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REVIEW

Perspectives on Talquetamab and its Utility in the Treatment of Multiple Myeloma: Safety, Efficacy and Place in Therapy

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Abstract: Despite recent advancements, most patients with multiple myeloma eventually develop resistance to available treatments, highlighting the need for new therapeutic strategies. G protein-coupled receptor class C group 5 member D (GPRC5D) has emerged as a viable novel therapeutic target on myeloma cells, leading to the clinical development of talquetamab, the first GPRC5D-directed bispecific T-cell engager (TCE). Talquetamab was granted accelerated approval in August 2023 by the Food and Drug Administration. Besides expected short-term toxicities including cytokine release syndrome, neurotoxicity and cytopenias, talquetamab commonly causes adverse events involving the oral cavity, nails, and skin, which can negatively impact quality of life and in some cases lead to treatment discontinuation. Despite these pitfalls, talquetamab yields responses in most treated patients, which in a subset are durable. There are now several clinical trials investigating talquetamab in different clinical contexts in multiple myeloma, as well as in combination with other anti-myeloma agents. Beyond results from these prospective trials, better biologic understanding of resistance mechanisms to talquetamab and improved strategies to mitigate common toxicities are key questions as talquetamab finds its place in the treatment of multiple myeloma.

Keywords: multiple myeloma, talquetamab, GPRC5D, toxicity management

Introduction

Multiple myeloma is the second most common blood cancer in the United States, with an estimated 35,780 new diagnoses projected in 2024.[1] Despite marked improvements in survival over the past two decades with incorporation of novel classes of drugs, most patients develop therapeutic resistance and eventually die from the disease.[2] Recent additions to the treatment armamentarium for relapsed/refractory multiple myeloma (RRMM) include chimeric antigen receptor (CAR) T cell therapies, antibody-drug conjugates (ADC), and bispecific T cell engagers (TCE) targeting B cell maturation antigen (BCMA), which is expressed on the surface of malignant plasma cells.[3–10] These immunotherapeutic agents have demonstrated remarkable response rates, with significant durability in subsets of patients. However, management of patients who progress on BCMA-directed agents is an ongoing challenge, and resistance is frequently mediated through BCMA downregulation or loss.[11–15] The clinical development of novel agents targeting alternate antigens remains an important challenge.[16,17]

G protein-coupled receptor class C group 5 member D (GPRC5D) was recently discovered to be a viable therapeutic target in multiple myeloma, leading to the development of several GPRC5D-directed bispecific TCEs and GPRC5D-targeted CAR T cell therapies.[18–21] Bispecific TCE facilitate formation of an immune synapse, leading to T cell-mediated cytolysis (Figure 1).

Advantages of bispecific TCEs include their ability to promote T cell mediated tumor killing independent of T cell receptor-major histocompatibility complex interactions, and their "off-the-shelf" property, which allows for immediate clinical use (unlike CAR T cell therapy).[22] In 2023, the bispecific TCE talquetamab became the first GPRC5D-targeted therapy approved by the Food and Drug Administration (FDA) for use in patients with RRMM who received ≥4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. In this review, we will discuss the preclinical and clinical development of talquetamab, results from clinical trials both as a single-

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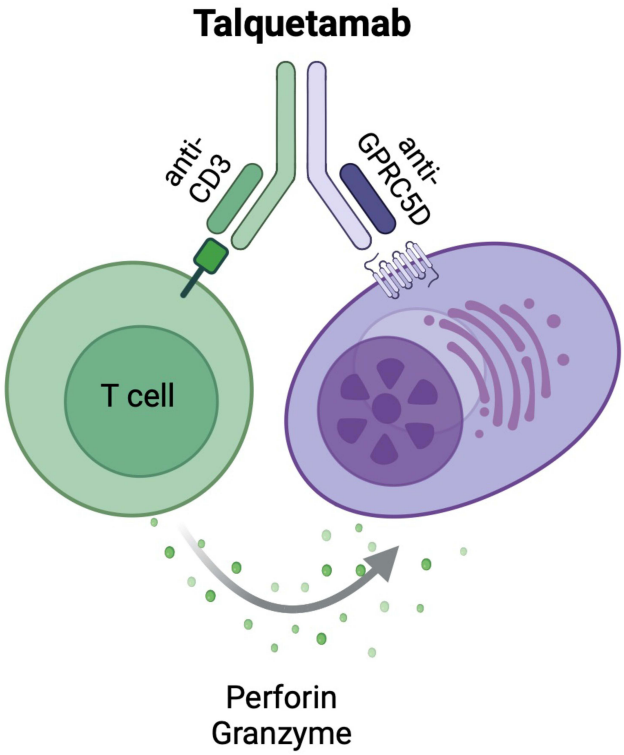


Figure 1 Mechanism of Talquetamab. Talquetamab concurrently binds to CD3 on T cells and GPRC5D on myeloma cells, leading to formation of an immune synapse that facilitates T cell mediated cytolysis via release of perforins and granzymes.

agent and in combination with other therapies, challenges associated with talquetamab including management of adverse events, and emerging data on mechanisms of resistance. Finally, we will highlight ongoing and upcoming clinical trials with talquetamab that may expand the utility of this agent in the treatment of multiple myeloma.

The Discovery of GPRC5D in Multiple Myeloma

GPRC5D, located on human chromosome 12p13, is highly expressed in the bone marrow of patients with multiple myeloma.[23] Additionally, as a 7-pass transmembrane receptor with a short extracellular N-terminal domain, GPRC5D is unlikely to be released from target cells into the serum, which may reduce the risk of decreased efficacy related to antigen sink effect.[24] In 2019, Smith et al demonstrated that GPRC5D is expressed on the surface of malignant plasma cells.[18] Importantly, GPRC5D expression has been shown to be otherwise limited to the hair follicle bulb, the nailbed, the base of filiform papillae on the tongue, and a subset of skin cells.[18,25] There is also evidence of low-level GPRC5D mRNA expression in the inferior olivary nucleus of the brain stem by in situ hybridization without detectable protein by immunohistochemistry.[26] Unlike BCMA, the downstream signaling pathway of GPRC5D in normal cells, as well as myeloma cells, has yet to be elucidated.

