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REVIEW

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Targeting GPRC5D for multiple myeloma therapy

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Abstract

Given its nearly ubiquitous expression on plasma cells and limited expression on essential normal tissue, the G protein-coupled receptor class C group 5 member D (GPRC5D) presents a promising opportunity for utilization as an immunotherapy target in multiple myeloma (MM). The therapeutic strategies targeting GPRC5D, such as bispecific antibodies (BsAbs), chimeric antigen receptor (CAR) T cells, and antibody–drug conjugates (ADCs), have been prominently emphasized in relapsed/refractory MM (R/R MM) in recent years. Further clinical trials are necessary to confirm the long-term efficacy of GPRC5D-targeting immunotherapies alone, explore their potentials co-targeting with other specific antigens, or investigate their combinations with existing treatments to overcome MM resistance. This review provides an overview of current research progress in GPRC5D, encompassing its biological characteristics and translational journey from laboratory to clinical application.

Keywords Multiple myeloma, G protein-coupled receptor class C group 5 member D, Chimeric antigen receptor T cell, Bispecific antibodies, Immunotherapy

Introduction

Multiple myeloma (MM) is characterized by clonal proliferation of malignant plasma cells in the bone marrow (BM) [1]. In recent years, immunotherapies expand rapidly and have significantly improved outcomes for both newly diagnosed and relapsed/refractory (R/R) MM patients. These therapies include monoclonal antibodies [2], antibody–drug conjugates (ADCs) [3–5], bispecific antibodies (BsAbs) [6–9], and chimeric antigen receptor (CAR) T cell [10, 11]. Daratumumab, the first FDA-approved CD38 monoclonal antibody for MM treatment, has demonstrated its activity in MM [12, 13]. B-cell maturation antigen (BCMA), a targeted antigen on myeloma cells, currently has been incorporated into several FDA-approved therapeutic products [14–20]. Despite the promising outcomes observed with the aforementioned therapies, MM patients undergo cycles of remission and relapse. Consequently, there remains an unmet need for additional innovative immunotherapeutic alternatives in R/R MM. The G protein-coupled receptor class C group 5 member D (GPRC5D) has garnered increasing attention as a novel therapeutic target for the treatment of MM in recent years (Fig. 1). This review focuses on elucidating the biology of GPRC5D and providing an overview of recent advancements in GPRC5D-targeting therapies, including their clinical efficacy and safety data.

Biology of GPRC5D

Location, structure, and distribution

GPRC5D is encoded by the *GPRC5D* gene, with murine *Gprc5d* located on chromosome 6G1 (NCBI Gene ID: 93746), and human *GPRC5D* located on chromosome 12p13.3 (NCBI Gene ID: 55507). In addition to RAIG1

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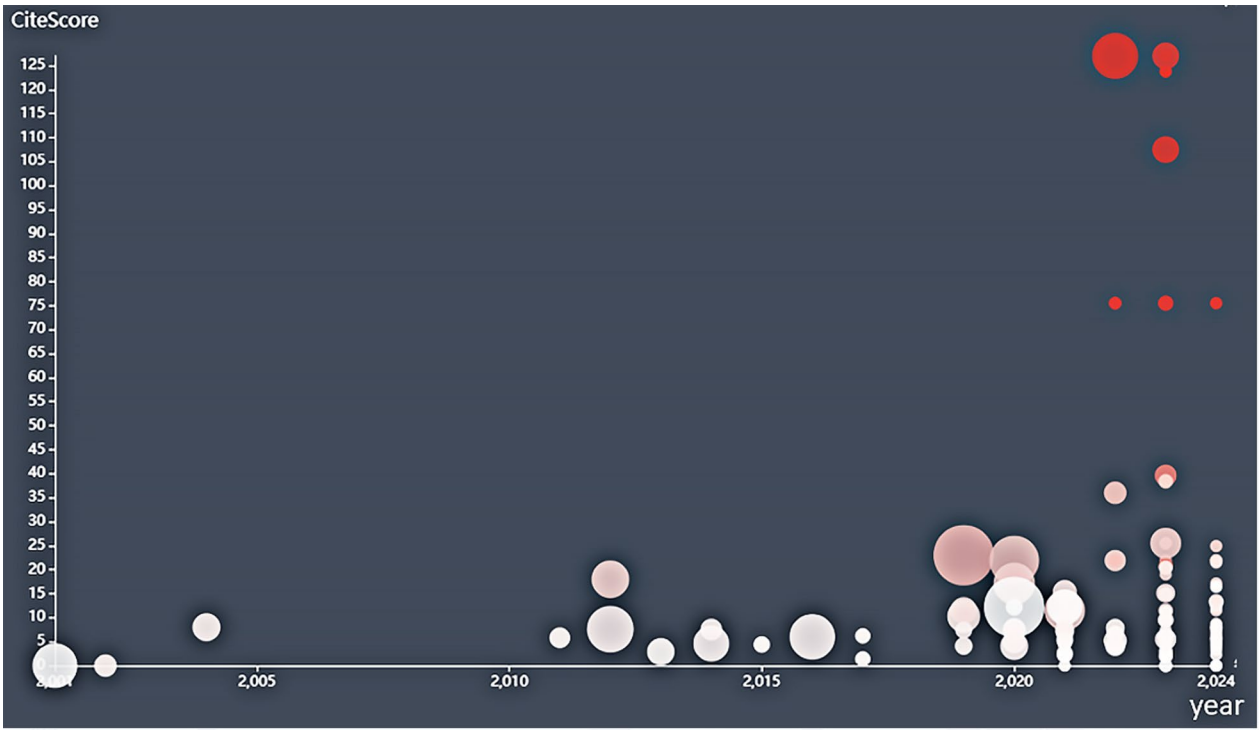

Fig. 1 The absolute number and authoritative index of papers related to GPRC5D over the past two decades. A comprehensive literature search was conducted on https://pubmed.ncbi.nlm.nih.gov utilizing the keywords "GPRC5D" to identify currently available publications (July 31, 2024)

(GPRC5A) [21], GPRC5B [22], and GPRC5C [23], GPRC5D was subsequently identified as the fourth member of G protein-coupled receptor family C cloned from a human adult testis cDNA library [24]. *GPRC5D* consists of three exons with lengths of 895, 68 and 75 nucleotides, separated by two introns of 7161 and 1411 nucleotides, and the first exon is the largest containing all seven transmembrane segments [24] (Fig. 2). The GPRC5D proteins in human are composed of predicted open reading frames (ORF) of 345 amino acid, without the presence of a signal peptide.

In normal adult human tissue, GPRC5D mRNA levels were found to be high in the pancreas, moderate in the kidney, small intestine, spleen and testis; low in the lung, colon, leukocyte, prostate and thymus; and undetectable in the heart, liver, placenta, skeletal muscle and

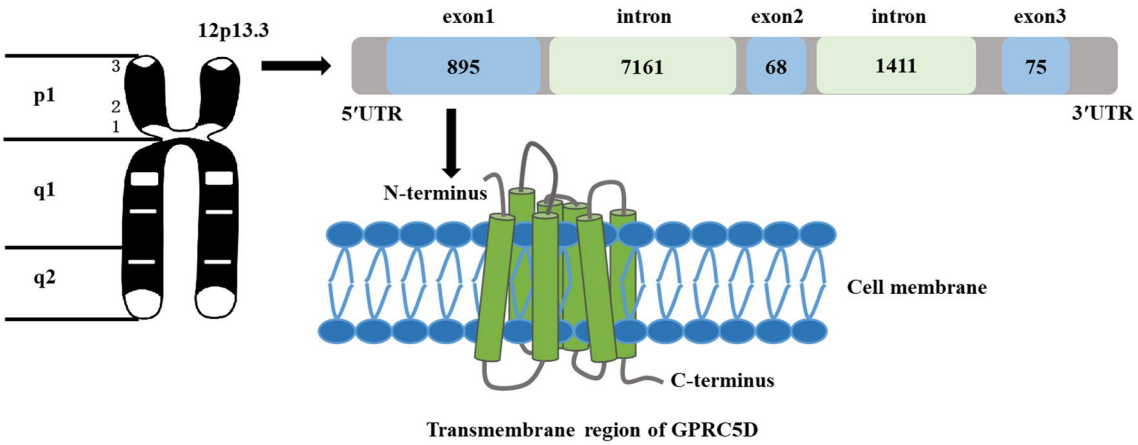

Fig. 2 Location and structure of GPRC5D. Graphical representation depicting the chromosomal location, gene locus structure, and the seven transmembrane α-helices along with a short N-terminal domain of human GPRC5D

ovary by RT-PCR [24]. Interestingly, a study by Eric et al. revealed that *Gprc5d* mRNA expression was not significantly elevated in any normal tissues except for plasma cells and skin [25]. This finding is consistent with previous research indicating its presence specifically within differentiating cells responsible for producing hard keratin such as cortical cells of the hair shaft or nail keratogenous zone through in situ hybridization [26]. In contrast to the widespread distribution of mRNA, the expression of GPRC5D protein is predominantly limited to $CD138^+$ bone marrow (BM) cells from healthy donors and hard keratinized tissues, as detected by immunohistochemistry or flow cytometry [25, 27, 28].

Biology of GPRC5D in MM

Although GPRC5D has been identified for over 20 years [24], its endogenous ligand(s), signaling mechanism, physiological function, and role in pathological conditions remain elusive. Hence, GPRC5D is still classified as an orphan G protein-coupled receptor. Recently, GPRC5D was identified as a prominent gene that distinguishes myeloma [29]. However, stable knockdown of GPRC5D by 70% in CAG myeloma line using lentiviral particles containing shRNA had no effect on short-term growth of these cells [30]. Subsequently, researchers attempted to analyze the correlation between levels of GPRC5D and the disease status of MM. There is no significant variation in the extent of GPRC5D protein expression among newly diagnosed MM (NDMM), daratumumab-naïve R/R MM, and daratumumab-refractory (DARA-R) MM patients [31]. These findings suggest that despite being predominantly localized on plasma cells, the functionality of GPRC5D appears to be independent of plasma cell biology.

