

2. Background

2.1 Multiple myeloma remains a devastating disease with a significant unmet clinical need

Multiple myeloma (MM) is a hematologic cancer affecting antibody-producing plasma cells.^{3, 4} Despite advancements in treatment options in recent decades, MM remains incurable.⁵ It is a complex and heterogeneous malignancy associated with significant morbidity and mortality.^{3, 6, 7} MM affects multiple organ systems, leading to an array of disabling and painful symptoms that can severely impact quality of life.^{6, 8-10} These include bone disease, blood disorders, frequent infections, fatigue, neurological effects, and renal impairment.^{6, 8-12}

MM is the second-most common hematologic malignancy and accounts for 1.8% of all cancers in the United States.¹³ In 2023, it is estimated that 35,730 new cases of MM will be diagnosed and 12,590 deaths due to MM will occur in the United States alone.¹³ While treatment advances have somewhat improved the prognosis for patients with MM, the overall incidence has remained fairly constant, and death rates are high, with a 5-year relative survival rate of only 59.8%.¹³ MM is primarily a disease of the elderly, with a median age at diagnosis of 69 years and median age at death of 75 years.^{6, 13}

Although therapeutic advancements have begun to improve outcomes overall, most patients continue to experience cycles of remission and relapse, requiring further treatment.¹⁴⁻¹⁶ Each remission period is typically shorter than the last as the tumor becomes more aggressive due to selective pressures and genomic instability, ultimately driving disease progression.^{4, 17} With each relapse, therefore, MM becomes increasingly difficult to treat. Not only do efficacy outcomes progressively decline with each additional line of therapy, but treatment toxicities can accumulate over time, increasing the risk of comorbidities or treatment discontinuation.¹⁸

Patients who received at least one treatment but do not respond or stop responding have relapsed/refractory MM (RRMM).¹⁹ As patients progress through successive lines of therapy, treatment selection becomes increasingly limited as they exhaust all available therapeutic options.¹⁵ This is particularly problematic for those who become triple-class exposed (TCE), having previously received treatment with an immunomodulatory drug (IMiD), proteasome inhibitor (PI), and anti-CD38 monoclonal antibody (mAb), which comprise the majority of current standard-of-care (SOC) therapies for patients with MM.^{14, 15, 20} Outcomes for patients with TCE RRMM are poor. The retrospective MAMMOTH study showed a median progression-free survival (mPFS) of 3.4 months and median overall survival (mOS) of 9.3 months after salvage therapy in patients with TCE RRMM who were refractory to an anti-CD38 mAb.²¹ In the prospective LocoMMotion study of real-world SOC in patients with TCE RRMM showed similarly poor survival outcomes, with mPFS and mOS of just 4.6 months and 12.4 months, respectively.²⁰ Furthermore, 92 unique treatment regimens were received by 248 patients, demonstrating that there is no clear and obvious SOC for this patient population.²⁰ Effective therapies with novel mechanisms of action (MOAs) are therefore needed to treat patients with relapsed and/or refractory disease, with a long-term goal of deepening treatment responses earlier in the disease course.^{22, 23}

There is an urgent, unmet need for improved therapeutic options that are well-tolerated and produce deeper and more durable responses at any point in a patient's treatment course.^{4, 8} TECVAYLI offers a novel therapeutic approach that leads to deep and durable responses with

manageable toxicity, demonstrating significantly improved outcomes over current SOC treatments.