Based on its promising expression profile, Smith et al developed GPRC5D-targeted CAR T cells, which were highly effective in vitro and in vivo models, with no severe toxicities noted in non-human primates.[18] This CAR T cell product was clinically developed as MCARH109, with promising results reported in a Phase 1 clinical trial. In 17 evaluable patients, objective response rate (ORR) was 71%, with 35% complete response (CR) rate, and a median duration of response (DOR) of 7.8 months.[19] In terms of toxicities, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and cytopenias occurred, in addition to nail loss (65%), dysgeusia (18%) and rash (18%). Furthermore, 2 patients (12%) who received the highest dose level of MCARH109 developed symptoms consistent with grade 3 cerebellar dysfunction despite unremarkable brain imaging and cerebrospinal fluid analysis. There have now been several other clinical trials investigating other anti-GPRC5D CAR T cells.[27–30] Ongoing trials with other constructs, as well as combination approaches co-targeting BCMA, are underway.

In parallel to CAR T cell therapies, bispecific TCEs were developed as an alternative therapeutic approach to target GPRC5D in multiple myeloma.[24,31] Pillarisetti et al published a report on promising preclinical studies of JNJ-64407564, a humanized IgG4 bispecific TCE antibody that binds to both GPRC5D and CD3 on T cells to facilitate formation of an immune synapse (Figure 1).[24] JNJ-64407564 induced robust T cell-mediated cytotoxicity in vitro and in murine xenograft models. Notably, given its relatively short extracellular domains, the exposed epitopes of GPRC5D are closer to the plasma membrane, which may facilitate tighter immunological synapses that drive greater cytotoxicity. Based on promising preclinical data, JNJ-64407564 was renamed and clinically developed as talquetamab.

Clinical Development of Talquetamab

MonumenTAL-1 is the pivotal phase 1/2 study evaluating the safety and efficacy of talquetamab in RRMM and led to its Food and Drug Administration (FDA) approval. Chari et al initially published results from 232 patients treated in the dose-escalation and dose-expansion phases with both intravenous (N = 102) and subcutaneous (N = 130) administration routes of talquetamab.[20] Patients were heavily pretreated with a median of 6 prior lines of therapy, and 79% were triple-class refractory and 25% had prior BCMA-targeted therapy. Subcutaneous talquetamab at weekly (0.4 mg/kg QW) and biweekly (0.8 mg/kg Q2W) schedules were ultimately chosen as recommended Phase 2 doses (RP2Ds), with a step-up dosing paradigm to mitigate the risk of CRS, an acute inflammatory syndrome that occurs as a result of high-level immune activation and characterized by fever and multi-organ dysfunction.

Considering toxicities in patients treated with subcutaneous talquetamab at the RP2Ds in a recent update by Schinke et al (N = 339), any grade CRS occurred in the majority (N = 260, 77%) of patients but grade ≥3 CRS was rare (N = 5, 1.5%).[32] ICANS was uncommon (8.2%). Most high-grade adverse events were cytopenias including neutropenia (overall 35%, grade ≥3 30%), anemia (overall 46%, grade ≥3 29%) and thrombocytopenia (overall 30%, grade ≥3 21%). Other notable toxicities include dysgeusia (N = 245, 72%), dry mouth (N = 122, 36%), nail changes (N = 188, 55%), and weight loss (N = 134, 40%, grade ≥3 3%). Skin-related events including rash occurred in majority of patients (N = 221, 65%). Skin-related adverse events and dysgeusia led to discontinuation of therapy in 5 patients. Any-grade infections occurred in 217 patients (64%), with grade ≥3 infections in 63 patients (19%). Opportunistic infection rate was low at 5%. Hypogammaglobulinemia (IgG <500 mg/dL) was also common (≥71% of patients).[20] Despite the side effect profile, overall rates of discontinuation related to adverse events after longer follow-up was uncommon (5% for 0.4 mg/kg QW dose, 10% for 0.8 mg/kg Q2W dose, and 5% in patients with prior T-cell redirecting therapy treated at either 0.4 mg/kg QW or 0.8 mg/kg Q2W).[33] Specifics on practical management of toxicities will be highlighted in a subsequent subsection of this review.

Regarding efficacy, in the initial report, patients treated at talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W doses had an ORR of 70% (57% with very good partial response [VGPR] or better and 23% with complete response or better) and 64% (52% with ≥VGPR and 23% ≥CR), respectively.[20] A recent update from the expanded RP2D cohorts demonstrated an ORR of 74% and 70% with 0.4 mg/kg QW (N = 143) and 0.8 mg/kg Q2W (N = 154) doses, respectively.[33,34] The median follow-up time with updated data was 29.8 and 23.4 months for the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohorts, respectively. The median DOR was 9.5 months in the 0.4 mg/kg QW cohort and 17.5 months in the 0.8 mg/kg Q2W cohort. In patients achieving ≥CR, the median DOR was 28.6 months with the 0.4 mg/kg QW dose and not reached with the 0.8 mg/kg Q2W dose. The median PFS was 7.5 (95% confidence interval [CI], 5.7–9.4) months and 11.2 (95% CI, 8.4–14.6) months for the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohorts, with 24-month OS rate of 60.6% (95% CI, 51.7%-68.4%) and 67.1% (95% CI, 58.3%-74.4%), respectively.

Talquetamab also demonstrated activity in a cohort of patients (N = 70) enrolled in the MonumenTAL-1 study who previously received BCMA-targeted T cell redirection therapies (CAR T cell therapy or bispecific TCE) or antibody-drug conjugates (ADC).[35] The reported ORR in aggregate was 65.7% (N = 46), but separating by class of therapy prior to talquetamab, there was an ORR of 72.9% (N=35/48), 52.2% (N=12/23), and 75% (N=6/8) in patients who received CAR T cells, bispecific TCEs, and ADCs, respectively. This study also demonstrated the clinical significance of the time interval between talquetamab initiation and last dose of prior T cell redirecting therapy, specifically bispecific TCEs. In the prior CAR T cell therapy group, ORR was comparable in patients who received CAR T cells as the immediate prior line compared to at any prior line before talquetamab. In the prior bispecific TCE group, the ORR was 45.5% in patients

with a time interval ≤6 months between the last dose of prior TCE and talquetamab, compared to 50% with 6–9 month interval, and 62.5% with ≥9 month interval, although the number of patients in each group was small. Further investigations in similar heavily pretreated patients will provide more insights into optimal sequencing of T cell redirecting therapeutic agents in the management of RRMM.