GPRC5D was identified as a promising biomarker for assessing the burden of MM cells as early as 2013 [29]. In accordance with previous findings, gene expression levels of *GPRC5D* were significantly higher in MM patients as compared with healthy controls [31]. Moreover, both normal and clonal plasma cells displayed markedly higher surface expression of GPRC5D than other immune cells types, including B, T, NK and NKT cells [31]. Furthermore, *GPRC5D* mRNA demonstrated robust and specific expression in 30 MM cell lines out of over 1000 diverse malignant cell lines screened computationally, while negligible expression was observed in other tumor types [25, 27]. Therefore, the widespread expression of GPRC5D on MM plasma cells coupled with its limited expression on other essential tissue cells, renders it a promising target for anti-myeloma interventions.

Regarding the potential correlations between GPRC5D and clinical outcomes of MM, conflicting data are currently reported. *GPRC5D* mRNA expression showed a significant correlation with overall survival of MM [32], as confirmed that patients in the CoMM pass cohort (n = 765) with GPRC5D expression above the median showed a shorter progression-free survival [25]. Song et al. confirmed that 21.8% plasma cells with BCMA, CD38, CD24, CD138, SLAMF7, and GPRC5D expression, while 51.8% of these plasma cells emerged at progression [33]. The latest data, however, revealed no significant correlation between GPRC5D expression levels and either progression-free survival or overall survival [31].

Although the relationship between the initial status of GPRC5D on plasma cells and the prognosis of MM remains controversial, it is evident that the gene aberration of GPRC5D correlates with the efficacy of MM immunotherapy. In Table 1, we provided a comprehensive summary of the *GPRC5D* gene mutations reported in MM patients. The analysis of whole-genome sequencing data from a cohort of 100 MM patients revealed that *GPRC5D* exhibited the highest frequency of heterozygous deletions (15%) prior to immunotherapy compared to *CD38* (10%) and *SDC1*(5%), with one biallelic event (del/mut) for *GPRC5D* [34]. Although heterozygous deletions did not exert a substantial impact on gene expression, this finding suggests that these *GPRC5D* deletions may potentially act as an initiator for subsequent homozygous deletion and consequent antigen-loss

Table 1 Gene aberrations of GPRC5D in MM patients

Immunotherapy	MM	Gene aberration	Expression	Consequence
Non-Immunotherapy	ND = 50 R/R = 50	GPRC5D heterozygous deletions (15%)	No change	A First hit drives the subsequent homozygous deletion and antigen loss
Anti-GPRC5D BsAb	R/R = 5	Biallelic mutations (n = 4) with convergent evolution (n = 2)	Loss of GPRC5D expression	Negative or mutant clones are tumor-intrinsic driver of relapse post-targeted therapies
Anti-GPRC5D BsAb	R/R = 3	Biallelic inactivation of GPRC5D (n = 1); Lack of GPRC5D Transcript (n = 2)	Silencing of GPRC5D expression	Resistance from genetic or long-range epigenetic silencing of GRPC5D
Anti-GPRC5D CAR T	R/R = 6	Biallelic loss of GPRC5D (n = 1)	Loss of GPRC5D mRNA and protein	Antigen escape after GPRC5D CAR T -cell therapy

relapse following targeted immunotherapy. Recently, emerging evidence has revealed that the relapse or resistance mechanisms associated with GPRC5D-targeted immunotherapies involved biallelic deletion or long-range epigenetic silencing of promoter and enhancer regions specific to *GPRC5D* [35–37]. Reduction (2 out of 6) or loss (4 out of 6) of GPRC5D protein expression was observed in all six progressed MM patients following anti-GPRC5D CAR T-cell (MCARH109) therapy [38]. Furthermore, the longitudinal changes of GPRC5D were compared and demonstrated a significant decrease in expression following treatment [39, 40]. The acquired genetic events enhance the evolutionary fitness level of myeloma propagating cells to survive and to result in relapse [41]. Therefore, the enhanced T cell immunotherapy will exert selective pressure on the tumor, resulting in modifications to the biological characteristics of GPRC5D.

Journey of GPRC5D research

Since the identification and cloning of GPRC5D in 2001, more than two decades have elapsed, and currently it has emerged as a promising target for immunotherapy against MM (Fig. 3). Despite early reports on the tissue distribution characteristics of GPRC5D, there has been a paucity of studies over the subsequent decade that elucidated the association between GPRC5D and MM [24, 26, 29, 32]. In 2019, Eric et al. published article in Sci Transl Med., identifying GPRC5D as an immunotherapeutic target and confirming the promising preclinical efficacy of GPRC5D CAR T-cells in the treatment of MM [25]. Subsequently, numerous clinical trials exploring GPRC5D-targeted BsAb and CAR T-cell immunotherapies have emerged, opening up a new chapter in the treatment of R/R MM [27, 31, 38, 42–44]. By 2023, anti-GPRC5D×CD3 BsAb (talquetamab)was approved by FDA and became the first immunotherapy product targeting GPRC5D [45–47]. Additionally, immunotherapy strategies targeting GPRC5D such as CAR-NK, ADCs, dual-targeting CAR T are currently being vigorously explored [48–51].

GPRC5D-targeted immunotherapies

GPRC5D has emerged as a promising immunotherapeutic target in patients with R/R MM. Currently, safety and efficacy of two BsAb and seven CAR T-cell products have been reported, while numerous GPRC5D-targeting agents are under investigation in preclinical trials (Fig. 4).

Efficacies of GPRC5D-targeted therapies

Efficacies of anti-GPRC5D BsAb

Talquetamab (JNJ-64407564) is an off-the-shelf, humanized immunoglobulin G4 BsAb with a proline, alanine, alanine (IgG4-PAA) scaffold that can bind to both GPRC5D on target cells and the epsilon chain of CD3 on T cells [27, 31, 45] (Fig. 4A). A first-in-human, multi-center, phase 1 MonumenTAL-1 trial of talquetamab (NCT03399799), was initiated in 232 patients with R/R MM (Table 2). All enrolled patients had received a median of 6 lines of previous therapies, of whom 79% had triple-refractory disease, 30% had penta-refractory disease. Of these patients, 102 (44%) received talquetamab intravenously (IV), and 130 (56%) received talquetamab subcutaneously (SC), including 30 (23%) patients with 405 μg SC weekly (QW), and 44 (34%) patients with 800 μg SC every 2 weeks (Q2W) [45]. The objective response rate (ORR) was 70% with 23% complete response (CR) or stringent CR (sCR) in the 405 μg SC cohort, and was 64% with 23% CR/sCR in the 800 μg SC cohort. Among patients who received the most active intravenous doses (20–180 μg/kg QW), the ORR was 72%, including 28 (39%) patients achieving CR/sCR.

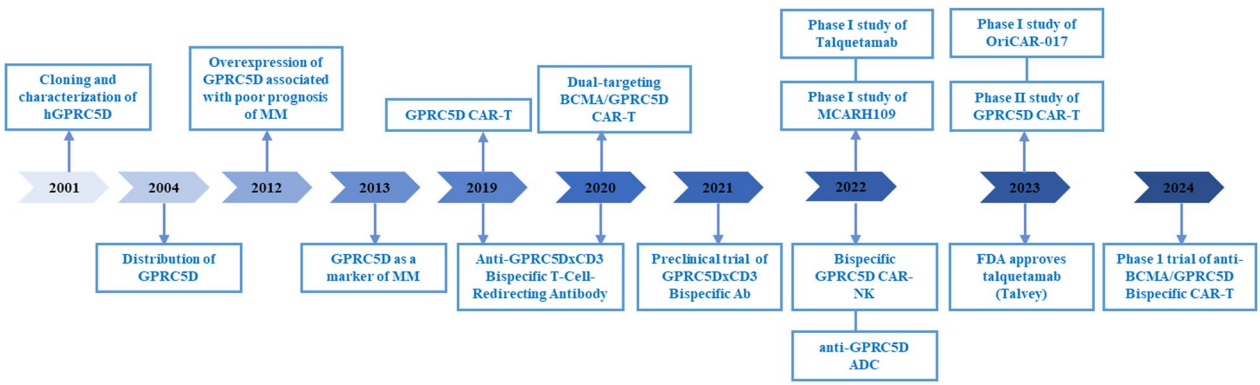

Fig. 3 The journey of GPRC5D research from bench to bedside. The key milestones of the initial cloning of the *GPRC5D* gene and subsequent clinical trials evaluating GPRC5D-targeting immunotherapies are highlighted

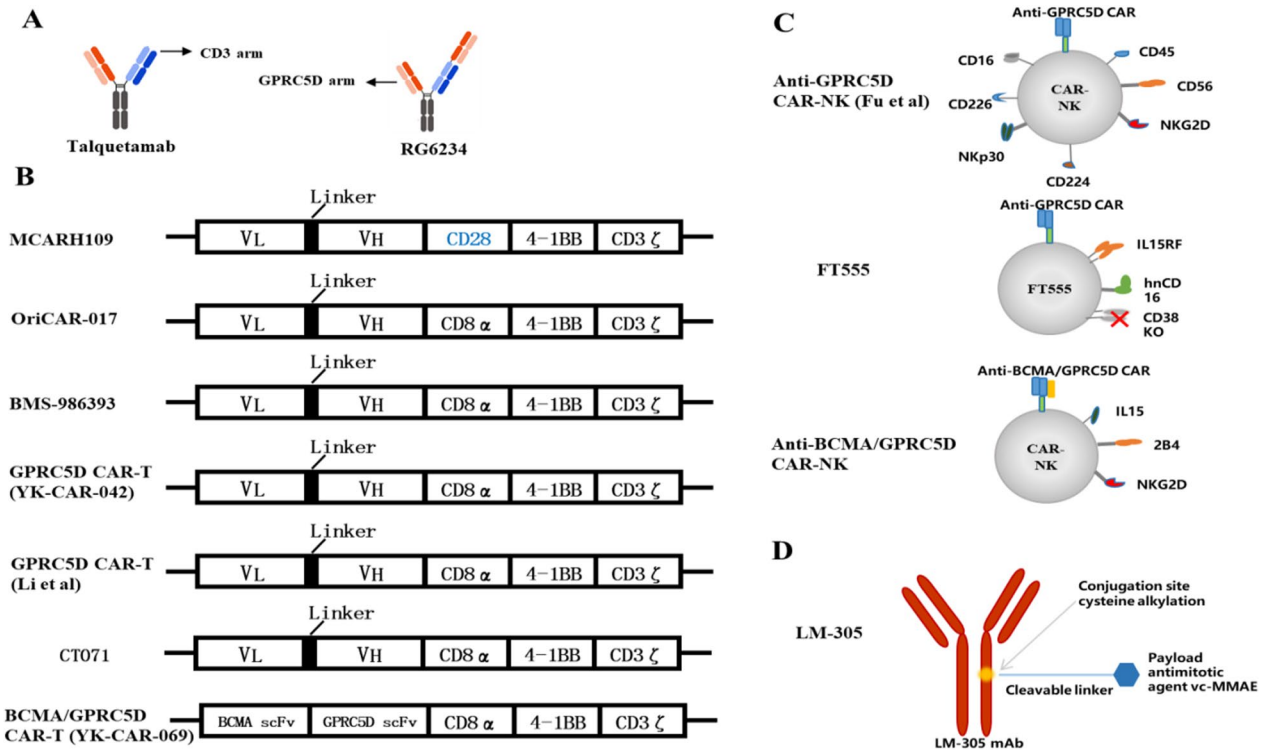

Fig. 4 Structures of GPRC5D-targeted products. **A** The structure of bispecific antibodies encompasses the anti-CD3, anti-GPRC5D, and Fc regions; **B** The generalized structures of anti-GPRC5D CAR T cells are depicted; **C-D** Cartoon graphs illustrate the GPRC5D-targeting CAR-NK cells and anti-GPRC5D ADC

