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**New Drug Update**

# Unlocking hope: talquetamab in multiple myeloma treatment: a bispecific breakthrough targeting CD3 and GPRC5D

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## ABSTRACT

Multiple myeloma (MM) presents a significant global health burden, with disparities in incidence and outcomes reflecting challenges in recognition and treatment. Talquetamab, a bispecific CD3 T-cell engager targeting G-protein coupled receptor family C group 5 member D (GPRC5D), has emerged as a promising immunotherapy for relapsed/refractory MM (RRMM). In August 2023, talquetamab received accelerated approval from the US FDA for RRMM treatment, followed by conditional marketing authorization from the EMA. Clinical trials demonstrated talquetamab's efficacy, with overall response rates (ORR) of 69% and 76% in heavily pretreated RRMM patients. The phase I monumenTAL-1 trial showcased talquetamab's effectiveness, particularly in high-risk MM and extramedullary disease, with ORRs around 71-74%. Subsequent phase 2 results reaffirmed its efficacy, even in patients with prior T-cell redirection therapies. Combination therapy with daratumumab further enhanced talquetamab's efficacy, addressing concerns of T cell exhaustion. Pharmacokinetic studies revealed sustained responses and manageable adverse events with subcutaneous administration, facilitating convenient dosing regimens. However, talquetamab carries risks of cytokine release syndrome (CRS) and neurologic toxicity, necessitating close monitoring and prompt management. Common adverse events included fever, CRS, musculoskeletal pain, and infections, although severe events were infrequent. Vigilant management strategies, including prophylactic measures and supportive care, mitigate these risks. In conclusion, talquetamab represents a significant advancement in RRMM treatment, offering a promising avenue for T-cell redirection therapy. Ongoing research aims to optimize treatment sequencing and combination strategies, fostering improved outcomes for MM patients. Continued investigation will refine the strategic integration of talquetamab and other immunotherapies, paving the way for enhanced treatment efficacy and patient care in RRMM.

**Keywords:** MM, Talquetamab, RRMM, Daratumumab

## INTRODUCTION

Multiple myeloma (MM) is a significant hematological malignancy that poses a considerable health challenge, with a global incidence of approximately 10%. This condition demands careful attention and management to ensure optimal outcomes for patients. The global incidence of MM is a staggering 160,000, with mortality reaching a grim 106,000. There are significant disparities in the incidence and outcome of MM across the globe. This disparity suggests that many regions suffer from suboptimal treatment and under-recognition of the disease. A more comprehensive approach to treating MM is necessary to address these challenges.[1] New immunotherapy treatments such as chimeric antigen receptor T (CART) cell therapy and bispecific antibodies (BsAb) offer promising options for treating RRMM. CAR T-cell therapy is effective but has a long manufacturing process, while BsAbs are readily available and highly effective in treating RRMM.[2]

## DRUG OVERVIEW AND MECHANISM OF ACTION

Recognizing this, in early August 2023, the US Food and Drug Administration (FDA) granted accelerated approval for talquetamab (also known as talquetamab-tgvs or TALVEY®), a bispecific CD3 T-cell engager that targets the GPRC5D-an orphan receptor, to treat MM. This is a type of cancer that affects plasma cells, which are a type of white blood cell that produces antibodies. Talquetamab works by binding to both GPRC5D, which is expressed on MM cells, and CD3, which is expressed on T cells, causing the T cells to attack and destroy the MM cells.[3] Furthermore, talquetamab-tgvs interacts with regular tissues, such as the epithelial cells found in keratinized regions of the skin and tongue. In laboratory experiments, talquetamab-tgvs stimulated T-cells, which then produced inflammatory signaling molecules, ultimately leading to the removal of MM cells.[4] The approval was based on the results of a clinical trial that showed that talquetamab had an ORR of 69% in patients with RRMM. Later that same month, the European medicines agency (EMA) granted conditional marketing authorization for talquetamab to treat adult patients with RRMM. The decision was based on the results of a clinical trial that showed that talquetamab had a clinical response rate of 76% in patients with RRMM. The approval of talquetamab represents an important step forward in the treatment of MM.[3]

