2 Background

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

MM is a hematologic cancer affecting antibody-producing plasma cells.[3,4] Despite advancements in MM treatment options in recent decades, MM remains incurable.[5,6] It is a complex and heterogenous malignancy associated with significant morbidity and mortality.[3,7,8] MM affects multiple organ systems, leading to an array of disabling and painful symptoms that can severely impact quality of life.[7,9-11] These include bone disease, blood disorders, frequent infections, fatigue, neurological effects, and renal impairment.[7,9-13]

MM is the second-most common hematologic malignancy and accounts for 1.8% of all cancers in the United States.[14] In 2023, it was estimated that 35,730 new cases of MM would be diagnosed, and 12,590 deaths due to MM will occur in the United States alone.[14] The overall incidence of MM has remained fairly constant, and death rates are high, with a 5-year relative survival rate of only 59.8%.[14] 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.[7,14]

Although therapeutic advancements have begun to improve outcomes overall, most patients continue to experience cycles of remission and relapse, requiring further treatment.[6,15,16] Each remission period is typically shorter than the last as the tumor becomes more aggressive because of selective pressures and genomic instability, ultimately driving disease progression.[4,17] Therefore, MM becomes increasingly difficult to treat with each relapse. 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 1 treatment but do not respond or stop responding have RRMM.[19] As patients progress through successive lines of therapy, treatment selection becomes increasingly limited as they exhaust all available therapeutic options.[16] This is particularly problematic for those who become triple-class exposed (TCE), having previously received treatment with a PI, an IMiD, and an anti-CD38 mAb, which comprise the majority of current standard-of-care (SOC) therapies for patients with MM.[15,16,20] Data from 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 RRMM who were refractory to an anti-CD38 mAb.[21] Results from 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 in the LocoMMotion study, 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 producing deeper and more durable responses at any point in a patient's treatment course.[4,9,22,23] TECVAYLI offers a novel therapeutic approach for the treatment of TCE RRMM as the first approved BCMA×CD3 bispecific antibody, with weight-based dosing and longest study follow-up of any bispecific antibody in MM, offering a chance for deep and durable responses with a tolerable safety profile. At median 30.4-month follow-up (clinical cut-off: August 22, 2023), 104/165 patients responded, giving an overall response rate (ORR) of 63%. Responses were deep: 98 (59.4%)

patients achieved a very good partial response or better (≥VGPR), and 76 (46.1%) patients achieved complete response or better (≥CR).[24]

2.2 Pathophysiology of multiple myeloma

Healthy plasma cells arising from normal B-cell development produce antibodies to recognize and neutralize harmful antigens.[25] Mechanisms underlying these processes are prone to genetic aberrations, giving rise to malignant plasma cells.[3,8] 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:[13]

- **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.[26]
- **R**enal failure. Renal disease impacts ~20–50% of patients with MM. It can be caused by excessive light chain production and hypercalcemia, cast nephropathy, dehydration, and amyloidosis.[27]
- **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.[26]
- **B**one lesions. Over 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.[28]

MM can also have neurological effects, including peripheral neuropathy, cranial nerve palsies, metabolic encephalopathies, and compression or displacement of nerves in the spinal cord because of infiltrating malignant plasma cells and accumulation of M protein.[12,29,30]

2.3 Therapeutic landscape in multiple myeloma

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 immunotherapies and cellular therapies that will begin to shape a new SOC in the coming years.

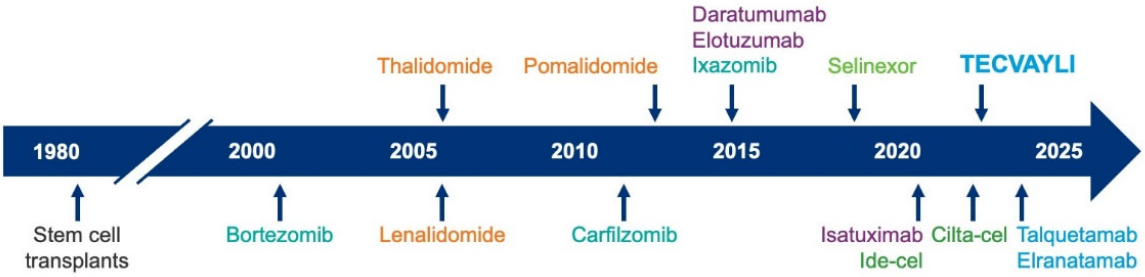

Figure 1: Timeline of the MM therapeutic landscape.[1,31-46] PIs are shown in teal, IMiDs in orange, mAbs in purple, CAR-T cell therapies in dark green, SINEs in light green, and bispecific antibodies in blue.

2.3.1 Current standard 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 re-infusion of stem cells to restore normal bone marrow function.[40] It was first implemented in the early 1980s but is now combined with effective induction agents to induce remissions of several years.[40,47,48] First-line treatment options for patients with newly diagnosed MM are largely determined by ASCT eligibility criteria.[47] ASCT, with induction and maintenance therapy, is the preferred regimen for patients who are eligible.[26] However, patients who have high-risk disease characteristics, such as frailty, certain genetic markers, or extramedullary disease (EMD), may not be eligible for ASCT.[47,48] 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; in patients who are ineligible for ASCT, particular consideration is given to health-related quality of life (HRQoL), tolerability, and duration of treatment.[48] Induction therapy may consist of various combinations of chemotherapies, IMiDs, PIs, mAbs, steroids, and other targeted treatments depending on the patient and disease characteristics.[47,48]

2.3.1.2 Immunomodulatory drugs

Three IMiDs (thalidomide, lenalidomide, and pomalidomide) are currently approved by the US Food and Drug Administration (FDA) for the treatment of MM. These drugs not only demonstrate direct cytotoxic effects but also enhance the activity of cytotoxic T cells and natural killer cells and disrupt the myeloma bone marrow microenvironement.[49,50]

TECVAYLI® (teclistamab-cqyv) US Prix Galien submission. June 30, 2024.

