

2 Background: Why CARVYKTI® is needed

2.1 Multiple Myeloma: A devastating disease with a high unmet need

Multiple myeloma (MM) is a hematologic malignancy that has long been considered to be incurable. In MM cancerous antibody-producing plasma cells excessively proliferate and overproduce abnormal immunoglobulins.¹⁻³ Complications of the disease include osteolytic bone disease, renal failure, blood hyperviscosity, peripheral neuropathy, increased risk of infections, and bone marrow failure.^{1,3,4}

MM accounts for 1.8% of all newly diagnosed cancers in the USA; in 2023 the estimated number of new MM cases is predicted to be 35,730 and the estimated number of deaths due to MM malignancy is predicted to be 12,590.⁵ In 2013–2019, the 5-year relative survival rate in the USA of patients with MM was 59.8%.

Most MM diagnoses are in elderly patients; 32% of new MM cases are in patients aged 65 to 74 years and 33% are in patients aged over 75 years old.⁵ Of note, in the USA, MM disproportionately affects patients who are Black (20% of patients are Black vs ~13% of the general US population),⁶ and men are ~1.5 times more likely than women to be diagnosed.⁵

Unfortunately, most patients with MM will invariably suffer disease relapse after each line of therapy, with the disease becoming non-responsive to more of the existing treatments with each recurrence. Data from real-world studies illustrate the need for effective treatment options for patients who have received many prior treatment lines. These analyses have highlighted the brevity of treatment durations for the first 5 lines of therapy (medians under 5 months)⁷ and the lack of clear standard of care (SOC) treatments for heavily pre-treated relapsed/refractory MM (RRMM). Over 90 different regimens were used in this setting, and progression-free and overall survival were short (less than 5 months and ~9–14 months[depending on drug refractoriness], respectively).^{8,9} Strikingly, 1 study found that about 50% of patients died before beginning their next line of therapy.¹⁰ These observations underscore the rapid exhaustion of available and effective treatment options for patients with MM.

This dire situation is emphasized by real-world data showing that only ~30% of patients with late-stage disease experience treatment response, and the vast majority of those who do have a response retain some tumor burden.^{8,9} The grave nature of MM is further underscored by the high rates of treatment attrition across all lines of therapy including after frontline treatment. After each of the first 4 lines of therapy, a large proportion of patients do not go on to receive a subsequent treatment because of death and loss to follow-up; 57% of patients who do not undergo stem cell transplant are lost to attrition after their first line of therapy, and attrition rates range from 31–46% for both transplant and non-transplant recipients after each of the next 3 lines of therapy.⁷ A potential contributor to these high attrition rates is the deterioration of health-related quality of life with additional lines of therapy.¹¹ The worsening of patient-reported outcomes is, in turn, associated with the pain, fatigue, and reduced physical function that patients experience and the continuous administration of SOC treatments and their side effects.^{11,12}

The great need for treatments that are highly effective in most, if not all, patients with MM and that provide long-lasting clinical benefit is one that has been only somewhat reduced by recently approved therapeutic agents for patients who have already received at least 4 lines of therapy.

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In registrational trials of these new options, the median duration of response ranged from 4.4–18.4 months, and median progression-free survival ranged from 3.7–11.3 months.¹³⁻¹⁵

CARVYKTI has shown deep and durable response in RRMM that can more aptly meet the need for RRMM treatments that are highly effective with appropriate safety management. It can furthermore address the need for new therapies that minimize treatment-associated disease burden to patients and their caregivers.

Alongside its demonstrated safety profile, CARVYKTI provided a median progression-free survival of 34.9 months to patients with heavily pre-treated RRMM¹⁶. Moreover, because CARVYKTI is administered via a one-time infusion, it grants patients a potential treatment-free period.

2.2 Pathophysiology of MM

MM is caused by genetic mutations that arise during the final stages of B-cell development, when cells have differentiated into plasma cells.¹⁷ Consequences of the malignancy are caused by the affected cell type. Plasma cells are an immune cell type that, following activation, is normally highly proliferative and secretes large amounts of immunoglobulins. They include changes to the bone marrow microenvironment⁴ and inflict collateral damage to other tissues and organs that further deteriorate patients' health, function, and quality of life. Among the clinical manifestations of MM are those collectively known as CRAB features:

- **C**alcium levels elevated (hypercalcemia). MM cells secrete factors that disrupt normal bone homeostasis skewing the balance towards osteolysis.^{4,18} Most patients with MM develop osteolytic bone lesions that can lead to high blood calcium levels.⁴
- **R**enal failure. The high levels of monoclonal immunoglobulin secreted by MM cells damage the kidneys. Consequently, renal failure is a frequent complication of MM that is not only associated with significant morbidity but also presents as a challenge for MM treatment.^{3,19}
- **A**nemia. As MM cells proliferate and disrupt the bone marrow microenvironment, cytopenias including anemia, thrombocytopenia, and leukopenia can develop, causing fatigue, shortness of breath, an increase in infection risk, and clotting disorders.^{1,3,20}
- **B**one lesions. The above-mentioned osteolysis causes osteoporosis and well-circumscribed or “focal” osteolytic bone lesions. In addition to hypercalcemia, these lesions are associated with bone pain (70–80%), pathologic fractures (50–60%), spinal cord compression (2–3%), poor mobility, and decreased quality of life.^{2,4}