Future Clinical Applications of Talquetamab

The single-agent activity of talquetamab in RRMM led to the development of an array of clinical trials investigating its use in combination or in sequence with other therapies, including CAR T cell therapies and other bispecific TCEs (summarized in Table 1). There are limited published reports on ongoing combination studies to date, but some emerging data.

Table 1 Summary of Talquetamab Clinical Trials

Trial Name	ClinicalTrials.gov ID	Combination(s)	Sequenced Therapy	Phase	Sponsor
Talquetamab Consolidation After BCMA CART Cell Therapy for Relapsed or Refractory Multiple Myeloma	NCT06066346		Talq after Idecabtagene vicleucel	2	Memorial Sloan Kettering Cancer Center
A Multi-arm Phase 1b Study of Talquetamab With Other Anticancer Therapies in Participants With Multiple Myeloma	NCT05050097	+Carfilzomib +Daratumumab +Lenalidomide +Pomalidomide		1	Janssen
An Open-Label, Non-Randomized, Multicenter, Phase II Study to Study the Efficacy of Talquetamab (JNJ-64407564) and Lenalidomide as Post Stem Cell Transplant Maintenance in Multiple Myeloma (OPTIMMAL)	NCT06461988	+Lenalidomide	Talq after autologous HCT	2	Stanford University
A Study of the Combination of Talquetamab and Teclistamab in Participants With Relapsed or Refractory Multiple Myeloma (RedirecTT-1)	NCT04586426	+Tec		1/2	Janssen
A Phase 1b, Multi-center, Study of Talquetamab in Combination With Iberdomide and Dexamethasone for the Treatment of Relapsed or Refractory Multiple Myeloma	NCT06348108	+Iberdomide and Dexamethasone		1	University of California San Francisco
A Phase 2, Open-Label, Multicenter Study of Ciltacabtagene Autoleucel and Talquetamab for the Treatment of Participants With High-Risk Multiple Myeloma	NCT06550895		Talq after Cilta-cel	2	Janssen
A Phase 1b/2 Study of Talquetamab Plus Concomitant Priming Radiotherapy in Multiple Myeloma With Extramedullary Disease	NCT06572605	+External Beam Radiotherapy		1/2	City of Hope Medical Center
A Phase 1b Study of Bispecific T Cell Redirection Antibodies in Combination With Checkpoint Inhibition for the Treatment of Participants With Relapsed or Refractory Multiple Myeloma	NCT05338775	+PD1 inhibitor		1	Janssen
A Phase 1b Study of Subcutaneous Daratumumab Regimens in Combination With Bispecific T Cell Redirection Antibodies for the Treatment of Subjects With Multiple Myeloma	NCT04108195	+Daratumumab +Daratumumab and Pomalidomide		1	Janssen

(*Continued*)

Table 1 (Continued).

Trial Name	ClinicalTrials.gov ID	Combination(s)	Sequenced Therapy	Phase	Sponsor
A Phase 3 Randomized Study Comparing Talquetamab in Combination With Pomalidomide (Tal-P), Talquetamab in Combination With Teclistamab (Tal-Tec), and Investigator's Choice of Either Elotuzumab, Pomalidomide, and Dexamethasone (EPd) or Pomalidomide, Bortezomib, and Dexamethasone (PVd) in Participants With Relapsed or Refractory Myeloma Who Have Received 1 to 4 Prior Lines of Therapy Including an Anti-CD38 Antibody and Lenalidomide	NCT06208150	+Pomalidomide +Tec +Elotuzumab, Pomalidomide, and Dexamethasone +Pomalidomide, Bortezomib and Dexamethasone		3	Janssen
A Study Comparing Talquetamab in Combination With Daratumumab or in Combination With Daratumumab and Pomalidomide Versus Daratumumab in Combination With Pomalidomide and Dexamethasone in Participants With Multiple Myeloma That Returns After Treatment or is Resistant to Treatment (MonumenTAL-3)	NCT05455320	+Pomalidomide +Daratumumab		3	Janssen
A Study of Teclistamab in Combination With Daratumumab and Lenalidomide (Tec-DR) and Talquetamab in Combination With Daratumumab and Lenalidomide (Tal-DR) in Participants With Newly Diagnosed Multiple Myeloma (MajesTEC-7)	NCT05552222	+Daratumumab and lenalidomide		3	Janssen
A Phase II Study Measuring MRD Negativity After Bispecific T-cell Redirectors Talquetamab and Teclistamab Consolidation in Sequence as Part of First Line Treatment in Transplant Eligible Multiple Myeloma Patients	NCT06505369		Induction: D-RVd Consolidation: Tec, then Talq	2	Janssen
Minimal Residual Disease-based Strategy With T-Cell Redirector After Treatment With Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone (D-VRd) in Newly Diagnosed Multiple Myeloma: A Phase 2 (IFM 2022–01)	NCT06353022	+Tec	Induction: D-RVd Consolidation: Tec+lenalidomide, *or* Tec +Talq	2	Nantes University Hospital, Janssen
An Open Label, Multicenter, Phase 2, Pilot Study, Evaluating Early Treatment With Bispecific T-cell Redirectors (Teclistamab and Talquetamab) in the Frontline Therapy of Newly Diagnosed High-risk Multiple Myeloma	NCT05849610	+Daratumumab	Induction: D-RVd Consolidation: Tec + Daratumumab *or* Talq + Daratumumab	2	PETHEMA Foundation, Janssen
A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of Different Sequences of Ciltacabtagene Autoleucel (Cilta-cel), Talquetamab SC in Combination With Daratumumab SC (Tal-D) and Teclistamab SC in Combination With Daratumumab SC (Tec-D) Following Induction With Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) in Participants With Standard-risk Newly Diagnosed Multiple Myeloma	NCT06577025	+Daratumumab	Induction: D-RVd Consolidation: Talq + Daratumumab then Cilte-cel *or* Cilte-cel then Talq + Daratumumab alternating with Tec + Daratumumab	2	Janssen

Abbreviations: D-RVd, Daratumumab, lenalidomide, bortezomib, dexamethasone; Tec, Teclistamab; Talq, Talquetamab; HCT, hematopoietic cell transplantation; Cilte-cel, Ciltacabtagene autoleucel.

