# The Immunotherapy Landscape for Multiple Myeloma

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## Introduction to Multiple Myeloma[1,2]

Multiple myeloma is the second most common haematologic malignancy after non-Hodgkin lymphoma.

It arises from the uncontrolled proliferation of abnormal plasma cells, which produce excessive immunoglobulins.

Multiple myeloma exists on a spectrum of plasma cell disorders, ranging from monoclonal gammopathy of undetermined significance (MGUS), to smouldering myeloma, multiple myeloma, and plasma cell leukaemia. The risk of progression from multiple myeloma to plasma cell leukaemia however is low.

**MGUS** → **Smouldering Myeloma** → **Multiple Myeloma** → **Plasma Cell Leukaemia**

It can lead to...

- **Renal dysfunction**
- **Lytic bone lesions**
- **Anaemia**
- **Hypercalcemia**

## Recent Developments and Future Outlooks[13-16]

In vivo CAR delivery approaches, such as ESO-T01, are showing promise and reducing manufacturing restrictions.

At ASH 2024, Anitocabtagene autoleucel (antio-cel), a novel CAR-T cell therapy showed a 95% overall response rate in relapsed/refractory multiple myeloma.

Trispecific antibodies like JNJ-79635322, which target BCMA, GPRC5D, and CD3, are designed to enhance efficacy and reduce the risk of antigen escape.

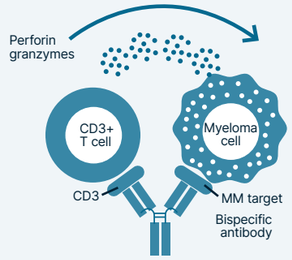
## Immunotherapeutic Approaches for Multiple Myeloma[3-12]

### Bispecific Antibodies[3-6]

These bind to two different proteins simultaneously; one on the antigen of the patient's T cell, called CD3, and one on the antigen of the myeloma cell, such as BCMA, GPRC5D, or FcHR5. E.g. There are currently three anti-BCMA BiTEs approved: teclistamab, elranatamab, and linvoseltamab.

+ Prove to be highly effective with response rates of over 60%.

- Can lead to severe hypogammaglobulinemia, necessitating regular intravenous immunoglobulin (IVIG) replacement to prevent infections.



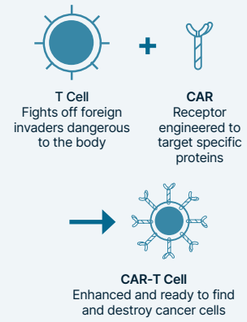

### Cellular Immunotherapy[7-9]

**CAR-T Cell Therapy:**

Patient T cells are genetically modified to express a chimeric antigen receptor targeting myeloma antigens such as BCMA. E.g. ciltacabtagene autoleucel (Cilta-cel) and idecabtagene vicleucel (ide-cel).

+ One time treatment requiring no maintenance therapy.

- Acute toxicities can include immunological effector cell-associated neurotoxicity syndrome (ICANs), cytokine release syndrome (CRS). Delayed toxicities can include parkinsonism, and enterocolitis.



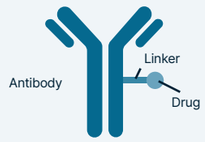

### Antibody-Drug Conjugates:[10]

This is a monoclonal antibody linked to acytotoxic agent, delivering chemotherapy directly to cancer cells. To note, there are currently no approved ADCs for multiple myeloma.

+ Targeted approach means there is less damage to surrounding healthy cells.

- Common toxicities include neuropathy, neutropenia, and anaemia.

- Keratopathy is also a toxicity with belantamab, requiring patients to have ophthalmologic evaluation while on treatment.




### Monoclonal Antibodies:[12]

These are complimentary and specific to one antigen protein on the myeloma cells, once bound they trigger an immune response. E.g. daratumumab, isatuximab, or elotuzumab.

+ High specificity targets myeloma cells with fewer side effects.

- Side effects can include allergic reactions and immunosuppression.

**Abbreviations**

A: advantage; D: disadvantage; MGUS: monoclonal gammopathy of undetermined significance; NK: natural killer.

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