Letter to the Editor

rare tumors

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Talquetamab: A promising immunotherapy for multiple myeloma

Amna Tariq[1], Abdul Wahid[2], Fatima Asif[2] and Mahnoor Khan[2]

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Dear Editor,

Multiple myeloma (MM) is a tumor of the plasma cell. This heterogeneous monoclonal malignancy accounts for about 15% of all yearly reported hematological tumor in the West.[1] There is no existing therapy available for multiple myeloma as of now, but it can be controlled with treatment. However, the treatment may not be effective in some individuals, or it may work at first but the cancer may relapse. This is known as relapsed or refractory multiple myeloma.[2]

Combinations of multiple agents from different classes are currently being used for myeloma therapies, these includes steroids, alkylating agents, proteasome inhibitors (PIs), immunomodulators, selective inhibitors of nuclear export, monoclonal antibodies, and B-cell maturation antigen (BCMA)-targeted therapies.[1] Although these T-cell redirecting therapies targeting BCMA have shown initial promise, the survival curves do not exhibit a stable plateau, and the majority of patients will develop the cancer.[3]

The cell surface expression levels of GPRC5D, an uncharacterized G protein-coupled receptor belonging to family C, group 5, member D, represent a promising and innovative focus for immunotherapy in multiple myeloma (MM). This 7-pass transmembrane protein was identified as a potential target for therapies to combat multiple myeloma. GPRC5D displays notably high and specific expression in MM cells, while in normal tissues, its presence is confined to cells responsible for the production of hard keratin, such as those found in hair follicles.[3]

Talquetamab is the first in class GPRC5D targeting BsAb, its mode of action is the co-current binding to CD3 on T-cell and GPRC5D on MM cells, this leads to T-cell redirection towards the tumor cell which causes an immune synapse. This results in the T-cell activation and degranulation which releases granzymes and perforins, causing tumor cell death.[4]

During preclinical investigations, talquetamab effectively stimulated T-cell-mediated destruction of multiple myeloma (MM) patient. In heavily pretreated relapsed/refractory (R/R) MM patients, the two subcutaneous (s.c.) doses recommended for a phase 2 study exhibited exceptional antitumor efficacy. At each dose level, over 32% of patients achieved complete remission (CR), and when considering the combined data, an overall response rate (ORR) of approximately 73% was observed. Specific adverse events (AEs) included dysgeusia, skin-related AEs, primarily low-grade nail disorders.[5] It also caused the development of grade 1 or 2 CRS in about 75% of the patients, and infections in more than half of them and few hematological AEs were also reported.[4]

The TRiMM-2 study is assessing several talquetamab-based combinations. Initial observations made from the data comprising combination of talquetamab and daratumumab showed a favourable efficacy profile with toxicity levels within range, producing better results than when the drugs are used separately. The preclinical justification for this combination is dependent on the immune-modulatory effects of daratumumab including removal of tregs as well as stimulation in the number of T-cells and enhancement in cytolytic activity of T-cells. Based on these outcomes, a Phase 3 study, currently underway, is focused on determining the effectiveness of talquetamab in combination with daratumumab. Combination regime of talquetamab with teclistamab has been evaluated in 93 MM patients with

[1]Jinnah Sindh Medical University, Karachi, Pakistan
[2]Karachi Medical and Dental College, Karachi, Pakistan

Corresponding author:
Abdul Wahid, Karachi Medical and Dental College, North nazimabad block M, Karachi 75400, Pakistan.
Email: abdulwaid.aw36.aw@gmail.com

extensive treatment histories (79.6% triple-class refractory). Patients who received dosage on different levels; 86.6%, experienced a partial response (PR) and within this group of people 40.2% achieved a better outcome (≥CR) The t reatment responses resulted in a median progression-free survival (PFS) of 20.9 months for the patients. Although sample size was small (n = 35) this combination was effective in patients with soft tissue plasmacytomas.[4]

This synergistic therapy with daratumumab and teclistamab has enhanced talquetamab's ability to destroy MM cells effectively. To sum it up, GPRC5D-targeting T-cell redirecting bispecific antibody talquetamab is a potential drug for multiple myeloma treatment.[3]

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ORCID iD

Abdul Wahid https://orcid.org/0000-0003-0265-8781

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