2.2 Pathophysiology of multiple myeloma

Healthy plasma cells arising from normal B-cell development produce antibodies to recognize and neutralize harmful antigens.²⁴ Mechanisms underlying these processes are prone to genetic aberrations, giving rise to malignant plasma cells.^{3, 7} MM is characterized by uncontrolled proliferation of malignant plasma cells and overproduction of monoclonal immunoglobulin, or M protein, in the bone marrow, which can circulate and infiltrate other organs in advanced disease.^{4, 17} Collectively, the diverse clinical manifestations of MM are known as CRAB features:

- **C**alcium (hypercalcemia): Increased calcium concentration in bones leads to invasive bone lesions which can cause pathologic fractures, bone pain, osteoporosis, and hypercalcemia. Skeletal-related events compromise mobility, reduce quality of life, and are associated with decreased survival.²⁵
- **R**enal failure: Renal disease impacts ~20% of patients with MM. It can be caused by excessive light chain production and hypercalcemia, cast neuropathy, dehydration, and amyloidosis.²⁶
- **A**nemia: Cytopenias, including anemia, thrombocytopenia, and leukopenia, are common in patients with MM. These can subsequently lead to fatigue, frequent infections, and clotting disorders.²⁵
- **B**one lesions: Up to 80% of patients with MM may have osteolytic bone disease at diagnosis or relapse. Increased osteoclast or decreased osteoblast activity causes bone pain and fractures.^{12, 27}

MM can also have neurological effects, including peripheral neuropathy, cranial nerve palsies, metabolic encephalopathies, and compression or displacement of nerves in the spinal cord due to infiltrating malignant plasma cells and accumulation of M protein.^{11, 28, 29}

2.3 Therapeutic landscape in MM

The treatment landscape of MM is rapidly evolving, and the past several decades have given rise to several major therapeutic advancements, forming the foundation for current SOC (**Figure 1**). The most recent developments feature novel MOAs with optimized treatment approaches that will begin to shape a new SOC in the coming years.

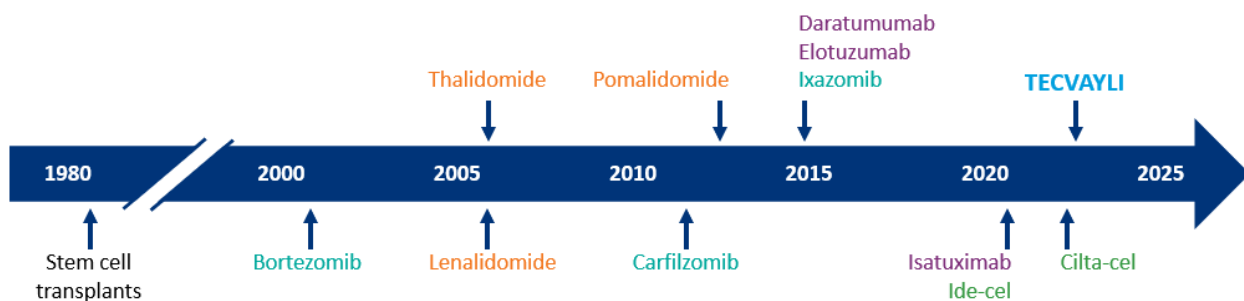


Figure 1: Timeline of the MM therapeutic landscape.^{1, 30-41} Proteasome inhibitors are shown in teal, immunomodulatory drugs in orange, monoclonal antibodies in purple, CAR-T cell therapies in green, and bispecific antibodies (TECVAYLI) in blue.

2.3.1 Current standards of care

2.3.1.1 Stem-cell transplantation

Autologous stem-cell transplantation (ASCT) involves the harvesting and preservation of a patient's stem cells prior to myeloablative chemotherapy, with subsequent reinfusion of stem cells to restore normal bone marrow function.³⁹ It was first implemented in the early 1980s but is now combined with effective induction agents to induce remissions of several years.^{39, 42, 43} First-line treatment options for patients with newly diagnosed MM are largely determined by ASCT eligibility criteria.^{42, 44} ASCT, with induction and maintenance therapy, is the preferred regimen in those who are eligible.^{25, 44} However, patients who have high-risk disease characteristics, such as frailty, certain genetic markers, or extramedullary disease (EMD), may not be eligible for ASCT.⁴²⁻⁴⁴ In either case, the primary goals of induction therapy for all patients are to gain rapid control of the disease and obtain the deepest remission possible, with particular consideration given to HRQoL, tolerability, and duration of treatment for patients who are ineligible.⁴³ Induction therapy may consist of various combinations of chemotherapies, IMiDs, PIs, mAbs, steroids, and other targeted treatments depending on patient and disease characteristics.^{42, 43}

