2 Background

Summary statement

Multiple myeloma is a hematologic malignancy characterized by the uncontrolled proliferation of plasma cells and overproduction of abnormal immunoglobulins. In 2023, an estimated 35,730 new MM cases and 12,590 deaths were reported in the U.S. MM primarily affects the elderly, with a median diagnosis age of 69 and a median age of 75 at death. Considered to be incurable, MM carries a high symptom burden and a 5-year relative survival rate of 59.8%.

MM is a complex disease characterized by genomic heterogeneity; the genetic aberrations that arise lead to treatment resistance and disease progression, with many patients exhausting the most effective agents early in treatment. Moreover, infections are a leading cause of mortality in MM due to both disease- and treatment-related immune suppression. Overall, real-world studies have found a median survival of only 12.4 months once patients have been exposed to the standard classes of therapy (proteasome inhibitors [PIs], immunomodulatory drugs [IMiDs], and anti-CD38 antibodies). The introduction of B cell maturation antigen (BCMA)-targeted T-cell–redirecting immunotherapies for patients with relapsed and refractory MM, including chimeric antigen receptor (CAR)-T cell therapies and bispecific antibodies, have significantly expanded the treatment landscape of MM. However, manufacturing CAR-T cells takes several weeks, and BCMA-targeted bispecifics have been associated with a high risk of severe infections, which is a significant cause of mortality in patients with MM. Those treated with a BCMA-targeted therapy also tend to have poor outcomes when treated with a second BCMA-targeted therapy, and outcomes continue to decline with each successive treatment. Available therapies with novel therapeutic targets are therefore critical to improve outcomes in heavily pretreated patients.

TALVEY™, with its novel GPRC5D target, high response rates in difficult-to-treat patients, and versatility in combination regimens, shows potential to address unmet needs in MM.

2.1 Despite recent advancements that have improved outcomes, most patients with MM become refractory to treatments and eventually relapse

2.1.1 Epidemiology

MM is a hematologic cancer in which antibody-producing plasma cells excessively proliferate and overproduce abnormal immunoglobulins.[1-5] The excessive growth and accumulation of abnormal immunoglobulins affects multiple organ systems leading to complications including bone disease, blood disorders, frequent infections, fatigue, neurological effects, and renal impairment.[6-11]

In the US, MM accounts for 1.8% of all new cancer cases, with an estimated 35,730 new cases diagnosed in 2023 and 12,590 MM-related deaths.[12] 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. In the US, men are approximately 1.5 times more likely to be diagnosed than women, and the incidence of MM in male patients who are Black is almost double that of male patients of all races (16.8 vs 8.7 cases per 100,000 persons). Black males also have higher mortality rates compared with male patients of all ethnicities with MM (death rate of 7.3 vs 3.9 per 100,000 persons).[12]

MM is associated with significant morbidity and mortality, which is reflected by the 5-year relative survival rate of 59.8% for patients with MM.[12] Infections are a leading cause of the observed morbidity and mortality in patients with MM due to a combination of the cumulative effect of the disease, host-related factors, and treatment-related immunosuppression.[13,14] MM has the highest disease burden of all hematological cancers, with pain and fatigue among the largest contributors to poor quality of life.[8,15] Patients with newly diagnosed MM have poor health-related quality of life (from the MM disease itself), which significantly worsens in patients with relapsed/refractory disease (RRMM).[10] In addition, many MM treatments contribute to poor patient health-related quality of life due to demanding treatment administration and monitoring schedules.[9,16-18]

2.1.2 Symptom burden

Disruptions within the bone marrow microenvironment due to proliferating malignant plasma cells and excessive accumulation of abnormal antibodies, or M protein,[6] may cause a variety of disabling, painful, and potentially life-threatening symptoms. Common symptoms include bone pain and fractures, cytopenia, renal failure, neurologic symptoms, and increased risk of infection, all of which can severely impact a patient's quality of life.[8-11] Moreover, while plasma cell proliferation is restricted to bone marrow in most patients at diagnosis, a subset of patients will develop soft-tissue plasmacytomas that have no contact with bony structures. Typical sites of such extramedullary disease (EMD) include the liver, kidneys, lymph nodes, central nervous system, breast, pleura, and pericardium.[19] EMD is an aggressive form of MM, with patients often presenting with high-risk genetic features, increased proliferation capacity, evasion of apoptosis, and resistance to standard therapies.[20] Patients with EMD typically experience substantially poorer outcomes than typical MM patients.

