

# Managing toxicities associated with GPRC5D-targeted therapies used to treat myeloma

## InfoSheet

**Targeting GPRC5D represents an important advancement in expanding treatment options for relapsed/refractory multiple myeloma patients. While very promising in research, GPRC5D-targeted therapies cause their own set of risks and a combination of side effects.**

**This InfoSheet gives more information on this new antigen target and explains how it is expressed on myeloma cells and other tissues. Learn how it affects your body and discover ways to manage the undesirable effects.**

### Definition and causes of GPRC5D-related toxicities

GPRC5D (G protein-coupled receptor class C group 5 member D) is another antigen target that is being used to develop new treatment approaches for multiple myeloma. Because this receptor is heavily expressed on myeloma cells, it makes it an effective target for myeloma drugs while limiting complications in other tissues. Explored as an alternative target to BCMA (B-cell maturation antigen), several new therapies are being developed to target GPRC5D. Notably, talquetamab (Talvey), a bispecific antibody that targets GPRC5D on myeloma cells and CD3 on T-cells, as well as AZD0305, an antibody-drug conjugate that targets GPRC5D on myeloma cells, or other CAR T-cell therapies and bispecific antibodies in development.

#### More on antigen targets :

For myeloma immunotherapy to work at its best, the goal is for the treatment to target antigens that are generally more numerous on the surface of myeloma cells, but not present on most healthy cells. Some antigens may also be on the surface of other cells, so they may not all be possible targets for myeloma immunotherapy. Several new immunotherapy approaches have been developed to target CD38 (clusters of differentiation 38) and BCMA (B-cell maturation antigen) because they are heavily expressed by nearly all myeloma cells but not by healthy plasma cells. There are also specific antigens on the surface of T-cells that could be helpful to “recruit” other T-cells and enhance myeloma cell destruction.

Figure 1 illustrates some myeloma cell antigen targets that have been studied or are being investigated (at the time of writing), in clinical trials.

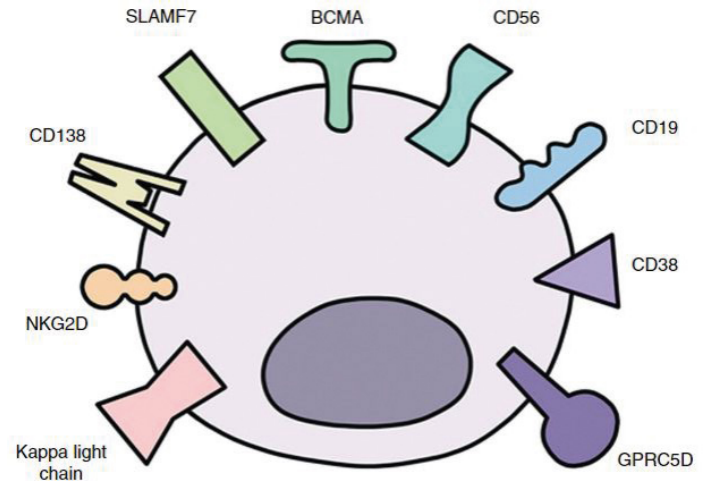


Figure 1 – Myeloma cell antigen targets

In his presentation entitled " **Using Different Targets to Destroy Multiple Myeloma** ", Dr. Joseph Mikhael, IMF Chief Medical Officer, explains how different bispecific antibodies work to destroy myeloma by attaching to antigens on myeloma cells.

New antigens like GPRC5D have been discovered on myeloma cells, expanding treatment options for patients. Since myeloma is still incurable to date, it is important that we discover new targets and develop drugs to attack those targets. We learned that diversifying targets helps combat myeloma's resistance to drugs and improves treatment outcomes, allowing for more time in remission. Over time, myeloma cells become resistant to the drugs we use. Thus, it is crucial to expand the ways we can treat this disease. *“Early work with these drugs shows that, much like teclistamab, they can be effective in achieving response rates of over 60% in heavily-pretreated patients”* says Dr. Mikhael.