2.3.1.2 Immunomodulatory drugs (IMiDs)

Three IMiDs (thalidomide, lenalidomide, and pomalidomide) are currently approved by the US FDA for the treatment of MM. These drugs not only demonstrate direct cytotoxic effects, but also enhance the activity of cytotoxic T cells and NK cells and disrupt the myeloma bone marrow microenvironment.^{45, 46}

First approved in 2006,³² thalidomide is the least potent of the approved IMiDs and is hampered by low tolerability due to adverse events including potentially permanent nerve damage and peripheral neuropathy.⁴⁵ Nevertheless, thalidomide is still used to treat both newly diagnosed MM (NDMM) and RRMM, although in the US its use is largely limited to patients who no longer respond to lenalidomide.⁴⁵

Lenalidomide in combination with dexamethasone was approved for the treatment of RRMM in 2006 and of NDMM in 2015.³³ Lenalidomide shows activity in patients who received prior thalidomide and is a key part of current SOC treatment due to its improved PFS and tolerability.^{45, 46}

The most recently approved IMiD is pomalidomide, which was approved in 2013 for the treatment of RRMM in patients who received ≥ 2 prior lines of therapy, including bortezomib and lenalidomide.³⁴ Metabolized in the liver, pomalidomide does not accumulate in patients with renal insufficiency, but has an increased likelihood of drug-drug interactions.⁴⁵

2.3.1.3 Proteasome inhibitors (PIs)

Proteasome inhibition leads to accumulation of misfolded proteins in the endoplasmic reticulum. The resulting cellular stress leads to a disruption in proliferative signals and cell cycle regulation, causing apoptosis. PIs may enact this effect through different MOAs depending on the target proteasomal subunit(s).⁴⁷

Bortezomib was the first approved PI in 2003 and quickly become a component of SOC therapy, currently indicated for patients with MM at any stage of treatment.^{35, 47} Carfilzomib was approved as a monotherapy for patients who had received at least 1 prior therapy in 2012.^{36, 47} It was later approved in combination with lenalidomide and dexamethasone in 2016 for those who received 1–3 prior lines.⁴⁸ Ixazomib also received approval in combination with lenalidomide and dexamethasone in 2015 for patients who had previously received at least 1 prior line of therapy.³⁷

2.3.1.4 Monoclonal antibodies (mAbs)

Monoclonal antibodies induce immune-mediated tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis of MM cells.^{45, 49, 50} Therapeutic mAbs can also exert their effects through additional mechanisms that may be target-antigen specific or otherwise unique to the product.⁵⁰

Elotuzumab is a humanized mAb targeting SLAMF7 and was approved for the treatment of RRMM in 2015.^{40, 45, 49} Elotuzumab enhances NK cell activity by engaging SLAMF7 and is often used in combination with IMiDs and PIs.⁴⁵

Daratumumab targets CD38 and has been shown to exert an off-target effect resulting in depletion of CD38+ Tregs and increase in cytotoxic, helper, and memory T cells.^{45, 49, 50} Following accelerated approval in 2015 for the treatment of RRMM, daratumumab was subsequently approved for NDMM in both transplant-eligible and transplant-ineligible patients.⁴¹ Daratumumab is currently available in intravenous and subcutaneous formulations; the subcutaneous formulation is generally preferred by patients and HCPs.⁴⁹

Like daratumumab, isatuximab targets CD38, although it targets a different amino acid sequence, and can induce direct apoptosis without cross-linking.^{45, 49} Isatuximab is approved in combination with pomalidomide and dexamethasone for patients with MM who received ≥ 2 prior therapies, including lenalidomide and PI, and in combination with carfilzomib and dexamethasone in patients with MM who received 1–3 prior lines of therapy.³⁸