The median time to response were 0.9 months (rang 0.2–3.8) and 1.2 months (rang 0.3–6.8), to a CR or better were 9.3 months (rang 1.7–17.1) and 2.3 (rang 2.1–6.8) months, and the median duration of response were 10.2 months (95% confidence interval [CI], 3.0 to not reached) and 7.8 months (95% CI, 4.6 to not reached) in the 405 μg and 800 μg SC cohort, respectively. Eleven (69%) achieved minimal residual disease (MRD) negativity among 16 patients with samples available for analysis of MRD [45] (Table 3). Talquetamab demonstrated significant efficacy against myeloma cells in patients with R/R MM, regardless of administration via SC or IV routes. In comparison to other recommended treatment regimens, such as selinexor plus dexamethasone or belantamab mafodotin, talquetamab exhibited superior clinical responses among patients with triple-class-refractory diseases. Given the promising efficacy observed in the phase 1 trial, a pivotal phase 2 MonumenTAL-1 trial evaluating talquetamab has been initiated [52]. The trial enrolled 288 patients who received talquetamab 0.4 mg/kg QW (n = 143) or 0.8 mg/kg Q2W (n = 145). In the QW and Q2W cohorts, 74% and 69% of patients were triple-refractory; 29% and 23% were penta-refractory [52]; the ORR were 74% (with a median follow-up of 14.9 months) and 73% (with a median follow-up of 8.6 months); the CR or better rates were 34% and 32%; the median duration of response (DOR) were 9.3 (95% CI 6.6–12.7) and 13.0 months (95% CI, 10.6 to not reached). After an extended follow-up period, a larger cohort of patients (n = 297) was included in the safety analysis. In the QW and Q2W cohorts, the ORR were 74.1% (with a median follow-up of 29.8 months) and 69.5% (with a median follow-up of 23.4 months), respectively; the CR or better rates were 32.9% and 40.3%; the median DOR were 9.5 (95% CI 6.7–13.4) and 17.5 months (95% CI, 12.5 to not reached); median progression free survival (PFS) were 7.5 (95% CI, 5.7–9.4) and 11.2 months (95% CI, 8.4–14.6) [53](Table 3).

RG6234 (also known as Forimtamig) is a novel T-cell BsAb targeting GPRC5D and CD3 with a unique 2:1 configuration [54–56] (Table 2, Fig. 4A). A phase 1 clinical trial of RG6234 (NCT04557150) enrolled 108 patients who received at least 2 prior lines of therapies, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD). Of these patients, 51 patients received RG6234 IV (dose range: 6–10,000 μg) and 57 received RG6234 SC (dose range: 30–7200 μg) in the dose-escalation phase. The ORR were 71.4% (with a median follow-up of 11.6 months) and 63.6% (with a median follow-up of 8.0 months), and CR or better rates were 34.7% and 25.5%

Table 2 Properties of GPRC5D-targeted agents

Product	Trial	Strategy	Type	Manufacturer	Patient population
Talquetamab	Phase 1/2 NCT03399799/ NCT04634552	BsAb	Off-the-shelf	Janssen Research & Development	Phase 1: R/R MM patients aged ≥ 18 years, an ECOG score of 0–1 Phase 2: R/R MM patients aged ≥ 18 years, an ECOG score of 0–1, ≥ 3 prior lines of treatment, including a Pi, an IMiD and an anti-CD38 antibody
RG6234 (Forimtamig)	Phase 1 NCT04557150	BsAb	Off-the-shelf	Hoffmann-La Roche	R/R MM patients with an ECOG score of 0–1, ≥ 2 prior lines of treatment, including a Pi and an IMiD
BR109	Preclinical	BsAb	Off-the-shelf	Hangzhou Hisun Biopharmaceutical Co., Ltd	–
GPA0039	Preclinical	BsAb	Off-the-shelf	Chugai Pharmaceutical Co., Ltd	–
MCARH109	Phase 1 NCT04555551	CAR T	Autologous T cells	Memorial Sloan Kettering Cancer Center	R/R MM patients aged ≥ 18 years, an ECOG score of 0–1, ≥ 3 prior lines of treatment, including a Pi, an IMiD and an anti-CD38 antibody
OriCAR-017	Phase 1 NCT05016778	CAR T	Autologous T cells	Shanghai Oricell Therapeutics	R/R MM patients aged 18–75 years, an ECOG score of 0–2, ≥ 3 prior lines of treatment, including a chemotherapy, a Pi, and an IMiD
BMS-986393	Phase 1 NCT04674813	CAR T	Autologous T cells	Juno Therapeutics	R/R MM patients with aged ≥ 18 years, an ECOG score of 0–1, ≥ 3 prior lines of treatment, including a Pi, an IMiD, an anti-CD38 antibody and an ASCT (if eligible)
GPRC5D CAR T (YK-CAR-042)	Phase 2 CHiCTR2100048888	CAR T	Autologous T cells	Shanghai YaKe Biotechnology Ltd	R/R MM patients aged 18–70 years with a Karnofsky Performance score ≥ 50
GPRC5D CAR T (Li et al.)	Phase 1 NCT05739188	CAR T	Autologous T cells	Guangzhou Bio-gene Technology Co., Ltd	R/R MM patients aged 18–75 years, an ECOG score of 0–2, ≥ 3 prior lines of treatment, including a chemotherapy, a Pi, and an IMiD
CT071	Phase 1 NCT05838131	CAR T	Autologous T cells	Shanghai CARsgen Therapeutics Co. Ltd	R/R MM patients with an ECOG score of 0–2, ≥ 3 prior lines of treatment, including a Pi, and an IMiD
BCMA/GPRC5D bispecific CAR T (YK-CAR-069)	Phase 1 NCT05509530	CAR T	Autologous T cells	Shanghai YaKe Biotechnology Ltd	R/R MM patients aged 18–75 years, an ECOG score of 0–3
GPRC5D CAR-NK (Fu et al.)	Preclinical	CAR-NK	iPSC	Shenzhen Cell Inspire Therapeutics	–
FT555	Preclinical	CAR-NK	iPSC	Fate Therapeutics Inc. and The Janssen Pharmaceutical Companies of Johnson & Johnson	–
BCMA/GPRC5D CAR-NK	Preclinical	CAR-NK	Off-the-shelf	Shanghai Simnova Biotechnology Co., Ltd	–
LM-305	Phase 1/2 NCT05647512	ADC	Off-the-shelf	LaNova Medicines, Shanghai	R/R MM patients aged ≥ 18 years, with an ECOG score of 0–1

ASCT, autologous stem-cell transplantation, ADC, antibody–drug conjugate, BsAb bispecifc antibody, BCMA B cell maturation antigen, CAR T chimeric antigen receptor T cell, CAR-NK chimeric antigen receptor NK cell, ECOG Eastern Cooperative Oncology Group, GPRC5D G protein-coupled receptor family C group 5 member D, IMiD immunomodulatory drug, iPSC induced pluripotent stem cells, Pi proteasome inhibitor,R/R MM relapsed/refractory multiple myeloma

Table 3 Clinical data of GPRC5D-targeted BsAbs

Product	Clinical trial	Pt characteristics	Dosage	Clinical response	Common AEs
Talquetamab	Phase 1	130 pts in SC cohort; median age 64; high-risk cytogenetics 16%; median prior therapies 6; triple-refractory 75% 102 pts in IV cohort; median age 65; high-risk cytogenetics 16%; median prior therapies 6; triple-refractory 85%	5–1600 μg/kg in SC cohort; 0.5–180 μg/kg in IV cohort	405-μg SC cohort: ORR 70%; CR/sCR 23% 800-μg SC cohort: ORR 64%; CR/sCR 23% IV cohort (20–180 μg/kg): ORR 72%; CR/sCR 28%	405-μg SC cohort: ≥ grade 3 anemia 30%, neutropenia 60%; thrombocytopenia 23%; CRS 80% (≥ grade 3, 3%); nail changes 57% 800-μg SC cohort: ≥ grade 3 anemia 23%, neutropenia 32%; thrombocytopenia 11%; CRS 80% (no ≥ grade 3); nail changes 27%; IV cohort: ≥ grade 3 anemia 33%, neutropenia 26%, thrombocytopenia 13%; CRS 54% (≥ grade 3, 5%); nail changes 20%
	Phase 2	143 pts in 0.4 mg/kg QW cohort; median prior therapies 5; triple-refractory 74% 145 pts in 0.8 mg/kg Q2W cohort; median prior therapies 5; triple-refractory 69%	0.4 mg/kg QW or 0.8 mg/kg Q2W	QW cohort: ORR 74%; CR/sCR 34%; median DOR 9.3 months Q2W cohort: ORR 73%; CR/sCR 32%; median DOR 13 months	QW cohort: CRS 79%; ICANS 11%; nail changes 54%; dysgeusia 50%; ≥ grade 3 infections 22% Q2W cohort: CRS 75%; ICANS 11%; nail changes 53%; dysgeusia 48%; ≥ grade 3 infections 16%
RG6234	Phase 1	51 pts in IV cohort; median age 62; high-risk cytogenetics 46.7%; median prior therapies 5; triple-refractory 62% 57 pts in SC cohort; median age 63; high-risk cytogenetics 47.4%; median prior therapies 4; triple-refractory 71.9%	6-10000 μg in IV cohort or 30-7200 μg in SC cohort	IV cohort: ORR 71.4%; CR/sCR 34.7%; median DOR 10.8 months SC cohort: ORR 63.6%; CR/sCR 25.5%; median DOR 12.5 months	IV cohort: ≥ grade 3 anemia 15.7%, neutropenia 11.8%; thrombocytopenia 13.7%; CRS 82.4% (≥ grade 3, 2%); no ICANS; hail and nail changes 23.5%; ≥ grade 3 infections 21.5% SC cohort: ≥ grade 3 anemia 38.6%, neutropenia 15.8%; thrombocytopenia 19.3%; CRS 78.9% (≥ grade 3, 1.8%); ICANS 1.8%; hail and nail changes 28.1%; ≥ grade 3 infections 26.4%