The selective expression of GPRC5D on MM cells makes it a potential target for immunotherapy in the treatment of MM. In this context, an analysis was conducted to determine the activity of talquetamab. The study employed a bioluminescence imaging (BLI)-based cytotoxicity assay on four MM cell lines with varying levels of GPRC5D expression. Additionally, a GPRC5D-negative lymphoma cell line (Raji) was also analyzed. These cell lines were incubated with serial concentrations of talquetamab for 48 hours in the presence of healthy donor-derived peripheral blood mononuclear cells (PB-MNCs). Results indicated that talquetamab did not affect the viability of GPRC5D-negative or Raji cells. However, dose-dependent lysis of the three GPRC5D-positive cell lines was observed, with near-complete elimination of MM cells starting at 0.16 µg/mL talquetamab.[5]

## CLINICAL TRIALS

The phase I MonumenTAL-1 trial showed talquetamab's efficacy in heavily pre-treated RRMM patients, with 79% triple-class refractory and 30% penta-refractory. Notably, 32% had extramedullary disease, 16% had high-risk cytogenetics, and higher ISS class II (45%) and III (19%) compared to teclistamab.[6,7]

Subcutaneous talquetamab, at both 800 mcg/kg Q2W and 405 mcg/kg QW, showed comparable efficacy in heavily pre-treated RRMM patients, with ORRs around 71-74% and significant rates of VGPR or better. FDA's breakthrough therapy designation was granted in June 2022. Updated phase 2 results presented at ASCO 2023 reaffirmed these findings, indicating the promising therapeutic potential for talquetamab, particularly in high-risk MM and extramedullary disease, akin to teclistamab.[6,8,9]

Of special interest is the efficacy in patients who have had prior T-cell redirection therapy such as CAR T cell therapy or other BsAb therapy due to concern for T cell fatigue or exhaustion.[10-12] The MonumenTAL-1 phase 2 results presented at ASCO 2023 revealed talquetamab's efficacy in patients with prior T-cell redirection therapies like CART or BsAb, with a 63% ORR and 53% achieving VGPR or better. The median PFS was 5.1 months.[7] Combining talquetamab with daratumumab might address T cell exhaustion, as daratumumab has shown potential to alter T cell subsets, increasing effector T cells and decreasing regulatory T cells, as evidenced by the TRIMM-2 phase 1b study.[13]

In the TRIMM-2 trial, talquetamab combined with daratumumab showed promising results in heavily pre-treated RRMM patients. With a median of 5 prior lines of therapy, including a PI and IMiD, the ORR was 78%, with 45% achieving CR/sCR and 66% VGPR or greater. Even in patient's refractory to anti-CD38, anti-BCMA, and BsAb therapy, significant response rates were observed (ORR: 76%, 64%, and 75% respectively).[14]

GPRC5D-targeted CART constructs show promising efficacy in BCMA CART-resistant MM, with a 58% response rate and a median duration of response of 7.8 months.[15,16] Other GPRC5D CART constructs demonstrate ORRs ranging from 86-100%, with bispecific antibody RG6234 also showing potential, with reported ORRs of 71.4-60.4%.[17]

## PHARMACOKINETICS AND PHARMACO-DYNAMICS

TALVEY's effectiveness as a standalone treatment was evaluated in patients with relapsed or refractory MM in the MonumenTAL-1 study. The 187 patients received either talquetamab-tgvs 0.4 mg/kg subcutaneously weekly or talquetamab-tgvs 0.8 mg/kg subcutaneously every two weeks. The primary group under analysis had undergone at least four prior therapies. The ORR was 73% in the 0.4 mg/kg weekly group and 73.6% in the 0.8 mg/kg biweekly group. 85% of responders maintained their response for at least 9 months.[18]

