Myeloma Patients Europe

FACTSHEET

MYELOMA PATIENTS EUROPE

TALQUETAMAB (TALVEY®)

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Myeloma Patients Europe (MPE) has developed a series of factsheets for patients and patient advocates, providing an overview of available treatment options for myeloma and covering some topics related to the disease.

The factsheets cover important issues around the treatment, so that patients can feel safe and informed when asking their doctor specific questions.

For each of the available therapies, the following topics will be addressed:

- What is myeloma?
- What is the particular treatment?
- How does the treatment work?
- What are the benefits?
- What are the side effects?
- How and when is the treatment given?

Myeloma treatment is constantly evolving and the factsheets will be updated regularly to reflect the latest developments.

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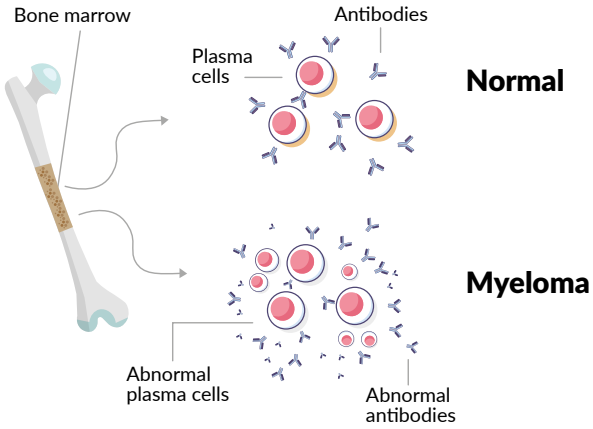
What is myeloma?

Myeloma is a rare cancer of the bone marrow. It causes the formation of abnormal plasma cells, also called myeloma cells, which divide uncontrollably. Usually, plasma cells help the body to fight infections by making antibodies that recognise and attack viruses, bacteria and fungi. Myeloma affects multiple places in the body (this is why it is sometimes referred to as 'multiple myeloma') where bone marrow is normally active, such as the bones of the spine, pelvis, rib cage and the areas around the shoulders and hips.

Myeloma causes pain, anaemia (low red blood cells), fatigue, fractures, recurring infection, bruising and high blood calcium (hypercalcaemia). These symptoms usually require treatment and could be followed by a period of remission where symptoms subside and may not require any treatment. This cycle of remission and recurrence (relapse) often occurs several times. Many patients, particularly in relapse setting, will receive treatment for a long period of time to ensure that their myeloma is kept at bay.

Treatment may involve taking a combination of drugs that have been found to be more effective than single drugs. Myeloma generally cannot be cured, but survival rates are increasing, due to the availability of new treatments and many patients are able to enjoy a good quality of life. A number of other new treatments have recently been approved or are under consideration for use following relapse, or for refractory myeloma.



What is talquetamab (Talvey®)?

Talquetamab is a bispecific antibody that received 'orphan drug' designation by the European Commission in 2020. An orphan drug designation is a status assigned to medicines developed for rare disease conditions that affect fewer than five patients per 10,000 inhabitants in the EU. Talquetamab has since been granted conditional marketing authorisation from the European Commission in July 2023. Conditional marketing authorisation is granted to new drugs based on less comprehensive data than normally required if the medicines address unmet medical needs and if the medicines' benefits are thought to outweigh their risks. The researchers must provide more comprehensive clinical data in the future to maintain approval status[1].

Talquetamab has been approved for the treatment of patients with relapsed/refractory myeloma, who have received at least three previous lines of therapy, including an immunomodulatory drug (IMiD) (such as lenalidomide or pomalidomide), a proteasome inhibitor (such as bortezomib or carfilzomib) and an anti-CD38 antibody (such as daratumumab or isatuximab), and whose disease has progressed since their last treatment[1].

How does talquetamab work?

Talquetamab is a bispecific antibody that binds to the GPRC5D receptor found on the surface of myeloma cells and the CD3 protein on T-cells (a type of immune cell) at the same time. Through this bispecific interaction, talquetamab facilitates tumor cell elimination by bringing the T-cell and myeloma cell into close contact with one another, allowing the T-cell to initiate an immune response and kill the myeloma cell more effectively[2]. GPRC5D is also expressed on keratinised tissues (e.g. skin, nails, tissue inside the mouth), which can lead to on-target, off-tumour toxicities. This means that normal tissues that have the shared expression of the talquetamab targeted antigen GPRC5D can be affected and cause symptoms.

What are the benefits of talquetamab?

There are currently multiple ongoing studies assessing the use of talquetamab in myeloma patients. MonumenTAL-1 is assessing talquetamab as monotherapy, while studies like TRIMM-2, RedirecTT-1, MonumenTAL-2,

MajesTEC-7, MonumenTAL-3, GEM-TECTAL and TRIMM-3 are investigating its use in combination with other myeloma therapies[3].

The phase 1 and 2 MonumenTAL-1 study and the TRIMM-2 study have published preliminary results[4].