AE adverse event, CRS cytokine release syndrome, CR complete response, DOR duration of response, ICANS immune effector cell-associated neurotoxicity, IV intravenous, MRD minimal residual disease, ORR overall response rate, pt patient, PR partial response, QW weekly, Q2W every other week, SC subcutaneous, sCR stringent complete response

in the IV and SC cohort, respectively. Median time to first response were 1.4 (95% CI, 1.2–1.8) and 1.6 months (95% CI, 1.2–2.1), and median duration of response were 10.8 (95% CI, 0.0–17.6) and 12.5 months (95% CI, 1.2–12.5) in the IV and SC cohorts [56] (Table 3). Similarly, RG6234 demonstrated comparable anti-tumor efficacy in both IV and SC cohorts, resembling the BsAb talquetamab. Notably, RG6234 can be conveniently accessed off the shelf and administered via SC route, thereby circumventing potential setbacks, attrition rates, and burdens associated with personalized CAR T-cell therapy generation.

Other GPRC5D-targeted BsAb BR109 exhibits binding affinity towards human GPRC5D and CD3ε. BR109 demonstrates favorable stability and antitumor activity, specifically inducing T-cell-mediated cytotoxicity against numerous GPRC5D-positive MM cell lines in vitro. Furthermore, the antitumor efficacy of BR109 is validated in xenograft mouse models with reconstituted human immune cells [42]. GPA0039 mediated target-dependent cell cytotoxicity via activation of human T cells by ligating human $CD3^+$ T cells and GPRC5D-expressing cells. In vitro and in vivo xenograft models demonstrated that GPA0039 suppressed tumor growth of GPRC5D-positive myeloma cells via T cell activation [47]. Although BR109 and GPA0039 exhibited potent anti-tumor cytotoxicity in animal models, no clinical data regarding safety and efficacy have been reported thus far.

Efficacies of GPRC5D-targeted CAR T cells

Currently, all clinically utilized anti-GPRC5D CAR T cells are second-generation CAR T-cell therapies incorporating a single anti-GPRC5D scFv derived from human B-cells or a dual-specific scFv, a 4-1BB (or CD28) costimulatory domain, and a CD3ζ signaling domain (Fig. 4B).

MCARH109 For the manufacture of MCARH109, patients' T cells were combined at a 1:1 ratio of CD4:CD8, activated, and transduced with the MCARH109 lentivirus and expanded [38]. A phase 1 trial (NCT04555551) of MCARH109 was initiated in a single center, enrolling 17 patients with R/R MM who had failed in at least 3 (median 6) previous lines of therapy, including a PI, an IMiD, a CD38 monoclonal antibody, and high-dose chemotherapy followed by autologous stem cell transplantation. Doses of 25×10^6, 50×10^6, 150×10^6, and 450×10^6 total CAR T cells were infused in the dose-escalation phase, of which a dose of 150×10^6 total CAR T cells was selected for the dose-expansion phase. The ORR was 71%, including 6 (35%) achieving CR or better, 4 (24%) very good partial response (VGPR), and 2 (12%) PR. The median duration of response was 7.8 months (95% CI, 5.7 to not reached). Eight (47%) patients with a response achieved MRD negativity [38] (Table 4). Even at a remarkably low dosage of 25×10^6, MCARH109 exhibited efficacy, underscoring the active targeting potential of GPRC5D in MM. Furthermore, it is noteworthy that diminished expression of the GPRC5D antigen, prior allogeneic hematopoietic stem cell transplantation, and extramedullary disease (EMD) do not impede the therapeutic activity of MCARH109.

OriCAR-017 A single-center, single-arm phase 1 trial (NCT05016778) of OriCAR-017 enrolled 10 patients with heavily pre-treated R/R MM who had a median of 5.5 previous lines of therapy. A single infusion dose ranging from 1×10^6 to 6×10^6/kg CAR T cells was administrated in the dose-escalation phase and the dose of 3×10^6/kg CAR T cells was selected in the dose-expansion phase [44]. By the cutoff date (January 16, 2024), an ORR of 100% was achieved, including 8 (80%) sCRs and 2 (20%) VGPRs. The median time to best response was 3.1 months (interquartile range [IQR], 2.0–5.1) and the median time to CR or better was 4.1 months (IQR, 2.0–5.9). All patients with a response achieved MRD negativity on day 28. The median DOR was 10.4 months (95% CI, 5.0–17.0) and median PFS was 11.4 months (95% CI, 5.9–18.0), while the median OS has not reached [57](Table 4). The positive responses observed in OriCAR-017 may be attributed to the utilization of nanobodies as targeting moieties for the development of functional CARs against two epitopes of GPRC5D. These nanobodies exhibit high humanization and low immunogenicity, potentially enhancing the persistence of CAR T cells in patients. Unlike scFv, nanobodies are more likely to adopt a double VHH structure, enabling recognition of two epitopes and potentially increasing the affinity of antigen binding by CAR T cells, thereby leading to enhanced antitumor capacity. Furthermore, nanobodies demonstrate greater stability as monomers compared to scFv, which have a tendency to aggregate and induce tonic signaling that contributes to CAR T-cell exhaustion.

BMS-986393 A first-in-human, multi-center, open-label, phase 1 trial (NCT04674813) of BMS-986393 enrolled 70 patients who received ≥ 3 prior treatment regimens, including a PI, an IMiD, an anti-CD38 therapy, and an autologous stem-cell transplantation (ASCT) (if eligible). Twenty-four (34%) patients had penta-refractory disease. Doses of 25×10^6, 75×10^6, 150×10^6, 300×10^6 and 450×10^6 total CAR T cells were tested in the dose-escalation phase, and doses of 75×10^6, 150×10^6, 300×10^6 and 450×10^6 total CAR T cells were selected for the dose-expansion phase (Table 3). ORR was 86% (55/64) in the entire cohort, including 24 (38%) CRs/sCRs and 11 (17%) PRs and 20 (31%) VGPRs [58] (Table 4). BMS-986393 showed durable responses and promising efficacy at all tested dose levels, including patients with high-risk cytogenetics, penta-refractory disease or extramedullary plasmacytomas.

Table 4 Clinical data of GPRC5D-targeted CAR T cells

Product	Clinical trial	Pt No	Pt characteristics	CAR T Dosage	Clinical response	Response with previous BCMA therapy	Common AEs
MCARH109	Phase 1	17 pts	Median age 60; high-risk cytogenetics 13 (76%); median prior therapies 6; triple-refractory 16 (94)%; previous BCMA therapy 10 (59%)	25–450 × 10^6 cells/pt	ORR 71%; CR/sCR 6 (35%); MRD negativity 8 (47%); median DOR 7.8 months	PR or better 7 (70%); CR/sCR 4 (40%); MRD negativity 3 (30%)	≥ grade 3 anemia 41%, neutropenia 100%; thrombocytopenia 65%; CRS 88% (≥ grade 3, 6%); ICANS 6%; nail changes 65%; cerebellar disorder 12%; ≥ grade 3 infections 12%
OriCAR-017	Phase 1	10 pts	Median age 64; high-risk cytogenetics 6 (60%); median prior therapies 5.5; previous BCMA therapy 5 (50%)	1–6 × 10^6 cells/kg	ORR 100%; CR/sCR 6 (60%); MRD negativity 10 (100%); median DOR not reached	PR or better 5 (100%); CR/sCR 2 (40%); MRD negativity 5 (100%)	≥ grade 3 anemia 70%, neutropenia 100%; thrombocytopenia 60%; CRS 100% (all grade 1 or 2); no ICANS; nail changes 30%
BMS-986393	Phase 1	70 pts	High-risk cytogenetics 32 (46%); previous BCMA therapy 32 (46%)	25–450 × 10^6 cells/pt	ORR 86%; CR/sCR 24/64 (38%); MRD negativity 10/10 (100%)	PR or better 21/28 (75%)	≥ grade 3 anemia 31%, neutropenia 69%; thrombocytopenia 30%; CRS 84% (≥ grade 3, 4%); ICANS 11%; nail changes 16%; ≥ grade 3 infections 16%
GPRC5D CAR T (YK-CAR-042)	Phase 2	33 pts	Median age 58; high-risk cytogenetics 13 (39%); median prior therapies 4; previous BCMA therapy 9 (27%)	2 × 10^6 cells/kg	ORR 91%; CR/sCR 21 (63%); MRD negativity 26 (79%); median DOR not reached	PR or better 9(100%); CR/sCR 4 (44%)	≥ grade 3 anemia 52%, neutropenia 100%; thrombocytopenia 45%; CRS 76% (all grade 1 or 2); ICANS 6%; nail changes 27%
GPRC5D CAR T (Li et al.)	Phase 1	7 pts	Previous BCMA therapy 3(42.9%)	3–10 × 10^6 cells/kg	ORR 85.7%; CR/sCR 3 (42.9%)	PR or better 2(66.7%); CR/sCR 1 (33.3%)	≥ grade 3 anemia 43%, neutropenia 85.7%; thrombocytopenia 43%; CRS 85.7% (all grade 1 or 2); no ICANS
CT071	Phase 1	14 pts	Median age 58.5; 80% high-risk cytogenetics; median prior therapies 3; 100% double-class exposed, 80% triple-drug exposed, 50% penta-drug exposed, 20% previous BCMA/CD19 CAR T cells exposed	1 or 3 × 10^5 cells/kg	ORR 90%; CR/sCR 5 (50%)	PR or better 2(100%); CR/sCR 1 (50%)	≥ grade 3 anemia 50%, neutropenia 60%; thrombocytopenia 50%; CRS 50% (all grade 1 or 2); no ICANS
BCMA/GPRC5D bispecific CAR T (YK-CAR-069)	Phase 1	14 pts	Median age 62; high-risk cytogenetics 10 (48%); median prior therapies 3; no patients with previous BCMA therapy	0.5–4 × 10^6 cells/kg	ORR 86%; CR/sCR 13 (62%)	–	≥ grade 3 anemia 48%, neutropenia 76%; thrombocytopenia 38%; CRS 71% (all grade 1 or 2); ICANS 5% (grade 1)