### Side effects of GPRC5D-targeted therapies

Key side effects of GPRC5D-targeted therapies, such as talquetamab, include:

- Cytokine Release Syndrome (CRS) – Refer to the [Cytokine release syndrome \(CRS\) InfoSheet](#)
- Skin peeling or rashes
- Hair thinning
- Nail changes or nail loss

- Taste changes (dysgeusia) including complete loss of taste, loss of appetite and weight loss
- Hematological effects such as neutropenia and thrombocytopenia – Refer to the InfoSheets entitled [Infections and neutropenia](#) and [Thrombocytopenia](#)
- Risk of infections (slightly lower compared to BCMA-directed bispecific antibodies) – Refer to the [Infections and neutropenia Infosheet](#)
- Neurological effects such as Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) – Refer to the [Neurotoxicity syndrome \(ICANS\) InfoSheet](#)
- Fatigue
- Nausea – Refer to the [Nausea and vomiting InfoSheet](#)

As we have seen, treatment for multiple myeloma targeting the GPRC5D on the myeloma surface has incidentally a direct impact on other tissues where this antigen is expressed. Let's learn more about the impact on skin, hair, nails and taste buds.

Dysgeusia is an abnormal or reduced sense of taste due to GPRC5D expression on taste buds. Results from studies<sup>1</sup> show that dysgeusia occurs in 71-72% of patients treated with talquetamab and its duration varies from 57 to 109 days for most patients.

Bispecific antibodies and antibody-drug conjugates that targets GPRC5D can also cause negative effects on nails. Incidence rates for nail toxicities associated with talquetamab are between 54-55% and the symptoms generally last for 74-89 days. Patients may experience different types of toxicities like separation of the nail from the nail bed, shedding, breakage or deformation of the nail, or even nail ridges or discoloration.

Hair-related side effects are common because GPRC5D is expressed in hair follicles. Patients may notice hair thinning or hair loss (alopecia) during treatment. Furthermore, we observe several skin-related side effects in 30-73% of patients treated with talquetamab due to GPRC5D expression in skin tissue. These skin toxicities include rash, dry skin, peeling and itching. The duration of the inflammation or irritation usually lies between 26-39 days for most patients.

<sup>1</sup> Catamero, D. *Practical Management of Patients with Relapsed/Refractory Multiple Myeloma Receiving Talquetamab*. International Myeloma Society (IMS), Athens, Greece, 2023.

## How are GPRC5D-related toxicities treated?

Clinical trials show that the undesirable effects of GPRC5D-targeted therapies are generally manageable, with low rates of treatment discontinuation.

Dysgeusia and other oral side effects, can be temporarily relieved using artificial saliva spray, mouth rinses, and vitamin support. When persistent, strategies to help patients maintain interest in food could be required. In this case, your nutritionist may suggest foods to stimulate your texture and taste functions. Make sure you are well hydrated by increasing your liquids intake.

Nails typically return to normal once myeloma treatment is completed. Your doctor may prescribe topical corticosteroids if needed. Nail-related toxicities may cause discomfort; using moisturizers and over-the-counter nail lacquer or vitamin E oil will help during the healing process. Make sure you wear comfortable shoes that that don't pinch your toes too tightly, along with soft and loose-fitting stockings. It is important to maintain good nail hygiene at all times.

Most GPRC5D-related side effects affecting hair, are generally mild to moderate in severity. There is no specific management strategy for hair-related side effects, but hair normally grows back after treatment. Close monitoring and supportive care are likely recommended.

Inflammation, irritation, and redness caused by skin-related side effects can be treated using topical corticosteroids. In more severe cases, your doctor may prescribe oral corticosteroids. Drink 6 to 8 glasses of water per day and use heavy moisturizers to help restore your skin's natural properties.

## Precautionary measures

- If you experience skin-related side effects, communicate with your healthcare team to find the appropriate treatment strategy. Ask a dermatologist for their guidance on how to control and manage your discomfort.
- It is important to communicate any hair-related changes to your healthcare team during treatment. Although the hair loss may be shocking and make you feel anxious or distressed, these side effects are usually not severe enough to require discontinuation of treatment and are often manageable with appropriate care. Support from a dermatologist is also suggested.
- In case of dysgeusia, patients will be monitored for weight loss (a few times per week), as taste changes can affect appetite and food intake. Your healthcare team will help find strategies to ensure proper nutrition is maintained during treatment and adapt or hold doses if needed.
- Avoid the use of artificial nails due to risk of infection.
- Do not stop or adjust medications without discussing it with your doctor or nurse. They may change your dose or schedule of medication to help reduce your discomfort and manage some side effects.
- Some of these side effects, notably CRS, can be potentially serious. Patients need to be monitored frequently for early indications of side effects, especially during initial treatment, and given rapid care and supportive treatment if needed.

To learn more about antigen targets and side effects associated to treatment of myeloma, consult Myeloma Canada's Resource library at [www.myeloma.ca](http://www.myeloma.ca).

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