First approved in 2006,[33] thalidomide is still used to treat both newly diagnosed MM (NDMM) and RRMM, although in the United States, its use is largely limited to patients who no longer respond to lenalidomide.[49]

Lenalidomide in combination with dexamethasone was approved for the treatment of RRMM in late 2005 and of NDMM in 2015.[34,50] Lenalidomide shows activity in patients who have received prior thalidomide and is a key part of current SOC treatment due to its improvements in progression-free survival (PFS) and better tolerability vs previously approved IMiDs.[49,50]

The most recently approved IMiD is pomalidomide, which was approved in 2013 for the treatment of RRMM in patients who received at least 2 prior lines of therapy including bortezomib and lenalidomide.[35]

2.3.1.3 Proteasome inhibitors

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).[51]

The first PI, bortezomib, was approved in 2003. It quickly became a component of SOC therapy, and is currently indicated for patients with MM at any stage of treatment.[36,51] In 2012, carfilzomib was approved as a monotherapy for patients who had received at least 1 prior therapy.[37,51] It was later approved in combination with lenalidomide and dexamethasone in 2016 for patients who had received 1–3 prior lines of therapy.[52] 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.[38]

2.3.1.4 Anti-CD38 monoclonal antibodies

mAbs induce immune-mediated tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis of MM cells.[49,53,54] Therapeutic mAbs can also exert their effects through additional mechanisms that may be target antigen–specific or unique to the product.[54]

Daratumumab targets CD38 and has been shown to exert off-target effects resulting in depletion of CD38+ regulatory T cells (Tregs) and an increase in cytotoxic, helper, and memory T cells.[49,53,54] Following accelerated approval in 2015 for the treatment of RRMM, daratumumab was subsequently approved for NDMM in both transplant-eligible and transplant-ineligible patients.[42] Daratumumab is currently available in intravenous and subcutaneous formulations; the subcutaneous formulation is generally preferred by patients and healthcare professionals.[53]

Like daratumumab, isatuximab targets CD38, although it targets a different amino acid sequence and can induce direct apoptosis without cross-linking.[49,53] Isatuximab is approved in combination with pomalidomide and dexamethasone for patients with MM who have received at least 2 prior therapies including lenalidomide and a PI, and it is also approved in combination with carfilzomib and dexamethasone for patients with MM who have received 1–3 prior lines of therapy.[39]

2.3.1.5 Chimeric antigen receptor (CAR)-T cell therapies

CAR-T cell therapies target cell-surface antigens on MM cells and have the potential to confer long-lived immunity against the target antigen after a single infusion.[55] 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.[56,57]

Idecabtagene vicleucel (ide-cel) is a CAR-T cell therapy targeting BCMA, a target that is highly expressed on the surface of malignant plasma cells.[32,58] Antigen-specific activation of ide-cel results in CAR-positive T-cell proliferation, cytokine secretion, and cytolytic killing of BCMA-expressing cells. In March 2021, ide-cel was approved for the treatment of patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.[32,58] In April 2024, ide-cel was approved for the treatment of patients with RRMM who have received at least 2 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.[59]

In February 2022, a second CAR-T cell therapy targeting BCMA, ciltacabtagene autoleucel (cilta-cel), was approved for the treatment of patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.[31,60] In March 2024, cilta-cel was approved for the treatment of patients with RRMM who have received at least 1 prior line of therapy including a PI and an IMiD and who are refractory to lenalidomide.[61] The cilta-cel CAR binds to BCMA-expressing cells and eliminates target cells via T-cell activation and expansion.[31,60,62]

2.3.1.6 T-cell redirectors

T-cell redirectors are a newer class of MM therapy, including full-size immunoglobulin G (IgG)-like bispecific antibodies, such as TECVAYLI.[63] Bispecific antibodies exert their effects by simultaneously binding to an antigen on a T cell and a malignant cell to bring them into close proximity, facilitating T-cell activation and subsequent lysis of malignant cells.[63-65] 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**).[63,66,67]

In October 2022, TECVAYLI became the first approved BCMA-targeting bispecific antibody for the treatment of patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb in the United States, and was approved in the EU for patients who have received at least 3 prior lines of therapy.[1,2]

Elranatamab, a BCMA-targeting bispecific antibody, was approved in the United States in August 2023 for the treatment of patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb.[46] Also in August 2023, talquetamab became the first approved bispecific antibody targeting G protein–coupled receptor family C group 5 member D (GPRC5D) for the treatment of patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb.[43] Both elranatamab and talquetamab are approved under accelerated approval based on response rate and durability of response, and continued approval may be contingent upon further verification of clinical benefits within clinical trials.

Figure 2: Structure of bispecific antibodies.[63] IgG, immunoglobulin G.

2.3.1.7 Other therapies

Elotuzumab is a humanized mAb targeting SLAMF7 and was approved for the treatment of RRMM in 2015.[41,49,53] Elotuzumab enhances natural killer cell activity by engaging SLAMF7 and is often used in combination with IMiDs and PIs.[49]

In July 2019, selinexor became the first approved selective inhibitor of nuclear export (SINE) for patients with RRMM who have previously received at least 4 prior lines of therapy and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb.[68,69] Treatment with selinexor, a 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.