Searle et al reported on the phase 1b MonumenTAL-2 trial combining talquetamab with pomalidomide in 35 patients with RRMM (NCT05050097).[36] The rationale for the study was that the mechanism of pomalidomide is in part T cell mediated, and thus pomalidomide is postulated to potentially augment TCE responses.[37] In reported abstracts from the study, the median number of prior lines of therapy was 3, and the minority of patients were triple-class refractory (N = 8, 23%) or pomalidomide-exposed (N = 8, 23%). The reported ORR was 88.6% with ≥CR in 51%. The 12-month DOR-rate was 74.4% after a median follow-up time of 16.8 months. Toxicities related to the combination included CRS (overall 74%, grade ≥3 3%), ICANS (overall 9%, grade ≥3 0%), neutropenia (overall 63%, grade ≥3 57%), dysgeusia (86%), and

nail changes (69%). Although cross-trial comparisons are specious due to heterogeneity of treated cohorts of patients, infections were common relative to talquetamab monotherapy and occurred in 80% of patients overall with grade ≥3 infections in 23%. Overall, 9 patients (26%) discontinued therapy due to adverse events.

Results from a cohort from the phase 1b TRIMM-2 study were also reported by Dholaria et al for patients treated with the combination of talquetamab and daratumumab (NCT04108195).[38] Similarly, beyond targeting CD38 on myeloma cells, daratumumab has pleiotropic effects on T cell subsets that provided mechanistic rationale for combination with TCEs.[39] In this study, the 65 patients who received talquetamab (0.4 mg/kg QW or 0.8 mg/kg Q2W) with daratumumab were heavily pretreated with a median of 5 lines of prior therapy. Additionally, 58% were triple-class refractory, and 88% were exposed to prior anti-CD38 monoclonal antibodies (including 78% who were refractory). After a median follow-up of 16.8 (range, 1.9–31) months for the talquetamab 0.4 mg/kg with daratumumab cohort, the ORR was 71.4% with ≥CR rate of 42.9%; median DOR was not reached; and 12-month PFS was 77.4% (95% CI, 44.9%-91.2%). After a median follow-up with 15 (range, 1.0–23.3) months for the 0.8 mg/kg Q2W with daratumumab cohort, the ORR was 84% including 52% achieving CR or better; median DOR of 20.3 months; and 12-month PFS was 67.4% (95% CI, 52.3%-78.6%). Notably, toxicities were comparable to talquetamab monotherapy, but the rate of infection was high (overall 63%, grade ≥3 25%).

Considering other potential combination strategies, given the expanding arsenal of BCMA-directed therapies in multiple myeloma, there is understandable interest in targeting both BCMA and GPRC5D concurrently. Prior studies demonstrated that GPR5CD expression patterns may be independent of BCMA on myeloma cells.[18,24] In addition, anti-GPRC5D CAR T cells have been shown to be effective in MM models of BCMA antigen loss.[18,40] Thus, there are numerous registered clinical trials investigating co-targeting strategies (see Table 1). The phase 1b RedirecTT-1 trial has results reported from 63 patients treated with the combination of talquetamab and teclistamab, a BCMA-directed bispecific TCE, at multiple dose-levels (NCT04586426). In the entire cohort, the median number of prior lines of therapy was 5, 78% were triple-class refractory, 33% had high-risk cytogenetics and 43% had extramedullary disease. In terms of toxicities, CRS occurred in 81% (grade ≥3 3%), and neurotoxicity occurred in 1 patient (1%). Dose limiting cytopenias were common. After a median follow-up time of 14.4 months, the ORR for the entire cohort was 84% with 34% achieving ≥CR. Among 44 patients treated at the RP2D of talquetamab 0.8 mg/kg with teclistamab 3 mg/kg every 14 days, the ORR was 80% in response-evaluable patients with 52% achieving ≥CR, and the 18-month DOR rate was 86%. Notably, any grade infections occurred in 86% of patients overall (grade ≥3 48%). Six patients (14%) treated at the RP2D discontinued therapy due to adverse events. Several other co-targeting strategies are underway, including use of talquetamab as consolidation after BCMA-directed CAR T cell therapy (NCT06066346, NCT06550895).