AE adverse event, BCMA B cell maturation antigen, CRS cytokine release syndrome, CR complete response, DOR duration of response, GPRC5D G protein-coupled receptor family C group 5 member D, ICANS immune effector cell-associated neurotoxicity, MRD minimal residual disease, ORR overall response rate, pt patient, PR partial response, sCR stringent complete response

GPRC5D CAR T (YK-CAR-042) A single-arm, phase 2 clinical trial of anti-GPRC5D CAR T (*YK-CAR-042*) in 33 patients with R/R MM has been completed. All enrolled patients had a median of 4 previous lines of therapy. The dose of 2.0×10^6/kg total CAR T cells was selected in the phase 2 trial based on the findings in the phase 1 dose-escalation trial. The ORR was 91%, including 21 (63%) sCRs/CRs, 4 (12%) VGPRs, and 5 (15%) PRs. The median time to first response was 0.5 month (range, 0.5–3.0), and the median time to best response was 1.8 months (range, 0.5–6.0). Twenty-six of 33 patients (79%) achieved bone marrow MRD negativity. Disease progression occurred in 3 (10%) of 30 patients who had clinical responses with a median follow-up of 5.2 months. Twenty-five of 26 (96%) patients with MRD negativity remained progression-free by the cutoff date [43] (Table 4). Compared to other second-generation CAR T-cell products with similar designs, such as MCARH109 and BMS-986393, YK-CAR-042 demonstrated higher rates of CR or superior responses. One possible explanation for this disparity could be due to the highly efficient transduction and suitable infusion dose of the CAR T cells. Additionally, it is noteworthy that the patients enrolled in Chinese clinical trials appeared to have undergone less intensive prior treatment compared to those participating in clinical trials conducted in Europe and the USA. More clinical studies and longer follow-up are needed to compare the early response and long-term efficacy between different GPRC5D-targeted CAR T-cell products in larger numbers of patients with similar disease characteristics and prior treatment.

GPRC5D CAR T(Li et al.) In a phase 1 trial (NCT05739188) of anti-GPRC5D CAR T cell conducted by Li et al., 10 R/R MM patients were enrolled. Doses of 3.0×10^6/kg, 6.0×10^6/kg, and 1.0×10^7/kg of CAR T cells were evaluated in the dose-escalation phase. The ORR was 90%, comprising 5 CRs/sCRs, 4 PRs, and 1 no response [59] (Table 4).

CT071 In a phase 1 trial (NCT05739188) of CT071, CT071 was administered as a single infusion at doses of 1.0×10^5/kg or 3.0×10^5/kg CAR T cells in 10 patients who had a median of 3 prior lines of therapies. The ORR was 90%, including 4 (40%) sCR, 1 (10%) CR, 1 (10%) VGPR, 3 (30%) PR a with a median follow-up of 2.76 months. All 9 patients with evaluable MRD assessment achieved MRD negativity [51] (Table 4).

BCMA/GPRC5D Bispecific CAR T (YK-CAR-069) A single-arm, phase 1 clinical trial of anti-BCMA/GPRC5D bispecific CAR-T (YK-CAR-069) enrolled 21 patients with R/R MM who had a median of 3 previous lines of therapy. A single infusion dose ranging from 0.5×10^6 to 4.0×10^6/kg CAR T cells was administrated in the dose-escalation phase and the dose of 2.0×10^6/kg CAR T cells was selected in the dose-expansion phase (Table 3). The ORR was 86%, including 13 (62%) sCRs/CRs, 5 (24%) VGPRs. In 12 patients who received dose of 2.0×10^6 CAR T cells/kg, the ORR was 92% (11/12), including 9 (75%) sCRs/CRs and 2 (17%) VGPRs. The median time to best response was 1 month (IQR, 0.75 to 2.5). Seventeen of 21 patients (81%) achieved bone marrow MRD negativity. Disease progression occurred in 2 (10%) of 21 patients who had clinical responses with a median follow-up of 5.8 months. During the follow-up, 16 (76%) patients remained in remission state including 15 (71%) patients with bone marrow minimal residual disease negativity by the cutoff date [60] (Table 4). The clinical responses of BCMA/GPRC5D bispecific CAR T cells were comparable to those of BCMA or GPRC5D single-targeted CAR T cells in the short term. However, the bispecific CAR T cells demonstrated enhanced efficacy in patients with negative expression of either BCMA or GPRC5D, which could potentially prevent relapse caused by antigen down-regulation or escape. Longer follow-up is necessary to assess the long-term outcomes.

In summary, CAR T-cell products targeting GPRC5D exhibited superior early response compared to BsAbs; however, no significant differences were observed in terms of median time to first or best response. Although GPRC5D CAR T-cell therapies have demonstrated better early clinical responses than GPRC5D×CD3 BsAbs, the preparation of CAR T-cell products requires a series of procedures including apheresis and manufacturing, which typically takes at least one month. On the other hand, BsAb products are readily available off-the-shelf, making them an ideal option for rapidly progressing patients who cannot afford to wait for the manufacture of CAR T cells. Additionally, compared with BCMA-targeted CAR T-cell, GPRC5D CAR T-cell showed similar efficacy (Table 5), which needs to be further confirmed in randomized controlled trials. Therefore, the choice between BsAb and CAR T-cell products targeting different myeloma antigens for R/R MM treatment should depend on patient prior therapies, disease conditions and clinical demands. Further investigations are warranted to elucidate the long-term outcomes of diverse GPRC5D-targeted immunotherapies.

Efficacies of GPRC5D-targeted CAR-NK cells

Recently, progress in CAR-NK cell therapy has been made in NK cell engineering, target design and combination with other agents to treat relapsed or refractory hematological malignancies, especially acute myeloid leukemia and MM [49]. Three CAR-NK agents targeting GPRC5D were undergoing preclinical trials (Fig. 4C).

Anti-GPRC5D CAR-iNK (Fu et al.) The induced pluripotent stem cells (iPSC)-derived CAR-NK cell was

Table 5 Comparison of efficacy in CAR T-cell therapies targeting different antigens

Target	Strategy	ORR (%)	CR or better (%)	MRD-negative (%)	PFS/DOR	OS
BCMA	ADC	31–34	3	NR	Median PFS: 2.9–4.9 months 4 months or longer DOR rate: 78%-87%	NR
	BsAb	63	39.4	26.7	Median PFS: 11.3 months Median DOR: 18.4 months	Median OS: 18.3 months
	CAR T	73–100	28.6–78.6	26–93	Median PFS: 8.8–17.8 months	Median OS: not reached
GPRC5D	BsAb	63.6–74	23–34.7	NR	Median DOR: 9.3–13 months	Median OS: not reached
	CAR T	71–100	35–63	47–100	Median DOR: 7.8 months—not reached	Median OS: not reached
CD19-BCMA	CAR T	92	60	77–83	Median PFS: 18.3–19.7 months Median DOR: 20.3 months	Median OS: 19.7 months
CS1-BCMA	CAR T	81	38	81	Median PFS: 9.0 months	Median OS: not reached
CD38-BCMA	CAR T	87	52	100	Median PFS: 17.2 months	
BCMA-GPRC5D	CAR T	92	75	81	10 months PFS rate: 67%	Median OS: not reached

ADC antibody–drug conjugate, BsAb bispecifc antibody, BCMA B cell maturation antigen, CAR T chimeric antigen receptor T cell, CR complete response, DOR duration of response, GPRC5D G protein-coupled receptor family C group 5 member D, MRD minimal residual disease, NR not reported, OS overall survival, PFS progression free survival

constructed by transducing anti-GPRC5D CAR into an iPSC line derived from a healthy donor [48] (Table 1). The anti-GPRC5D CAR-iNK expressed a high level of CD45 and CD56 (>99.9%), CD16 (63.6%), the NK cell activating receptor NKG2D (96.3%), NKp30 (98.7%), the co-stimulatory receptors CD244 (99.6%) and CD226 (97.8%) (Fig. 4C). Cytotoxicity assay in vitro demonstrated that anti-GPRC5D CAR-iNK had similar cytotoxicity against K562 cells (No GPRC5D antigen) to cord blood-derived NK cells (CB-NK), wide type (WT) iNK and anti-BCMA CAR-iNK. However, anti-GPRC5D CAR-iNK showed stronger abilities (approximately 90% killing rate) against myeloma cells (with high level of BCMA and GPRC5D expression) than the CB-NK (no killing) and WT iNK (around 10% killing rate). Furthermore, the anti-GPRC5D CAR-iNK also showed superior abilities to kill MM cells to anti-BCMA CAR-iNK [48].

FT555 FT555 was another iPSC-derived anti-GRPC5D CAR-NK cell (Table 1), which showed persistent specific anti-tumor activity against GPRC5D-positive myeloma cells compared to isogenic GPRC5D knockout targets in the preclinical study. In the disseminated in vivo xenograft model of MM, FT555 exhibited robust killing kinetics and tumor clearance, which contributed to prolonging the duration of disease remission and improving survival. The study also demonstrated that a combination of daratumumab with FT555 was able to further enhance the durability of FT555 and deepen tumor growth inhibition in mouse models [61].

BCMA/GPRC5D dual-targeted CAR-NK cells To prevent BCMA-antigen escape and achieve a deeper and more persistent response in MM, Yang et al. developed a new dual-targeted CAR-NK cell product (Table 1) consisting of anti-BCMA VHH and anti-GPRC5D VHH antibodies, NKG2D and 2B4 co-stimulation signaling domains, and IL-15. BCMA/GPRC5D CAR-NK cell showed high activity to kill of both $BCMA^+$ and $GPRC5D^+$ myeloma cells with remarkable persistence and antigen-mediated amplification. Compared with single-targeted BCMA CAR-NK cell, BCMA/GPRC5D CAR-NK cell could also effectively lyse BCMA-negative MM cells. Additionally, it achieved more sustained tumor control than single-targeted BCMA CAR-NK cells in BCMA-antigenic escape model. They also demonstrated that combination of BCMA/GPRC5D CAR-NK with anti-PDL1-IL15 showed more durable tumor control [62].

