

## 2 Background

### 2.1 MM remains a devastating disease with a significant unmet clinical need

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

MM is the second-most common hematologic malignancy and accounts for 1.8% of all cancers in the USA.<sup>14</sup> 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 USA alone.<sup>14</sup> 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%.<sup>14</sup> 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.<sup>7,14</sup>

Although therapeutic advancements have begun to improve outcomes overall, most patients continue to experience cycles of remission and relapse, requiring further treatment.<sup>6,15,16</sup> 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.<sup>4,17</sup> 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.<sup>18</sup>

Patients who received at least 1 treatment but do not respond or stop responding have RRMM.<sup>19</sup> As patients progress through successive lines of therapy, treatment selection becomes increasingly limited as they exhaust all available therapeutic options.<sup>16</sup> 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.<sup>15,16,20</sup> 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.<sup>21</sup> 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.<sup>20</sup> 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.<sup>20</sup> 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.<sup>4,9,22,23</sup> TECVAYLI offers a novel therapeutic approach for the treatment of RRMM as the only approved B-cell maturation antigen (BCMA)×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule that leads to deep and durable responses with manageable toxicity.

## 2.2 Pathophysiology of MM

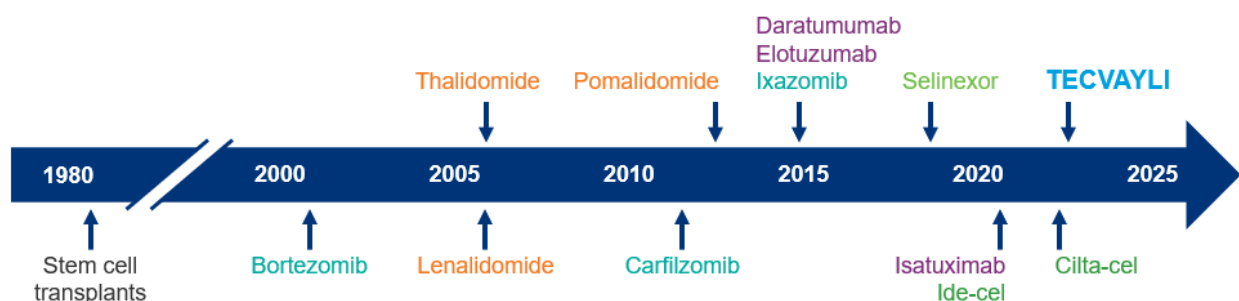
Healthy plasma cells arising from normal B-cell development produce antibodies to recognize and neutralize harmful antigens.<sup>24</sup> Mechanisms underlying these processes are prone to genetic aberrations, giving rise to malignant plasma cells.<sup>3,8</sup> MM is characterized by uncontrolled proliferation 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.<sup>4,17</sup> Collectively, the diverse clinical manifestations of MM are known as CRAB features:<sup>13</sup>

- **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.<sup>25</sup>
- **R**enal failure. Renal disease impacts ~20–50% of patients with MM. It can be caused by excessive light chain production and hypercalcemia, cast neuropathy, dehydration, and amyloidosis.<sup>26</sup>
- **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.<sup>25</sup>
- **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.<sup>27</sup>

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.<sup>12,28,29</sup>

## 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**<sup>1,30-41</sup>

PIs are shown in teal, IMiDs in orange, mAb in purple, CAR-T cell therapies in dark green, SINEs in light green, and bispecific antibodies (TECVAYLI) in blue.

### 2.3.1 Current SOC

#### 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.<sup>39</sup> It was first implemented in the early 1980s but is now combined with effective induction agents to induce remissions of several years.<sup>39,42,43</sup> First-line treatment options for patients with newly diagnosed MM are largely determined by ASCT eligibility criteria.<sup>42</sup> ASCT, with induction and maintenance therapy, is the preferred regimen for patients who are eligible.<sup>25</sup> However, patients who have high-risk disease characteristics, such as frailty, certain genetic markers, or extramedullary disease, may not be eligible for ASCT.<sup>42,43</sup> 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.<sup>43</sup> Induction therapy may consist of various combinations of chemotherapies, IMiDs, PIs, mAbs, steroids, and other targeted treatments depending on the patient and disease characteristics.<sup>42,43</sup>

#### 2.3.1.2 IMiDs

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 microenvironment.<sup>44,45</sup>

First approved in 2006,<sup>32</sup> thalidomide is the least potent of the approved IMiDs and is hampered by low tolerability because of adverse events (AEs), including potentially permanent nerve damage and peripheral neuropathy.<sup>44</sup> Nevertheless, thalidomide is still used to treat both newly diagnosed MM (NDMM) and RRMM, although in the USA, its use is largely limited to patients who no longer respond to lenalidomide.<sup>44</sup>