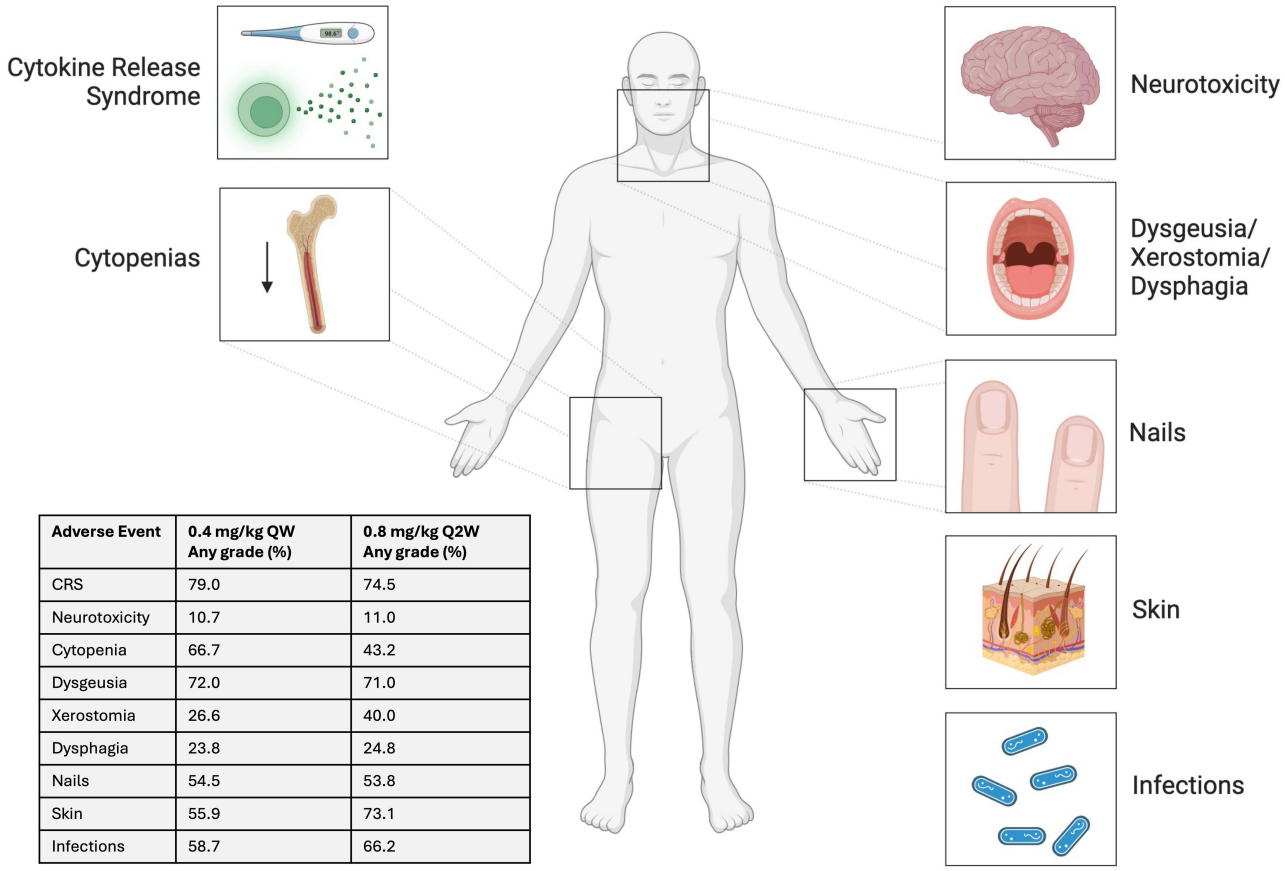
Given the long manufacturing times of CAR T cells, use of talquetamab as bridging therapy prior to CAR T cell therapy may prove to be a useful strategy in patients with symptomatic relapse and/or rapidly progressive disease. In a study by Dhakal et al, 77 patients received talquetamab bridging after BCMA-directed CAR T apheresis with the intention to proceed with CAR T cell therapy, of which 58 patients were successfully infused with idecabtagene vicleucel (N=13), and ciltacabtagene autoleucel (N = 45).[41] The median time on talquetamab was 22 days (interquartile range, 10–41). Among the 72 response-evaluable patients, ORR with talquetamab was 62%. Talquetamab bridging was not associated with increased risk of post-CAR T CRS (overall 65%, grade ≥3 3%) or ICANS (overall 8.6%, grade ≥3 1.7%). At day +30 post-CAR T infusion, ORR was 97.5% in the 40 response-evaluable patients including 35% achieving a CR. These results provide preliminary evidence of the safety of a short course of talquetamab to facilitate receipt of BCMA-directed CAR T cells. Further studies will be needed to elucidate if talquetamab bridging can potentiate the clinical efficacy of CAR T cell therapy.

It is clear from these trials that the combination of talquetamab with other anti-myeloma agents have promising efficacy, but careful consideration to mitigating toxicities including cytopenias and infections are warranted. Translational insights from these studies interrogating the immune microenvironment will help shed light on mechanism of talquetamab combinations. For example, a recent abstract examined phenotypic changes in subsets of T cell populations in patients treated with combination of talquetamab, pomalidomide and daratumumab.[42] Further investigations could help refine the design of future iterations of clinical trials with these combinations to maximize clinical benefit for patients.

Practical Management of Talquetamab Adverse Effects

Due to its immune-mediated mechanism of action, as well as the presence of GPRC5D expression on other tissues apart from myeloma cells, talquetamab causes significant toxicities that require careful attention and management (Figure 2). Short-term, the more significant considerations include CRS, ICANS and cytopenias, which usually resolve within the first few weeks of treatment. Cytopenias occasionally are present after several cycles but frequently respond to supportive measures. However, long-term adverse events affecting the oral cavity, nails, and skin of patients can have a significant impact on tolerability and quality of life. In addition, treatment emergent infections are a significant concern. It is noteworthy that in MonumenTAL-1, among patients treated with talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W, 15% and 10% required dose reductions due to adverse events, and 5% and 10% stopped therapy altogether, respectively.[33]

There are ongoing efforts to determine the optimal management of talquetamab adverse events.[43] Interestingly, Chari et al reported on patients on MonumenTAL-1 who required dose reduction or frequency of talquetamab due to emergent side effects.[44] In 19 patients who achieved ≥PR prior to de-escalation down to either 0.4 mg/kg Q2W or 0.8 mg/kg Q4W dosing, it was noted that responses deepened in the majority of patients, and the 6-month DOR rate was 88.9%. In addition, improvement or resolution of oral-, nail- and skin-related toxicities was noted in a subset of patients, with several patients reporting complete resolution of toxicities. Further research is required, but these data suggest that in patients who develop toxicities, decreased dosing frequency may not significantly negatively affect anti-myeloma responses and could improve tolerability. Regardless, specific supportive measures are helpful in the management of talquetamab-related toxicities (Table 2), which will be discussed in the following subsections.



Adverse Event	0.4 mg/kg QW Any grade (%)	0.8 mg/kg Q2W Any grade (%)
CRS	79.0	74.5
Neurotoxicity	10.7	11.0
Cytopenia	66.7	43.2
Dysgeusia	72.0	71.0
Xerostomia	26.6	40.0
Dysphagia	23.8	24.8
Nails	54.5	53.8
Skin	55.9	73.1
Infections	58.7	66.2

Figure 2 Adverse Events with Talquetamab. Talquetamab is associated with several common adverse events, summarized here. Using data from MonumenTAL-1, rates of any-grade adverse events are depicted for patients treated with 0.4 mg/kg weekly (QW) or 0.8 mg/kg every 2 weeks (Q2W) dosing schedules.[20,33]

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Table 2 Mitigation and Supportive Strategies for Key Talquetamab-Related Adverse Events