Efficacy of anti-GPRC5D ADC drug

LM-305 was a novel anti-GPRC5D ADC drug (Fig. 4D). Anti-tumor evaluation in vitro revealed that LM-305 could bind to GPRC5D over-expressing cell lines and GPRC5D endogenously expressing MM cells with high affinity in a dose-dependent manner. LM-305 displayed potent cytotoxicity when co-cultured with MM tumor cells (NCI-H929 and MM.1R). In vivo xenograft models demonstrated that LM-305 resulted in dose-dependent inhibition of tumor growth. Additionally, LM-305 exhibited CR in the GPRC5D high-expressing MM cell line derived xenograft models at a dose of 3 mg/kg. Therefore, this study suggested that LM-305 could be a promising therapeutic candidate for the treatment of R/R MM patients expressing GPRC5D [63] (Table 1). A phase 1/2 trial (NCT05647512) of LM-305 has been initiated to enroll R/R MM patients, but the interim analysis of the trial has not been reported.

Response for patients with prior BCMA-targeted immunotherapies

The potential efficacy of immunotherapies targeting GPRC5D in patients with R/R MM following BCMA-targeted immunotherapies represents a significant clinical challenge.

GPRC5D × CD3 BsAb A total of 70 patients with prior T-cell redirection therapy were enrolled in the phase 2 trial for talquetamab. Of these patients, 58 (83%) and 29 (41%) were triple- and penta-refractory, respectively. Forty-three of 70 patients received prior BCMA CAR T cells, 18 received prior BCMA BsAb, and 5 received both. The ORR was 65.7%, while the ORR in patients receiving prior BCMA BsAb was lower than that in patients receiving prior BCMA CAR T (52.2% versus 72.9%). Median DOR in patients receiving prior BCMA CAR T was similar to that in the whole cohort (12.3 months versus 12.3 months), but longer than that in patients receiving prior BCMA BsAb (6.5 months) [64]. In patients who received RG6234 in the IV and SC cohorts, 5 (5/10) patients and 6 (6/11) patients who had received prior anti-BCMA therapies obtained responses in the IV and SC cohorts [56] (Table 3). It is intriguing that patients with prior BCMA CAR T-cell therapy exhibited enhanced clinical responses and prolonged DOR following anti-GPRC5D BsAb treatment, in comparison to those who received prior BCMA BsAb therapy. This disparity in outcomes may be attributed to distinct mechanisms of action employed by T cells against myeloma cells, which could potentially result from the exhaustion and resistance of anti-tumor effector T cells due to repeated activation strategies.

GPRC5D CAR T After the therapy of MCARH109, 47% of patients had received previous BCMA CAR T-cell therapies. A PR or better response was noted in 6 of 8 (75%) patients in this cohort [38]. All 5 (100%) patients with prior anti-BCMA CAR T-cell therapies achieved responses, including two (20%) patients with a sCR and 3 (30%) with a VGPR after infusion of OriCAR-017 [44]. In the phase 1 clinical trial of BMS-986393, 32 (46%) patients had received prior BCMA-targeted therapy, including BCMA-directed CAR T-cell therapy in 25 (36%) patients. In efficacy-evaluable patients, 21 of 28 (75%) patients who were treated with prior BCMA-directed therapies achieved a PR or better response, including 10 (63%) patients with CRs/sCRs. In refractory patients to prior BCMA-directed therapies, ORR was 85% (11/13), and CR rate was 46% (6/13) [58] (Table 3). After the treatment of YK-CAR-042, all 9 (100%) patients with prior anti-BCMA CAR T-cell therapy obtained a PR or better response, including 4 patients achieving a CR [43]. In the phase 1 clinical trial of GPRC5D CAR T by Li et al., 3 patients had prior BCMA CAR T-cell treatment. Of these patients, two patients achieved responses, including 1 CR and 1 PR, and 1 patient with no response [59]. Both of the 2 patients who received CT071 with prior BCMA/CD19 CAR T achieved responses (1 sCR and 1 PR) [51]. No patients with prior BCMA-directed therapies were enrolled in the phase 1 trial of YK-CAR-069 [60] (Table 4). Despite small sample sizes in various clinical trials, current studies have demonstrated the potential of GPRC5D-targeted immunotherapies as alternative options for MM patients who have progressed after or are refractory to BCMA-targeted therapy. However, there is a lack of data comparing the efficacy of GPRC5D-targeted CAR T-cell between patients with prior BCMA BsAb and those with prior BCMA CAR T-cell treatment, which requires further investigation.

Efficacy for EMD in patients with R/R MM

EMD represents an uncommon and aggressive manifestation of MM. Extramedullary progression, especially extra-osseous plasmacytomas, is inherently a high-risk stage of MM and the current literature has identified it as a poor prognostic feature. Despite several significant advances in MM treatment strategies, treatment outcomes remain less than satisfactory for EMD in MM patients [65]. The pivotal phase 2 trial for talquetamab enrolled 26 patients with EMD in the SC cohort. The ORR was 45.5% with 9.1% CR/sCR in the 405 μg SC cohort, and was 40% with 13.4% CR/sCR in the 800 μg SC cohort [52]. However, the efficacy significantly increased after the combination with teclistamab (a GPRC5D × CD3 BsAb) in the RedirecTT-1 study [66]. The ORR was 73% (19/26) among evaluable patients with EMD and the rate of CR/sCR was 31% (8/26). Four (40%) patients with EMD were enrolled in the phase 1 trial of OriCAR-017. All of the 4 patients (100%) achieved a response, including 3 patients with complete resolution of extramedullary lesion after CAR T-cell infusion [44]. In the phase 1 trial of YK-CAR-069, 4 (19%) patients had EMD at baseline. Three (75%) patients obtained PR or better response, including 1 (25%) patient with VGPR and 2 (50%) patients with sCR [60]. The RedirecTT-1 study showed superior clinical response in the treatment of EMD, which revealed that a combination of immunotherapies targeting different myeloma antigens might be a feasible strategy to improve the efficacy of EMD, and even to improve the long-term outcomes for patients with R/R MM. It would be valuable to also explore the safety and efficacy in the treatment of EMD with a combination of CAR T-cell therapies targeting different antigens, since there are no relevant clinical data presented up to now.

Toxicities of GPRC5D-targeted therapies

Hematological toxicities

Therapy-related adverse events (AEs) is an important consideration for new CAR T-cell products, which might elicit exacerbation of conditions and treatment-related deaths. Hematological toxicities were the most common AEs in GPRC5D-targeted immunotherapy. Early hematological toxicity was regarded to be a result of lymphodepleting chemotherapy. Immunotherapy related hematological toxicity is causing more and more attention [67]. Baseline hematopoietic reserve and the systemic inflammation induced by the host might play essential role in the mechanisms of CAR T cells related hematological toxicity [68]. There are some unique features in CAR T cells related hematological toxicity. Cytopenias can persist long after the resolution of clinical CRS and has been reported as long as months to years following CAR T-cell infusion [69]. Additionally, patients can develop very severe bone marrow aplasia that is often refractory to therapeutic measures such as growth factor support [70, 71].

GPRC5D*×*CD3 BsAb In the MonumenTAL-1 trial for talquetamab, hematological toxicities were the most common grade 3 or 4 AEs, including neutropenia [405-μg SC cohort (60%), 800-μg SC cohort (32%), IV cohort (26%)], anemia (30%, 23%, 33%), and thrombocytopenia (23%, 11%, 13%) [45]. In the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohort of the phase 2 trial for talquetamab, grade ≥ 3 hematologic toxicities were including anemia (31.5%, 25.3%) and neutropenia (30.8%, 21.4%) [53]. In the IV and SC cohort of the phase 1 trial for RG6234, grade ≥ 3 hematologic AEs included anemia (IV 15.7%, SC 38.6%), thrombocytopenia (IV 13.7%, SC 19.3%), and neutropenia (IV 11.8%, SC 15.8%) [56] (Table 3). The incidence of hematological toxicity was lower in patients treated with GPRC5D-targeted BsAb than those treated with CAR T cells. Hematological toxicities after GPRC5D-targeted BsAb recovered more quickly, and prolonged hematological toxicities were seldom reported. One of the important reason was that patients did not need to receive lymphodepleting chemotherapy before the BsAb treatment, while they must receive lymphodepletion before CAR T-cell treatment. Therefore, GPRC5D-targeted BsAb might be better choices for patients with serious hematological toxicities at baseline.

GPRC5D CAR T In the phase 1 trial for MCARH109, grade 3 or 4 hematologic toxicities included neutropenia (100%), thrombocytopenia (65%), and anemia (41%) [38]. After infusion with OriCAR-017, grade 3 or 4 hematologic toxicities were observed as neutropenia (100%), thrombocytopenia (90%), and anemia (70%) [44]. Grade 3 or 4 hematologic toxicities occurred in 64/70 (91%) patients who received BMS-986393 therapy, including neutropenia (69%), anemia (31%), and thrombocytopenia (30%) [58]. Grade 3 or 4 neutropenia(100%), anemia (52%), and thrombocytopenia (45%) occurred in patients with the treatment of YK-CAR-042 [43]. In the phase 1 trial for GPRC5D CAR T by Li et al., grade 3 or higher hematological toxicities were noted as neutropenia (85.7%), anemia (43%), and thrombocytopenia (43%) [59]. In the phase 1 trial for CT071, the grade 3 or higher hematological toxicities included lymphopenia (100%), leukopenia (80%), neutropenia (60%), anemia (50%) and thrombocytopenia (50%) [51]. In patients who received YK-CAR-069, the grade 3 or 4 hematological toxicities manifested as neutropenia (76%), anemia (48%), and thrombocytopenia (38%) [60] (Table 4). Anti-BCMA/GPRC5D bispecific CAR T cells did not show higher incidence or severity of hematological toxicity than anti-GPRC5D CAR T cells, which indicated that modifying T cells targeting dual antigens of tumor cells was a safe strategy to overcome limitations of single-target CAR T-cell therapy.