Lenalidomide in combination with dexamethasone was approved for the treatment of RRMM in late 2005 and of NDMM in 2015.<sup>33,45</sup> Lenalidomide shows activity in patients who have received prior thalidomide and is a key part of current SOC treatment due to its improved PFS and tolerability.<sup>44,45</sup>

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.<sup>34</sup> Metabolized in the liver, pomalidomide does not accumulate in patients with renal insufficiency, but it does have an increased likelihood of drug-drug interactions.<sup>44</sup>

#### 2.3.1.3 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).<sup>46</sup>

TECVAYLI™ (teclistamab-cqyv) US Prix Galien submission. June 26, 2023.

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.<sup>35,46</sup> In 2012, carfilzomib was approved as a monotherapy for patients who had received at least 1 prior therapy.<sup>36,46</sup> It was later approved in combination with lenalidomide and dexamethasone in 2016 for patients who had received 1–3 prior lines of therapy.<sup>47</sup> 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.<sup>37</sup>

#### **2.3.1.4 mAbs**

mAbs induce immune-mediated tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis of MM cells.<sup>44,48,49</sup> Therapeutic mAbs can also exert their effects through additional mechanisms that may be target-antigen specific or unique to the product.<sup>49</sup>

Elotuzumab is a humanized mAb targeting SLAMF7 and was approved for the treatment of RRMM in 2015.<sup>40,44,48</sup> Elotuzumab enhances natural killer cell activity by engaging SLAMF7 and is often used in combination with IMiDs and PIs.<sup>44</sup>

Daratumumab targets CD38 and has been shown to exert an off-target effect resulting in depletion of CD38+ Tregs and an increase in cytotoxic, helper, and memory T cells.<sup>44,48,49</sup> Following accelerated approval in 2015 for the treatment of RRMM, daratumumab was subsequently approved for NDMM in both transplant-eligible and transplant-ineligible patients.<sup>41</sup> Daratumumab is currently available in intravenous and subcutaneous formulations; the subcutaneous formulation is generally preferred by patients and healthcare professionals.<sup>48</sup>

Like daratumumab, isatuximab targets CD38, although it targets a different amino acid sequence and can induce direct apoptosis without cross-linking.<sup>44,48</sup> 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.<sup>38</sup>

### **2.3.2 Different 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 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.<sup>50,51</sup>

#### **2.3.2.2 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.<sup>52</sup> 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.<sup>53,54</sup>

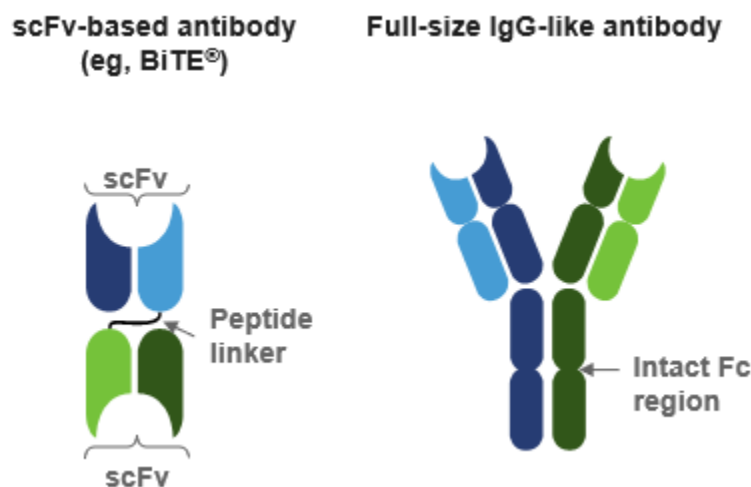
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Idecabtagene vicleucel (ide-cel) is a CAR-T cell therapy targeting BCMA, a target that is highly expressed on the surface of malignant plasma cells.<sup>31,55</sup> Antigen-specific activation of ide-cel results in CAR-positive T-cell proliferation, 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.<sup>31,55</sup>

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.<sup>30,56</sup> The cilta-cel CAR binds to BCMA-expressing cells and eliminates target cells via T-cell activation and expansion.<sup>30,56,57</sup>

### 2.3.2.3 T-cell redirectors

T-cell redirectors are a novel class of MM therapy. They include single-chain variable fragment (scFv)-based bispecific antibody constructs, such as bispecific T-cell engagers (BiTE®), and full-size immunoglobulin G-like bispecific antibodies, such as TECVAYLI.<sup>58</sup> Both constructs 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.<sup>58-60</sup> 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**).<sup>58,61,62</sup>



**FIGURE 2: Structure of scFv-based vs full-size bispecific antibodies<sup>58</sup>**