Adverse Event	Time to Onset (days)	Time to Resolution (days)	Management
Xerostomia (dry mouth)	19–26	57–89	- Hydration - Artificial saliva (saliva substitutes, sialogogues) - Sugar free chewing gums, hard candies, ice chips - Limit intake of caffeine and alcohol.
Dysgeusia	13–20	95–130	- Baking soda mouth rinses - Experiment with food of - Different textures and tastes - Enhance the taste of food with addition of spicy, sour or other aromatic flavor additives
Dysphagia	21–29	73–174	- Small bites (sips of liquid between bites) - Frequent small meals - Avoid dry food - Soft or mashed food - Sitting upright when eating
Nail-related (discoloration, onycholysis, dystrophy)	64–69	74–122	- Emollients - Nail hardeners - Vitamin E oil - Biotin supplements
Skin-related - Rash - Non-rash (dry skin, pruritus, skin exfoliation)	20–27 26-30	15–28 32-39	- Hydration - Emollients - Topical/oral antihistamines and/or steroids.
Weight loss (≥10% decrease from baseline)	87–91	50–403	- Nutrient dense food - Calorie boosting food - Appetite stimulants

Dysgeusia

Dysgeusia is an alteration of the quality of taste sensation. In MonumenTAL-1, dysgeusia, ageusia (loss of taste), and hypogeusia (reduced ability to taste), and general taste disorders were included under the umbrella term of dysgeusia. Based on Common Terminology Criteria for Adverse Events (CTCAE), dysgeusia has a maximum severity of grade 2, defined as altered taste with a change in diet and presence of noxious, unpleasant, or loss of taste, and grade 1 defined as altered taste with no change in diet. This grading system is highly subjective, and a robust evaluation method for dysgeusia has not yet been established. In updated data from MonumenTAL-1 patients treated with 0.4 mg/kg QW and 0.8 mg/kg Q2W dosing schedules, dysgeusia was reported in 72.0% and 71.4% of patients, respectively; most events were grade 1 (59.2% and 58.3%, respectively).[34] Among patients with dysgeusia treated with 0.4 mg/kg QW and 0.8 mg/kg Q2W doses, concurrent decreased appetite occurred in 10.7% and 11.7%; dry mouth occurred in 19.4% and 16.5%; and weight loss of ≥10% from baseline occurred in 20.4% and 15.5%, respectively. Finally, 7.0% and 3.9% of patients required dose modifications due to dysgeusia, respectively, and 3 patients (1.9%) in the 0.8 mg/kg Q2W cohort discontinued talquetamab due to dysgeusia.

MonumenTAL-1 recommended that patients with dysgeusia be managed with mouth rinses, such as salt water or liquid corticosteroids, pain medications, and short courses of oral corticosteroids. The most common medications used for management of dysgeusia included dexamethasone, triamcinolone and nystatin. Other strategies such as mineral and vitamin supplementation with zinc and biotin, salivary stimulants, and oral hydration have been used. Dose modifications, including reductions, delays, or skips, were helpful management strategies for dysgeusia.

Xerostomia (Dry Mouth)

In MonumenTAL-1, talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W dosing schedules were associated with xerostomia (all grade ≤2) in 26.6% and 40% of patients, respectively. Xerostomia occurred concurrently with decreased appetite in 7.9% and 12.1%, dysphagia in 5.3% and 9.0%, and weight loss ≥10% from baseline in 13.2% and 6.9%, respectively. No patients discontinued treatment due to xerostomia. Common medications employed to manage xerostomia in MonumenTAL-1 included xylitol and sorbitol to support dental health, glycerol and artificial saliva for lubrication, as well as glucose oxidase, lysozyme, lactoferrin, and lactoperoxidase as antibacterial agents. Patients were recommended to increase oral hydration and use intraoral topical agents such as topical saliva sprays or sugar-free chewing gum to stimulate saliva flow. Sodium lauryl sulfate-free toothpastes may be better tolerated than other toothpastes. As with dysgeusia, dose modifications may be a potentially effective management strategy for xerostomia.

Dysphagia

Saliva is necessary to swallow, and most cases of dysphagia associated with talquetamab may be in part secondary to xerostomia. Dysphagia occurred in 23.8% and 24.8% of patients treated with 0.4 mg/kg QW and 0.8 mg/kg Q2W of talquetamab, with the majority being low grade. No patients discontinued talquetamab due to dysphagia. In MonumenTAL-1, the most common interventions administered to manage dysphagia were sodium bicarbonate, sodium chloride, fluconazole, nutritional support, and omeprazole. Additionally, tramadol and oxycodone were used for pain management for odynophagia. Corticosteroids were used for management of oral inflammation, as well as magic mouthwash (compounded product that contains at least 3 of an antihistamine, anesthetic, antacid, antifungal, corticosteroid, and/or antibiotic). Dose reductions, delays, and skips can be an effective strategy for the management of dysphagia.

As part of preventative or management strategies for oral adverse events, early referral to a dietician or nutritionist at the onset of therapy is encouraged to provide patients with guidance on how to maintain a balanced diet and weight while on talquetamab. Routine dental evaluation including regular cleanings and examination should be encouraged due to the increased risk of dental and periodontal disease associated with dry mouth. Referral to a gastroenterologist may be considered in patients with high-grade or worsening severe dysphagia to evaluate for other aero-digestive track abnormalities such as cytomegalovirus or other causes of infectious esophagitis. Clinical trials to define optimal strategies for the management of oral events, including dysgeusia, xerostomia, and dysphagia are required to improve the tolerability of talquetamab. The TALISMAN trial is a randomized, multicenter, open-label, phase 2 study exploring various prophylactic strategies for talquetamab-related adverse events including dexamethasone mouthwash, oral pregabalin, and dissolving clonazepam tablets.[45]

Skin-Related Toxicity

Talquetamab is associated with rash and non-rash skin adverse events, including exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. In MonumenTAL-1 patients treated with 0.4 mg/kg QW and 0.8 mg/kg Q2W dosing schedules, 39.9% and 29.7% of experienced rash, whereas non-rash skin toxicities were reported in 55.9% and 73.1% of patients, respectively. The majority of skin-related toxicities were grade ≤2. No patients discontinued talquetamab due to rash, and 3 patients discontinued due to non-rash skin toxicities.

In MonumenTAL-1, topical corticosteroids were recommended for rashes occurring during the first treatment cycle with early consideration of a short course of oral corticosteroids to reduce risk of rash progression. Based on clinical experience from MonumenTAL-1 prevention and management of skin toxicities should begin at the start of treatment with liberal use of emollients and skin hydration methods, including ammonium lactate cream, heavy moisturizers, and oral hydration. For skin toxicity, topical steroids have been used with varying potencies depending on site and severity of event. For generalized rashes not controlled by topical steroids or involving large body surface area, short pulses of oral steroids should be considered. Dermatologic consultation may be considered in the event of persistent or high-grade skin toxicities.