CRS and ICANS

GPRC5D*×*CD3 BsAb In the MonumenTAL-1 trial for talquetamab, CRS was the most common non-hematological AEs, of which were seen in 77% (grade ≥ 3: 3%) patient in the 405 μg SC cohort, 80% (grade ≥ 3: 0) patients in the 800 μg SC cohort, and 49% (grade ≥ 3: 5%) patients in the IV cohort. Treatment-related neurotoxic events occurred in 10% of the patients in the 405 μg SC cohort and in 5% of those in the 800 μg SC cohort. All the neurotoxic events were of grade 1 or 2 and resolved [45]. In subsequent phase 2 trial for talquetamab, CRS were observed in 79% and 75% of patients, and ICANS were noted in 11% and 11% of patients in the 0.4 mg/kg QW cohort and 0.8 mg/kg Q2W cohort, respectively. Most of the CRS and ICANS were grade 1/2 and clinically manageable [52]. For patients who received RG6234 in the IV and SC cohorts, CRS occurred in 82.4% (grade ≥ 3: 2.0%) and 78.9% (grade ≥ 3: 1.8%) of patients. ICANS occurred in 9.8% (grade ≥ 3: 2.0%) and 12.3% (grade ≥ 3: 3.6%) of patients [56] (Table 3). Compared with IV dosing, SC administration reduced peak cytokine levels and induced delayed cytokine release, suggesting a more subtler immune activation and a potential safety benefit for patients.

GPRC5D CAR T After the treatment of MCARH109, fifteen (88%) patients had CRS, of which most cases were grade 1 or 2, except 1 patient who received 450×10^6 total CAR T cells had a grade 4 CRS. ICANS (grade 4) was seen in 1 (6%) patient [38]. In patients who received OriCAR-017, all (100%) patients had CRS, of which all cases were grade 1 or 2, and no ICANS was noted [44]. In the phase 1 trial for BMS-986393, CRS occurred in

59 (84%) patients: 56 (80%) patients with grade 1 or 2 events, 2 (3%) with grade 3 or 4 events, and 1 (1%) with a grade 5 event. ICANS occurred in 8 (11%) patients, of whom 6 (9%) had grade 1 or 2 events and 2 (3%) had grade 3 events [58]. After infusion of YK-CAR-042, CRS occurred in 25 (76%) patients, and no grade 3 or higher CRS was observed. ICANS was noted in 2 (6%) patients, of whom 1 (3%) was grade 2 and the other was grade 3 [43]. In the phase 1 trial for GPRC5D CAR T by Li et al., CRS occurred in 9 (90%) of 10 patients, of which all cases were grade 1, and no patients had ICANS [59] (Table 3). Five patients (50%) who received CT071 had CRS, of which all were grade 1or 2. No ICANS was observed [51]. The incidence and severity of CRS were comparable between patients who received GPRC5D BsAb and those who received GPRC5D CAR T-cell treatments. However, the incidence of ICANS appeared to be higher and more serious in patients after GPRC5D-targeted BsAb than those receiving CAR T-cell treatment. Given the limited sample sizes and predominantly single-center clinical trials involving GPRC5D CAR T cells, it is imperative to enroll a larger number of patients in multicenter trials for validation purposes.

In the phase 1 trial of YK-CAR-069, 71% of patients had CRS, of which all cases were grade 1 or 2. Grade 1 ICANS was observed in a patient (5%) who received 4.0×10^6 CAR T cells/kg [60] (Table 4). Patients with anti-BCMA/GPRC5D CAR T-cell treatment did not have higher incidence and severity of CRS, typically attributed to on-target effects induced by binding of the bispecific CAR T-cell receptors to their respective antigens and subsequent activation of bystander immune cells and non-immune cells. This indicated that modifying CAR T cell targeting multiple tumor antigens was safe and may not induce amplifying and uncontrolled inflammatory responses.

On-target, off-tumor toxicities

GPRC5D×CD3 BsAb In the MonumenTAL-1 trial for talquetamab, on-target, off-tumor toxicities related to GPRC5D expression were common, including nail changes [405 μg SC cohort (57%), 800 μg SC cohort (29%), IV cohort (20%)], skin-related events (67%, 72%, 24%), rash-related events (47%, 46%, 26%), dysgeusia (63%, 57%, 37%), dry mouth (30%, 57%, 7%), and dysphagia (37%, 27%, 5%), which were mostly grade 1/2 [45] (Table 3). It is still controversial whether dysgeusia is a direct on-target, off-tumor effect because GPRC5D immunoreactivity in salivary glands is limited to resident plasma cells, and while GPRC5D is also expressed on filiform papillae, they are not responsible for taste. However, the larger class of family C metabotropic G-protein coupled receptors include taste receptors, which may explain the taste-associated AEs experienced with GPRC5D targeted therapies. In subsequent phase 2 trial for talquetamab, nail-related AEs were observed in 54% and 53% of patients, while dysgeusia were noted in 50% and 48% of patients in the 0.4 mg/kg QW cohort and 0.8 mg/kg Q2W cohort, respectively. Most of the nail-related AEs and dysgeusia were grade 1/2 and clinically manageable [52] (Table 3). In the IV and SC cohort of the phase 1 trial for RG6234, on-target, off-tumor toxicities manifested as skin-related AEs in 78.4% (grade ≥ 3: 11.8%) and 86% (grade ≥ 3: 22.8%); hair and nail changes in 23.5% (all grade 1–2) and 28.1% (all grade 1–2); and mucosal toxicities in 72.5% (all grade 1–2) and 77.2% (grade ≥ 3: 5.3%) of patients [56] (Table 3).

GPRC5D CAR T In patients who received MCARH109, on-target, off-tumor toxicities were observed as grade 1 nail changes in 11 (65%) patients, grade 1 rash in 3 (18%) patients, and grade 1 dysgeusia or dry mouth in 2 (12%) patients [38]. The frequency and severity of rash and dysgeusia were lower in patients treated with MCARH109 as compared with the GPRC5D×CD3 BsAbs. Two (12%) patients obtained a grade 3 cerebellar disorder [38]. Reports of delayed Parkinsonism-like neurologic toxic effects have also been reported in 1–5% of patients treated with cilta-cel and is attributed to potential expression of BCMA in the basal ganglia. Therefore, the cerebellar disorders were currently thought to be related to low-level expression of GPRC5D in the cerebellum or the inferior olivary nucleus. In the phase 1 trial for OriCAR-017, on-target, off-tumor toxicities were noted as grade 1 nail changes in 3 (30%) patients, grade 1 and 2 pruritus in 2 (20%) patients, and grade 2 dry skin in 1 (10%) patient. No adverse events of cerebellar disorders were reported in the trial [44] (Table 3). After the treatment of BMS-986393, on-target, off-tumor toxicities included skin-related AEs in 17 (24%) patients, nail disorders in 11 (16%) patients, and dysgeusia/dysphagia in 2 (3%) patients. Cerebellar toxicity was observed in 2 (3%) patients by the cutoff date [58]. In the phase 2 trial for YK-CAR-042, on-target, off-tumor toxicities manifested as grade 1 nail changes in 9 (28%) patients and a grade 2 cutaneous AE in 1(3%) patient and no cerebellar disorders were reported in the trial [43]. Nail-related AEs were low grade, reported frequently, and sometimes managed with emollients, nail hardeners, vitamin E oil, as well as hydration, biotin, and protective nail coverings or resolved without intervention. In the phase 1 trial for CT071 and GPRC5D CAR T by Li et al., no patients had cerebellar disorders by the cutoff date [51, 59]. In patients who received YK-CAR-069, on-target, off-tumor toxicities included grade 1 nail loss in 5 (24%), grade 1 and 2 rash in 5 (24%), and dry skin in four (19%) patients. No therapy-related cerebellar toxicities were observed by the

cutoff date [60] (Table 4). Differences in observed rates of GPRC5D-related AEs between GPRC5D×CD3 BsAbs and CAR T-cell therapies may be due to continuous dosing versus single-infusion dosing, different epitopes, or differences in drug distribution. Overall, the pattern of AEs did not always correspond with the location of keratinized tissue.

Current data from different clinical trial demonstrated that on-target, off-tumor effects related to GPRC5D expression, including nail changes, skin-related AEs, dysgeusia seemed more frequent in patients from Europe and the USA than those from China with GPRC5D-targeted therapies. It is unclear whether it was due to the discrepancy of GPRC5D expression in patients from different races, and needs to be furtherly investigated. Cerebellar toxicity was observed in 2 GPRC5D-targeted CAR T-cell products, while it was not reported in patients with GRPC5D-targeted BsAbs by now. Further investigation is required to better understand the presence of rare cerebellar events after GPRC5D-targeted therapies.

Infection and hypogammaglobulinemia

Infection is one of the most common complications after T-cell-redirecting immunotherapies [72]. Profound and long-lasting B-cell aplasia and consecutive hypogammaglobulinemia can add to the incidence and severity of infection. Importantly, severe infections are a major driver of both morbidity and non-relapse mortality following T-cell-redirecting therapies [73, 74]. GPRC5D×CD3 BsAbs did not lead to a reduction in $CD19^+$ B-cell levels over time based on experience with talquetamab [75]. Hypogammaglobulinemia rates by IgG values were 64.3% in the 0.4 mg/kg QW cohort, and 65.5% in the 0.8 mg/kg Q2W cohort. Roughly 20% of patients had grade 3/4 infections with low rates of opportunistic infections after the treatment of talquetamab. In the phase 1 trial of MCARH109, infections were noted in 3 patients (18%), including 2 (12%) patients with grade 3 events (bacterial infection and parvovirus infection). After the infusion of YK-CAR-042, all enrolled patients developed B-cell aplasia. Hypoimmunoglobulinemia already existed in 29 (88%) patients before CAR T-cell infusion. Recovery of serum IgM to a normal level was observed in 40% of patients after 3 months, and IgG and IgA had not recovered to the normal range by data cutoff. In patients who received YK-CAR-069, all enrolled patients developed B-cell aplasia, and hypoimmunoglobulinaemia already existed in 20 (95%) patients before CAR T-cell infusion and became more serious after infusion. Infections were observed in 5 (24%) patients, including 3 patients with viral infections, 1 with bacterial infection, and 1 with fungal infection, and all the infection cases were grade 1 or 2.