Results from Phase 1 and 2 of the MonumenTAL-1 trial has led to talquetamab being granted approval by the European Commission[5]. In phase 1 of the MonumenTAL-1 study, 232 patients who had relapsed/refractory myeloma received talquetamab once a week or every two weeks at a higher dose. 70% of patients achieved a response to treatment with the average length of response lasting 10.2 months in the group that received 0.4mg/kg and 7.8 months in the 0.8mg/kg group[6]. The phase 2 of the MonumenTAL-1 study investigated talquetamab in patients with or without prior exposure to T-cell redirection therapy. It included a subgroup of patients with relapsed/refractory myeloma who had previously received T-cell redirection therapy like CAR T-cell therapy, or bispecific antibodies. Of the patients who had received T-cell redirection therapy, 65.7% responded to treatment with talquetamab[7]. The time until disease progression was 7.5 months in the weekly dosing group, 11.9 months in the biweekly group and 5.1 months in the group of patients who had prior T-cell redirection therapy[8]. The ongoing MonumenTAL-2 trial will further test talquetamab in combination with carfilzomib, daratumumab, lenalidomide or pomalidomide[9].

In the TRIMM-2 study, 65 myeloma patients who had received at least three prior lines of therapy, including a proteasome inhibitor, immunomodulatory agent and anti-CD38 medications, were given talquetamab once a week, or every two weeks at higher dose, in combination with daratumumab. In the weekly dosing group, 71.4% of patients achieved a response compared to 78.9 % of patients in the biweekly dosing group. Patients who received 0.8mg/kg (the biweekly dose) did not show signs of progression of disease for 19.4 months. The data on disease progression and duration of response to therapy in the lower dose group is still under investigation, however, is showing promising signs, as more than half of the patients are still receiving therapy[10].

What are the side-effects of talquetamab?

The MonumenTAL-1 study found that the most common side effects of talquetamab, affecting approximately 60% of patients, include[2]:

- Cytokine release syndrome (CRS)
- Taste disturbances
- Hypogammaglobulinaemia (low levels of antibodies in the blood)
- Infections

CRS occurs when the immune system reacts aggressively to certain types of medications including immunotherapy drugs such as bispecific antibodies like talquetamab or CAR T-cell therapy. CRS can cause severe, sudden symptoms such as fever, nausea, fatigue, pain and shortness of breath[11]. CRS is given a grade to describe the severity of the adverse events with grade 1 being a mild reaction, treated with supportive care only and grade 4 being life-threatening complications. In the MonumenTAL-1 study, CRS occurred in over 70% of patients in all three groups (0.4mg/kg once a week, 0.8mg/kg biweekly and patients who received prior T-cell redirection therapy, however, were mostly grade 1 and 2 and manageable by the medical team[8].

Patients are also more likely to have an increased risk of bacterial and viral infections[2]. 57% of patients in the weekly dosing group and 50% in the biweekly dosing group had infections as a side effect. Of these, two patients died from contracting COVID-19 during treatment[8].

The following adverse events may affect 20% of patients[2]:

- Skin changes, including rash, nail changes, and severely dry and itchy skin
- Muscle and joint pain
- Anaemia (low levels of red blood cells)
- Thrombocytopaenia (low levels of platelets causing increased bruising and bleeding)
- Lymphopaenia (low levels of white blood cells)
- Fatigue
- Weight loss and decreased appetite
- Dry mouth
- Nose and throat infections
- Difficulty swallowing
- Diarrhoea
- Cough
- Headache

Another serious adverse event of talquetamab is immune effector cell-associated neurotoxicity syndrome (ICANS), which can cause confusion and disturbances in speech and writing. In severe cases, it can also cause life threatening effects like loss of consciousness, seizures and swelling in the brain[12]. In phase 2 of MonumenTAL-1, ICANS occurred in 11% of patients

in both dosing groups and in 3% of patients who had received prior T-cell redirection therapy[8]. To ensure patients receive care in a timely manner for serious side effects it is recommended by the manufacturer that patients who show early signs of these symptoms remain hospitalised for 48 hours following dose administration. Medications such as dexamethasone and anti-seizure medication should also be provided to manage symptoms[13]. Other neurological side effects, including changes to motor skills (loss of control, often of the arms or legs), have been reported.

Approximately 5% of patients discontinued treatment due to side effects[8] and the dose was reduced in 14.7% and 6.2% of patients due to adverse events in the 0.4mg/kg and 0.8mg/kg groups respectively[4].

How and when is talquetamab given?

Talquetamab is given subcutaneously (SC), as an injection under the skin, on either a weekly or biweekly (once every two weeks) dosing schedule. Patients on the weekly dosing schedule will first receive a starting dose of 0.01mg/kg on day one, then 0.06mg/kg on day four and 0.4mg/kg on day seven. This is called a step-up dosing schedule, where the dose of talquetamab is increased progressively to limit adverse events. Patients will then continue to receive 0.4mg/kg weekly thereafter. The biweekly dosing schedule starts the same way with a 0.8mg/kg dose on day 10. Biweekly doses of 0.8mg/kg will be given thereafter. Other medications are also given alongside talquetamab to reduce the risk of developing CRS during step-up phase. This includes dexamethasone, diphenhydramine (a type of antihistamine) and paracetamol either orally or intravenously 1-3 hours before receiving talquetamab[13]. In order to treat severe adverse events in a timely manner, talquetamab should be administered by an experienced doctor who can monitor patients and provide medical support if necessary[2].

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MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries and helps inform and raise awareness at a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor. If there is anything that is not clear to you, please always ask your clinical team.

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