Nail-Related Toxicity

Nail-related toxicity, which includes nail discoloration, nail disorder, onycholysis, onychomadesis, onycholysis, nail dystrophy, and nail ridging, was observed in 54.5% and 53.8% of patients treated at the 0.4 mg/kg QW and 0.8 mg/kg Q2W dosing schedules in MonumenTAL-1, respectively. All nail-related toxicity events were grade ≤2. There was no discontinuation of talquetamab due to nail-related toxicities. Management of nail-related toxicities can include nail soaks,

topical moisturizers, and topical corticosteroids. Emollients are commonly used, as well as vitamin E oil, systemic hydration, biotin, and protective nail coverings (eg socks and gloves). Avoidance of nail hardeners, acrylics, and gels is recommended as these may increase the risk of onychomycosis.

Cytokine Release Syndrome

CRS is an acute systemic inflammatory syndrome associated with CAR T cell therapies and bispecific TCEs. Fever is the predominant feature of low-grade CRS, with hypotension, hypoxemia and other end-organ damage occurring in more severe cases. Among patients in MonumenTAL-1 treated at the RP2Ds, any-grade CRS occurred in the majority of patients.[34] A step-up dosing paradigm is required for talquetamab to mitigate risk of severe CRS. Patients are recommended to be admitted for at least 48 hours after each of the step-up doses of talquetamab (0.01 mg/kg, 0.06 mg/kg, 0.4 mg/kg, and if given on Q2W schedule, 0.8 mg/kg). In MonumenTAL-1, time to onset of CRS was 2 days from most recent dose of talquetamab (range, 1–22), with a median duration of 2 days (range, 1–5). To treat CRS, 58% of patients received tocilizumab, but corticosteroid use was rare (1%). The International Myeloma Working Group (IMWG) recently published guidelines regarding management of CRS as well as ICANS in patients treated with bispecific TCEs.[46] First-line therapy with tocilizumab is recommended for patients with grade ≥2 CRS, and can be considered even with grade 1 CRS particularly for persistent signs and symptoms despite administration of acetaminophen. For higher grade CRS, corticosteroids are recommended, and early consultation with intensive care specialists may be warranted.

Neurotoxicity/ICANS

Neurotoxicity, namely manifesting as ICANS, is relatively less common with bispecific TCEs including talquetamab compared to CAR T cell therapy. In MonumenTAL-1, the median time to onset of ICANS was 1–2 days with a median duration <24 hours. For the management of ICANS, corticosteroids are recommended as the first-line treatment, with a similar philosophy to CRS where recommendation is to start dexamethasone with grade ≥2 ICANS, but treatment can be considered for grade 1 ICANS particularly in patients deemed high-risk. Prophylactic anti-epileptic administration is typically indicated for patients with grade ≥2 ICANS. Thorough evaluation is recommended to exclude other potential causes of neurologic symptoms, including toxins, metabolites, and infections. Acquisition of an electroencephalogram, brain imaging, and cerebrospinal fluid analysis may be indicated for more severe cases as part of a comprehensive diagnostic evaluation. Finally, for patients with severe ICANS not responding to high-doses of corticosteroids, alternative agents such as anakinra may be considered.[47]

Infections

Prior studies revealed that mean surface GPRC5D receptor density does not significantly differ between malignant and normal plasma cells.[24] Thus, therapeutic targeting of GPRC5D with talquetamab eliminates the majority of normal plasma cells in the bone marrow. This is akin the elimination of both normal plasma cells and subsets of mature B cells with BCMA-directed bispecific TCEs and BCMA-targeted CAR T cells. Unsurprisingly, hypogammaglobulinemia is common with both GPRC5D and BCMA-directed TCE therapy, which may underlie consequent risk of infections.[48] Although imperfect, cross-trial comparisons and retrospective reports have shown the rate of severe infections with talquetamab appears to be significantly lower compared to BCMA-directed TCE.[49] This may in part be due to the lack of GPRC5D expression on mature B cells, unlike BCMA.

Recent guidelines have been developed by the IMWG to address prevention of infections in patients treated with bispecific TCEs.[46] It is recommended that all patients receive intravenous immunoglobulin (IVIg) replacement for IgG <400 mg/dL, even without a history of recurrent infections. This recommendation is based on emerging data from several groups demonstrating significant reduction in infection incidence with primary IVIg prophylaxis.[50,51] In addition, standard antiviral and pneumocystis prophylactic medications are recommended in all patients. Optimal vaccination against seasonal influenza, SARS-CoV-2, and other pathogens per institutional guidelines is also advised. For patients with treatment emergent neutropenia, granulocyte colony-stimulating factor administration is recommended and the institution of antibacterial prophylaxis considered. In neutropenic patients exposed to high doses of corticosteroids or with other risk factors, anti-fungal/mold prophylaxis may be considered as well. Monitoring for cytomegalovirus reactivation is recommended for all patients. Finally, patients should be screened for hepatitis B, hepatitis C, and human immunodeficiency virus, and corresponding antiviral medications should be given when indicated to prevent viral reactivation.

Primary Resistance and Relapse on Talquetamab

There is immense interest in discovering mechanisms of primary resistance and relapse with bispecific TCE therapies in multiple myeloma.[14,52] With respect to GPRC5D-targeted therapies, several studies have recently been published investigating mechanisms of acquired resistance. First, it is important to note that loss of GPRC5D expression is relatively common after treatment with GPRC5D-targeted CAR T cell therapy, which is distinct from BCMA-directed CAR T cell therapy, where complete BCMA loss is rare. For example, in patients who had an initial response then relapsed in the trial of MCARH109 reported by Mailankody et al, 66% demonstrated complete loss of GPRC5D at the time of relapse.[19] One of these patients acquired biallelic deletions encompassing the *GPRC5D* locus on short arm of chromosome 12.[53]

Interrogating relapse after treatment with talquetamab, Lee et al recently described varied biallelic *GPRC5D* deletions, translocations and point mutations that precipitated loss of GPRC5D expression in several patients.[13] Derrien et al also recently described a patient who at the time of relapse displayed evidence of lost chromatin accessibility at *GPRC5D* promoter and enhancer elements, leading to significant downregulation of expression.[54] They also characterized a patient with a baseline monoallelic *GPRC5D* deletion who acquired 7 different subclones with distinct genetic aberrations in the *GPRC5D* locus after treatment with talquetamab that impacted protein translation, including frameshift indels, nonsense mutations and deletions at the transcription start site. Taken together, acquisition of *GPRC5D* loss via myriad types of genomic events suggest that *GPRC5D* may be relatively dispensable during tumor evolution, and GPRC5D loss may be a major mechanism of resistance to talquetamab.