2.3.2 *Other mechanisms of action*

2.3.2.1 Selinexor

Treatment with Selinexor, a selective inhibitor of nuclear export (SINE), results in retention of oncoprotein RNA and tumor-suppressor proteins in the nucleus. In the presence of steroids, it also induces the glucocorticoid receptor, suppressing the expression of oncoproteins such as Myc and cyclin D. In July 2019, Selinexor became the first approved SINE for patients with RRMM who previously received ≥ 4 prior lines of therapy and whose disease is refractory to ≥ 2 PIs, ≥ 2 IMiDs, and an anti-CD38 mAb.^{51, 52}

2.3.2.2 Chimeric antigen receptor (CAR)-T cell therapies

Chimeric antigen receptor-T cell therapies target cell-surface antigens on MM cells, with the potential to confer long-lived immunity against the target antigen after a single infusion.⁵³ To produce CAR-T cells, patients must undergo leukapheresis. T cells are then separated from leukocytes, activated, genetically modified, and expanded, before being infused back into the patient.^{54, 55}

Idecabtagene vicleucel is a CAR-T cell therapy targeting BCMA, a target that is expressed on the surface of normal and malignant plasma cells.^{31, 56} Antigen-specific activation of idecabtagene vicleucel results in CAR-positive T-cell proliferation, cytokine secretion, and cytolytic killing of BCMA-expressing cells, and in March 2021, idecabtagene vicleucel was approved for the treatment of patients with RRMM who received at least 4 prior lines of therapy, including a PI, an ImiD, and an anti-CD38 mAb.^{31, 56}

In February 2022, a second CAR-T cell therapy targeting BCMA, ciltacabtagene autoleucel, was approved for the treatment of patients with RRMM who received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb.^{30, 57} The ciltacabtagene autoleucel CAR binds to BCMA-expressing cells and eliminates target cells via T-cell activation and expansion.^{30, 57, 58}

2.3.2.3 T-cell redirectors

T-cell redirectors are a novel class of MM therapy, including single-chain variable fragment (scFv)-based bispecific antibody constructs (eg, bispecific T-cell engagers [BiTE][®]), and full-size, IgG-like bispecific antibodies (eg, TECVAYLI).⁵⁹ Both constructs exert their effects by simultaneously binding to an antigen on a T cell and malignant cell to bring them into close proximity, facilitating T-cell activation and subsequent lysis of malignant cells.⁵⁹⁻⁶¹ Unlike scFv-based constructs, full-size antibodies include an Fc domain, resulting in a more stable construct and longer half-life, which may allow for less frequent dosing (**Figure 2**).^{59, 62, 63}

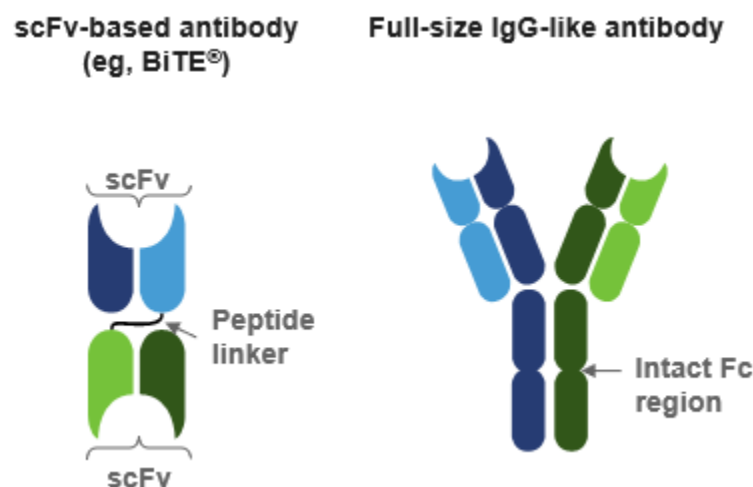


Figure 2. Structure of scFv-based vs full-size bispecific antibodies.⁵⁹