As written by Chari et al, 232 patients received different doses of talquetamab either subcutaneously or intravenously with subcutaneous administration showing less fluctuating and sustained pattern on a concentration-time graph than after intravenous administration. Among patients, 65% of those who received talquetamab at the 405-µg dose level and 70% of those who received it at the 800-µg dose level had a response.[6] Talquetamab's

subcutaneous administration allows for QW or Q2W dosing, with patients admitted for step-up dosing to monitor complications. The 405 mcg QW dosing offers quicker target dose attainment with two step-up dosing (10 and 60 mcg per kg), while the 800 mcg Q2W requires longer admission but fewer visits requiring three step-up doses (10, 60, and 300 mcg). Side effects are comparable, with 800 mcg Q2W showing fewer infections and neurotoxicity but slightly higher grade 3 rashes.[17]

## EFFICACY AND SAFETY

TALVEY™ presents a comprehensive safety profile that warrants the attention of healthcare professionals and patients alike. Its safety measures are unparalleled, making it the optimal choice for those who prioritize safety and efficacy. TALVEY™ has a Boxed Warning, which is the highest level of warning that the US FDA can require, emphasizing the potential risks associated with CRS and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). These risks can be severe and life-threatening. In addition to the boxed warning, TALVEY™ has vital warnings and precautions. These include warnings about oral toxicity, weight loss, infections, cytopenias (reduced blood cell counts), skin toxicity, hepatoxicity (liver toxicity), and embryo-fetal toxicity. These risks can be serious and can require medical attention.[4]

When considering adverse reactions, some affecting more than 20% of patients include fever, CRS, taste disturbances (dysgeusia), nail issues, musculoskeletal pain, skin problems, rashes, fatigue, weight loss, dry mouth, dry skin (xerosis), difficulty swallowing (dysphagia), upper respiratory tract infections, diarrhea, hypotension, and headaches.[4] All patients experienced adverse events (AEs), with grade 3 or 4 AEs occurring in 78% but no deaths were related to talquetamab use, unlike teclistamab which had 5 deaths (3%).[7,8] CRS occurred in 78% of patients, with a median duration of 2 days, none were grade 3 or greater. Other common AEs included hypogammaglobulinemia, oral issues, infections (63%, 22% grade 3/4), anemia, asthenia, and skin exfoliation (>40%). Neutropenia occurred in 38% (26% Grade 3/4), and hypogammaglobulinemia in 85%. Infections affected 58.7% and 66.2% at 0.4 mg/kg and 0.8 mg/kg doses respectively, with opportunistic infections in 3.5% and 5.5%. COVID-19 infection occurred in 13% and 2% at 405 mcg and 800 mcg doses respectively, with no fatalities.[6,19] Serious AEs occurred in 43% and 34% of patients receiving 405 mcg and 800 mcg doses respectively. In phase 2, 14.7% and 8.3% had dose reductions, and 4.9% and 8.3% had dose discontinuations in 0.4 mg/kg QW and 0.8 mg/kg Q2W groups respectively. Despite potential skin and oral AEs, only five discontinuations occurred across 288 patients.[6,9,17]

Initiating talquetamab requires close monitoring with access to tocilizumab and critical care facilities. Nail issues can be managed with creams and Vaseline; skin changes with topical steroids. Oral adverse events necessitate vigilance and management with saliva substitutes, biotin sprays, and mouthwashes. Infections are addressed with prophylactic medications and vaccination, with immunoglobulin repletion for low levels.[17]

## CONCLUSION

Talquetamab, a bispecific antibody emerges as an additional avenue for T-cell redirection therapy in patients with RRMM. Ongoing trials aim to elucidate the most effective sequencing of these therapies and identify optimal combinations. Through continued research and clinical investigation, we anticipate gaining deeper insights into the strategic utilization of T-cell redirecting therapies, ultimately enhancing treatment outcomes for RRMM patients.

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