In bone, MM may present as hypercalcemia, painful lytic lesions, pathologic fractures, and spinal cord compression, with osteolytic bone disease affecting 79% of patients.[11] Bone lesions not only result in compromised mobility and independence due to the most debilitating manifestation of MM, ie, bone pain,[21] but are also associated with decreased survival rates.[22]

Disruptions to the bone marrow microenvironment can result in cytopenia, which is associated with fatigue, frequent infections, and clotting disorders. Nearly all patients with MM experience anemia at some point in the disease.[22]

The overproduction of abnormal antibodies and free light chains produced by plasmacytomas, along with hypercalcemia, can lead to complications such as cast nephropathy, amyloidosis, dehydration, and renal failure.[23]

Neurologic symptoms, including peripheral neuropathy, cranial nerve palsies, metabolic encephalopathies, and compression or displacement of nerves in the spinal cord,[24] may result from infiltrating plasmacytomas and the accumulation of M protein.[7,25,26]

Patients with MM are also at increased risk of infection due to multifactorial immunodeficiency.[13] Complications associated with infections remain the leading cause of death in myeloma, and up to 10% of myeloma patients die within 60 days after diagnosis.[27] Disease-related deficits in the immune system and patient-related factors, such as tumor burden and the cumulative effects of previous therapy on the immune system, contribute to the risk of infections.[13]

2.2 Most patients relapse and mortality is high

MM is a complex disease characterized by genomic heterogeneity.[4,11,28] The genetic aberrations frequently arise through branching pathways, leading to clonal evolution that drives treatment resistance and disease progression, even in patients with previously deep responses to therapy.[29]

Despite advances in treatment options, patients continue to experience cycles of remission and relapse on standard therapies,[2,30-32] with each remission period typically shorter than the last and each successive relapse with a poorer prognosis.[5,33,34] Further improvements in treatment options remain necessary. The recent advances beyond standard treatments (ie, PIs, IMiDs, anti-CD38 antibodies) include selinexor, a selective inhibitor of nuclear export protein[35,36] and therapies targeting BCMA such as antibody-drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptor (CAR)-T cell therapies.[37-42] Selinexor and belantamab, a BCMA-targeted ADC, have demonstrated relatively low overall response rates (ORRs) in patients with RRMM (30% and 26%, respectively)[35,36], and ORRs for BCMA-targeted bispecific and CAR-T therapies are ~60%.[37-42] As the efficacy of therapies decline over each successive treatment, risk of therapy discontinuation increases, comorbidities become more common, and treatment-related toxicities accumulate.[40,43,44] Data from electronic medical records and claims databases suggest that 56–74% of patients are not treated beyond the second line of therapy and fewer than 1 in 5 are treated by the fourth line.[43,45]

Due to the lack of standard of care in this heavily treated patient population, novel therapeutic targets along with appropriate sequencing approaches including new combination regimens are needed to expand treatment options and improve outcomes. TALVEY™, with its novel GPRC5D target, high ORR (≥70%), and versatility in combination regimens, can potentially fill the unmet need in this patient population.[46]

2.2.1 Lack of standard of care in patients with RRMM

Many patients exhaust the most effective agents early in treatment, resulting in multi-drug resistance[47-49]; therefore, treatment selection becomes increasingly limited as patients progress through successive lines of therapy.[50] For example, many patients with RRMM may be nonresponsive to the anti-CD38 antibody daratumumab and the PI lenalidomide because of their widespread use in early lines of therapy. Patients who have relapsed after treatment with the 3 standard classes of therapy (a PI, an IMiD, and/or an anti-CD38 antibody) are said to be triple-class exposed. These patients have a short median progression-free survival (PFS) of 3–5 months and a median overall survival (OS) of <15 months, highlighting the need for novel treatment options to halt disease progression and improve patient survival and quality of life.[33,51-56] Real-world analysis of treatment patterns in patients with triple-class exposed RRMM show that the regimens patients receive are highly heterogeneous[52]; in the LocoMMotion study, 92 unique treatment regimens were received by 248 patients.[51] The lack of standard of care and unmet need in these patients can potentially be addressed with new therapeutic agents along with approaches to incorporate prior therapies into new, complementary, multi-target combination regimens to achieve improved responses and survival outcomes.

The introduction of a number of BCMA-targeted T-cell–redirecting immunotherapies for patients with RRMM over the past several years, including 2 approved CAR-T cell therapies and 3 approved bispecific antibodies, have further expanded the treatment landscape of MM. However, novel treatments are needed for patients who will become resistant to these therapies

and eventually relapse.[57-59] In clinical studies, half of patients treated with BCMA-directed therapy progressed after 9 months with ide-cel, after 11–17 months with a bispecific antibody therapy, and after 33 months with cilta-cel.[39,60-62] Evidence suggests that patients who have received a BCMA-targeted therapy have worse outcomes when treated with a second BCMA-targeted therapy.[63] Additionally, BCMA-targeting T-cell–redirecting therapies may cumulatively increase the risk of infection through on-target, off-tumor effects, including the elimination of normal (non-MM) BCMA-expressing plasma cells and the development of neutropenia and hypogammaglobulinemia,[13,14,64-68] adding to the unmet need for new treatment options for patients with triple-class exposed RRMM.

Outcomes are worse for patients with high-risk features, such as EMD (ie, soft-tissue plasmacytomas).[20,69-71] The proportion of patients achieving a response is lower and PFS is shorter in patients with EMD vs typical patients with MM (without EMD).[72] BCMA-targeting CAR-T therapies have improved rates of response in patients with EMD; however, durability of response and PFS with CAR-T therapies were shorter in these patients compared with the overall study population.[73,74] Therefore, additional treatment options and combination regimens are needed to improve survival outcomes in this high-risk patient population.