Blood hyperviscosity is another clinical manifestation that occurs because of the accumulation of monoclonal immunoglobulins. Additionally, MM cells can accumulate in soft tissues and form plasmacytomas that can compromise organ function or cause spinal cord compressions;²¹ they can also create immune-evasive environments that allow malignant cells to escape immune control.²²

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2.3 MM treatment landscape before CARVYKTI®

Many therapeutic agents developed and authorized during the last couple of decades are members of the following drug classes: IMiD, PI, and anti-CD38 monoclonal antibody.

- IMiDs are small molecules that have immunomodulatory properties.²³ The primary IMiDs deployed to treat MM are thalidomide, lenalidomide and pomalidomide.²⁴ Thalidomide and lenalidomide were first indicated for MM in the USA in 2006,^{25,26} and pomalidomide was initially authorized in 2013.²⁷
- PIs are small molecules that inhibit component(s) of the proteasome, intracellular machinery that degrades proteins.²⁸ The class includes bortezomib, carfilzomib, and ixazomib. In 2003, bortezomib was the first PI to be approved for MM in the USA,²⁸ followed by carfilzomib and ixazomib in 2012 and 2015, respectively.^{29,30}
- Anti-CD38 antibodies are monoclonal antibodies that bind CD38, a membrane protein present on immune cells, including B cells, and upregulated on MM cells.^{22,31} Both daratumumab and isatuximab are anti-CD38 antibodies approved in the USA to treat MM. Daratumumab was initially approved in 2015³² and isatuximab in 2020.³³

2.3.1 SOC treatments for early RRMM

In MM, most IMiDs, PIs, and anti-CD38 antibodies were all initially indicated for the treatment of RRMM, in some cases specifically after patients had received other members of these drug classes.^{25-30,32,33} They are being used with increasing frequency at earlier stages in the patient treatment journey including in the first-line setting; notably, lenalidomide is currently used in the earliest lines of therapy, as well as being a mainstay of maintenance regimens.^{24,34,35} Moreover, IMiDs, PIs, and anti-CD38 antibodies are often used in combinations; second-line to fourth-line treatments for RRMM are commonly triplets, and nearly all of the regimens recommended by the National Comprehensive Cancer Network include a representative of one or more of these drug classes.²⁴

Unfortunately, MM is becoming non-responsive to lenalidomide earlier in the treatment journey, including in the second-line setting, because of its widespread use in early lines of therapy.³⁴ Since other IMiDs, as well as PIs and anti-CD38 antibodies, are also being administered at earlier lines of therapy, refractoriness to these agents will likewise manifest earlier in treatment journeys. Coupled with nearly all patients experiencing a relapse along the treatment continuum, there is a growing population of patients with RRMM that does not respond to commonly used SOC treatments.

In fact, recent analyses of real-world data have shown that the vast majority of patients are refractory to at least 1, and often 2 or more, of these agents by the fourth line of therapy. Findings from prospective and retrospective real-world studies have revealed that over 50% of heavily pre-treated patients are refractory to an IMiD, a PI, and/or an anti-CD38 agent. In addition, evidence from these studies showed that patients rapidly reach fourth- and fifth-line treatment, where few effective treatment options remain; real-world data showed low rates of treatment response (less than 35% for the immediate next line of therapy), short median progression-free survival, and short median overall survival.^{8,9}

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Several additions to the second-line to fourth-line treatment landscape in the last ~2 years include new combinations of IMiDs, PIs, and anti-CD38 antibodies, eg, daratumumab-carfilzomib-dexamethasone and isatuximab-carfilzomib-dexamethasone. The registrational trials of these combinations showed that they improved long-term outcomes compared with older, 2-drug combination SOC regimens. However, there remains a need for effective treatments that can be administered after relapse to these 3-drug regimens as patients in these studies only remained on treatment for a median of about 1.3–1.5 years.³⁶⁻³⁹

2.3.2 New drug classes: Fifth-line and later lines of treatment for RRMM

Treatments with new drug targets and mechanisms of action that were introduced to the MM therapeutic landscape shortly before and after CARVYKTI have shown efficacy benefits in registrational trials. New drug targets included exportin 1 and BCMA, and the new treatment modalities were antibody-drug conjugates, bispecific antibodies, and CAR-T cell therapies.^{13,14,40-42} These recently developed therapies are primarily used in later lines of treatment,²⁴ where there remains an urgent need for new therapies that can improve chances for complete response as well as prolong the median durations of response and progression-free survival to beyond 1 year.