Infections were reported less frequently in trials of GPRC5D×CD3 BsAbs compared with trials of BCMA-targeting BsAbs [75, 76], which may be due to the more limited expression profile of GPRC5D in the immune compartment compared with the expression profiles of these other target antigens [25, 47]. Additionally, the lower expression of GPRC5D on normal plasma cells compared with malignant plasma cells may preserve normal plasma cells during treatment [75]. The lower incidence of severe infections by GPRC5D×CD3 BsAbs may be helpful to shorten the length of hospitalization, decrease financial burden and improve the outcomes of disease for R/R MM patients. The infection rate of GPRC5D CAR T-cell products seems close to that of GPRC5D×CD3 BsAbs. However, due to the limited clinical data of infections after GPRC5D CAR T-cell therapies, it is hard to compare the incidence and severity of infection between GPRC5D CAR T cells with BCMA-targeted or other CAR T cells at present.

Dose-limiting toxicities and fatal AEs

In the MonumenTAL-1 trial for talquetamab, four dose-limiting toxicities were observed during the dose-escalation phase, including 1 grade 4 increased lipase level and 3 grade 3 rashes. Three fatal adverse events occurred, including 1 neuroendocrine carcinoma, 1 sepsis and 1 basilar-artery occlusion in patients in 800 μg SC cohort. None of these deaths were considered by the investigators to be related to talquetamab [45]. Three of 5 (60%) patients with MCARH109 infusion obtained dose-limiting toxicities who received the dose of 450×10^6 total CAR T cells, including 2 patients with grade 3 cerebellar disorders and 1 patient with grade 4 CRS, ICANS and macrophage activation syndrome. No fatal AEs was reported in this trial [38]. No DLT was observed and no fatal AEs was noted in the trial for OriCAR-017 [44]. In the phase 1 trial for BMS-986393, two DLTs of prolonged neutropenia and/or thrombocytopenia were reported in 2 patients who received 25×10^6 and 75×10^6 CAR T cells, but no fatal AEs was reported [58]. In patients who received YK-CAR-042, two DLTs were observed in patients with the dose of 3.0×10^6/kg CAR T cells, which manifested as grade 3 ICANS and prolonged grade 4 hematological toxicities (neutropenia and thrombocytopenia). One patient died of intracranial hemorrhage decreased platelet count and platelet transfusion dependent [43], while this death was not considered to be related to CAR T-cell treatment. No DLT and fatal AEs were reported in the trial for CT071 and GPRC5D CAR T by Li et al [51, 59]. After the therapy of YK-CAR-069, two patients who received more than the maximum tolerated dose (MTD) had dose-limiting toxicities, of whom one died of subarachnoid hemorrhage. This death was

considered to be related to the patient disease situation at screening and conditioning therapy, and was not deemed to be related to the CAR T-cell infusion [60]. Dose-limiting toxicities could be observed both in patients with GPRC5D-targeted BsAbs and CAR T-cell treatment, but most of which were reversible and not fatal, such as skin-related AEs, abnormality of laboratory examinations and hematological toxicities. For patients receiving less than MTD of BsAbs or CAR T cells, no fatal AEs were noted, except for 3 fatal AEs in patients after the treatment of talquetamab, which were not considered to be related to the treatment.

Future perspectives

BCMA is an ideal target for R/R MM [77, 78]. Immunotherapies targeting BCMA have yielded remarkable efficacy in patients with R/R MM [14, 79, 80]. However, disease recurrence was inevitable, and relapse with down-regulated or diminished surface BCMA expression was recognized as a regular cause of treatment failure [15, 79–81]. GPRC5D is regarded as another promising target for anti-myeloma immunotherapies [25, 82, 83], and current studies have demonstrated that anti-GPRC5D therapies achieved impressive responses in patients with R/R MM [38, 43, 44]. According to current evidence, the expression of GPRC5D protein on plasma cells from primary marrow samples exhibits a distribution similar to that of BCMA, yet remains independent [25, 27] (Fig. 5). GPRC5D CAR T-cell therapy has shown comparable efficacy and similar toxicity to BCMA CAR T-cell therapy. However, there are no head-to-head trials of these two modalities. Therefore, choosing between the two modalities will depend on a variety of practical considerations. Determining the preferential use of the CAR T-cell therapies targeting GPRC5D or BCMA for patients with R/R diseases deserves to be further explored in future by randomized controlled trials.

Considering the high response rates, potential response durability, and limited toxicity, GPRC5D-targeted immunotherapies may ultimately prove most useful in the upfront or early relapse setting. Moreover, part of MM patients lose the chance to get GPRC5D-targeted CAR

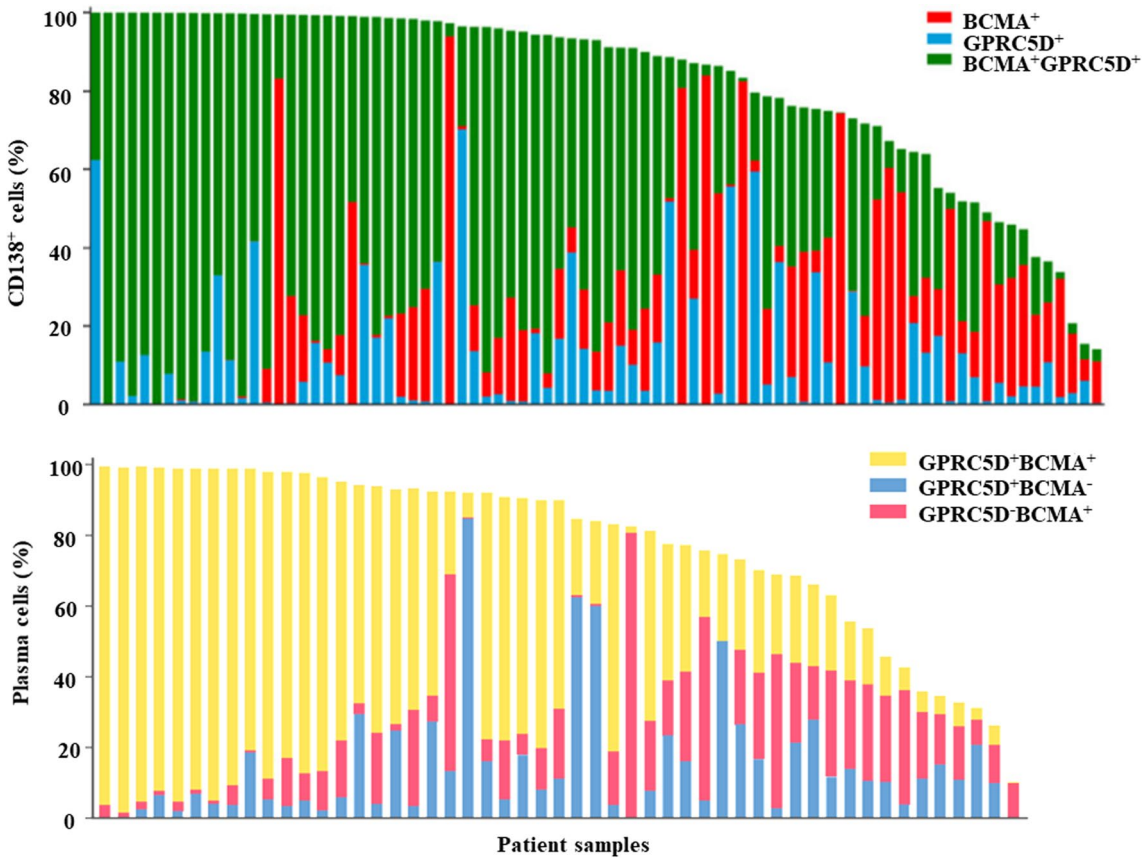

Fig. 5 The correlation between the expression of GPRC5D and BCMA in MM patients. GPRC5D protein is expressed on CD138$^+$ MM cells from primary marrow samples with a distribution that was similar to, but independent of BCMA. The upper and lower charts are derived from the articles published in Sci Transl Med. 2019;11(485):eaau7746, and Blood. 2020;135(15):1232–1243, respectively [25, 27]

T-cell treatment due to their comorbidities, toxicities from previous treatment, or unqualified conditions of T cells for manufacture of CAR T after multiple lines of prior therapies. So there is significant potential and necessity for GPRC5D-targeted immunotherapies to move into earlier lines of therapy.

For patients who were relapsed or refractory to prior BCMA-targeted immunotherapies, GPRC5D-targeted immunotherapies have also shown encouraging activity and manageable toxicity [38, 43, 44, 51, 58, 59, 83]. But due to the small sample sizes, more patients with longer follow-up need to be enrolled to validate the long-term efficacy of GPRC5D-targeted therapies after anti-BCMA therapies.

Mechanisms of resistance to immunotherapies are not well understood at present and deserve further study by sequential or combined use of the various immunotherapies targeting different targets to achieve deep and durable remissions [84]. Interestingly, some studies showed that the efficacy appeared to be better in patients with prior exposure to anti-BCMA therapies who received talquetamab in combination with either teclistamab or daratumumab [66, 85]. It is necessary to enhance anti-tumor activities of anti-GPRC5D therapies by exploring applicable combinations with existing treatment modalities. Immunotherapies targeting GPRC5D and BCMA may be more easily incorporated with each other duo to different anti-tumor targets and their non-overlapping toxicity.

Modifying T cells expressing bispecific CARs may be a good strategy to overcome limitations of single-target CAR T-cell therapy and potentiate CAR T-cell functions [86–88]. A preclinical study demonstrated that CAR T-cell therapy targeting BCMA and GPRC5D could reduce the relapse due to BCMA antigen escape and eliminate BCMA-negative MM cells in mouse models [50]. Furthermore, Yael C Cohen and colleagues demonstrated a further improvement in ORR and efficacy for EMD when anti-BCMA and anti-GPRC5D bispecific antibodies were given in combination to R/R MM patients [66, 89]. Recently we reported that anti-BCMA/GPRC5D bispecific CAR T cell also showed good safety profile and encouraging efficacy in patients with R/R MM [60]. These data suggested that broader antigen coverage by redirecting T cells to two tumor surface antigens is an effective mean to harness the immune system to deplete cancer cells. T-cell-redirecting therapies targeting dual or more antigens to increase the targetable antigens on tumor cells would enhance anti-tumor activities and improve long-term efficacy, as well as potentially reduce the incidence of antigen-negative escape [50, 87, 88]. Therefore, it has great clinical significance to develop dual or multiple-target T-cell-redirecting therapies.

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Declarations

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