Lee et al analyzed whole genome sequencing (WGS) data from 896 patients in the CoMMpass dataset and determined that 13.17% of multiple myeloma patients harbor monoallelic loss of *GPRC5D* at diagnosis.[13] In another WGS data set of 28 patients with RRMM who were naïve to GPRC5D-targeted therapies, 21.4% had monoallelic *GPRC5D* deletions. The fact that response to talquetamab treatment cannot be solely explained by monoallelic and biallelic deletions of *GPRC5D* suggests a knowledge gap in our understanding of the underlying mechanisms or patterns of resistance. Hence, further research focusing on the molecular underpinnings of resistance to bispecific TCEs is generally warranted. To illustrate, Han et al performed WGS using talquetamab-resistant myeloma cells obtained from a patient with monoallelic loss of *GPRC5D*. Interestingly, the authors noted hypermethylation of two regulatory regions within the *GPRC5D* gene that completely abolished or silenced its expression. Hence, epigenetic dysregulation may represent an additional molecular mechanism that confers resistance to talquetamab.[55]

Unlike BCMA, which has an extracellular domain that can be cleaved and shed into the serum as soluble BCMA, GPRC5D is a 7-pass transmembrane protein and thus has no known cleavable surface epitope. Recent studies have revealed that soluble BCMA abrogates the effect of BCMA-directed TCE via a ligand sink effect.[56] High tumor burden is correlated with high soluble BCMA levels, which may explain why patients with RRMM with high tumor burden are significantly more likely to exhibit primary refractoriness to BCMA-directed TCEs.[9,10] It follows that talquetamab may have advantages over BCMA-directed TCEs for patients with high tumor burden, but this hypothesis must be addressed in clinical trials. It also remains unknown if GPRC5D expression levels and/or receptor density correlate with clinical responses.

There have been several recent studies correlating features of the immune microenvironment, namely frequency of T cell phenotypic subsets in the peripheral blood and bone marrow, to response with bispecific TCEs in multiple myeloma. In an analysis aimed at correlating patient immune profiles with talquetamab response specifically, Vishwamitra et al recently described that talquetamab non-responders exhibited a more exhausted T-cell phenotype at baseline.[42] This was typified by lower T-cell counts, higher frequencies of Tregs, and higher expression of coinhibitory markers (LAG-3, TIM-3) on CD8+ T cells. Furthermore, samples obtained from patients who eventually progressed after an initial response to talquetamab revealed a T-cell phenotype that mirrored the initial non-responders, with increased expression of coinhibitory receptors (LAG-3, TIM-3, CD38, PD-1/LAG-3, PD-1/TIM-3) on peripheral CD4+ or CD8+ T cells. Further investigations are warranted to unravel the optimal immune microenvironment that may facilitate responses to TCEs including talquetamab.

Conclusion

As the number of immune-based therapies for the treatment of multiple myeloma expands, targeting GPRC5D with talquetamab appears to be a promising strategy that can induce responses in highly treatment-refractory patients. Further, data from early clinical trials suggest a subset of responses are durable and can last for more than 12 months despite

modifications in dose intensity or schedule. However, besides practical considerations regarding management of short-term side effects like CRS, ICANS and cytopenias, the biggest impediments to the use of talquetamab are treatment-emergent side effects that can significantly diminish patient health-related quality of life. In addition, risks of infection are significant and require optimal prophylaxis strategies and swift clinical recognition.[57]

To manage side effects associated with talquetamab, there is emerging data to support decreased intensity or dosing frequency can lead to improvement or resolution of toxicities in a subset of patients without loss of response.[44] Future clinical trials should consider testing fixed-duration treatment or dose de-escalation in patients with deep responses to potentially lessen the severity of talquetamab-related adverse events.[58] Until then, treatment recommendations regarding dose de-escalation or cessation of therapy should be based on individual clinical circumstances. Innovative supportive care strategies to mitigate long-term side effects from talquetamab remains a key area of unmet need.[45]

The optimal sequencing of BCMA- and GPRC5D-directed therapies in the treatment of multiple myeloma is not yet known. It is tempting to speculate on the sequential impact of immune-based approaches, including prior BCMA-targeted therapies on the efficacy of talquetamab. As previously mentioned, patients in MonumenTAL-1 treated with prior anti-BCMA CAR T cell therapy had a better ORR compared to those with prior bispecific TCE.[20] Clearly, talquetamab has efficacy in these subgroups, but further research is required to determine reasons for refractoriness or relapse, including tumor intrinsic factors (eg acquired *GPRC5D* loss/mutations) or extrinsic factors (eg baseline or acquired host immune dysfunction). Better understanding of the relative components could help identify upfront patients at risk of treatment failure or those who may benefit from novel sequential or combination strategies to improve efficacy.

In the near future, there is increasing optimism about building on current treatment regimens to produce deep responses and durable treatment-free intervals for patients with their upfront therapy in multiple myeloma, guided by biomarkers such as minimal residual disease (MRD).[59] Given evidence of efficacy in treatment-refractory patients, several clinical trials are testing the use of first-line regimens that incorporate talquetamab either as initial induction therapy, consolidation or maintenance, with the goal of increasing rates of MRD-negativity (NCT06461988, NCT05552222, NCT06505369, NCT06353022, NCT05849610, NCT06577025). There is also a clinical trial testing the combination of talquetamab or teclistamab with daratumumab in patients with high-risk smoldering multiple myeloma (NCT06100237). Clinical and translational data from these upfront immunotherapy approaches are eagerly awaited. In summary, talquetamab clearly has a role in the treatment arsenal for RRMM, and continued investigative efforts will enlighten our understanding of its optimal place in therapy.

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