantitative systems pharmacology model of BCMA- and GPRC5D-targeted CAR-T therapy suggests that this integration is already within reach: by combining clinical trial and real-world data, it has identified tumor burden, antigen expression, and CAR-T killing capacity as the principal drivers of response and relapse[10]. Notably, when the model simulated sequential combination therapy, it predicted a better response with anti-GPRC5D CAR-T given first, followed by anti-BCMA CAR-T – consistent with the sequence evaluated by Zhang et al[8]. Ultimately,

the goal should not simply be limited to establishing a fixed sequence of BCMA and GPRC5D therapies. Rather, we should move toward biologically informed sequencing, in which the mechanism of resistance to one cellular therapy helps determining the next option. The study by Zhang et al. represents an important step in that direction: failure of one CAR-T product does not necessarily close the door to another, particularly when the target changes.

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Figure 1. Sequencing CAR-T therapies in relapsed/refractory multiple myeloma.

(**A**) Reciprocal sequencing of GPRC5D- and BCMA-directed CAR-T at a single center. Twenty patients received BCMA-directed CAR-T after progression on a prior GPRC5D-directed CAR-T (this study); a previously reported cohort of 37 patients received the reverse sequence. Outcomes were not significantly different between sequences. (**B**) Proposed framework for biologically informed sequencing after CAR-T failure. When resistance is predominantly antigen-specific, switching target (GPRC5D ↔ BCMA) may restore sensitivity; when failure instead reflects impaired T-cell fitness or an unfavorable microenvironment, a target switch alone may be insufficient. CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; PFS, progression-free survival. The figure was drafted with the assistance of Claude (Claude Sonnet 5.5, Anthropic; accessed October 2026) using text and data supplied by the authors. The authors reviewed, verified and edited the figure and take full responsibility for its content.

A Two sequences, mirror images of one another

Salvage CAR T-cell therapy directed at the alternative antigen after relapse from the first product.

THIS STUDY — GPRC5D FIRST

GPRC5D CAR-T (first infusion) → Relapse — antigen escape → BCMA CAR-T (salvage, n = 20)

65%	45%	9.2	20.8
ORR	sCR	PFS, months	PFS if sCR

PRIOR COHORT — BCMA FIRST

BCMA CAR-T (first infusion) → Relapse — antigen escape → GPRC5D CAR-T (salvage, n = 37)

84%	35%	4.5	NR
ORR	CR	PFS, months	PFS if ≥CR

B Towards biologically informed sequencing: what has failed?

