2 Background: Why CARVYKTI is needed

2.1 CARVYKTI offers promise for patients with multiple myeloma, a devastating disease with a high unmet need

In patients with MM, a hematologic malignancy, cancerous antibody-producing plasma cells excessively proliferate and overproduce abnormal immunoglobulins. Complications of the disease include osteolytic bone disease, renal failure, blood hyperviscosity, peripheral neuropathy, increased risk of infections, and bone marrow failure.[1-3]

MM accounts for 1.8% of all newly diagnosed cancers in the United States; the estimated number of new MM cases in 2025 is predicted to be 36,110 and the estimated number of deaths due to MM malignancy is predicted to be 12,030. In the United States, the 5-year relative survival rate for patients with MM was 62.4% from 2015 to 2021.[4]

Most patients with MM will suffer disease relapse after each line of therapy, and unfortunately, the treatment landscape after relapse is challenging as the disease quickly becomes nonresponsive to the major drug classes.[5-8] For patients with heavily pretreated RRMM, previous studies reported a median progression-free survival of <6 months and median overall survival of ~1 year.[9,10] CARVYKTI, a BCMA-directed CAR-T cell therapy, led to deep and durable responses in heavily pretreated patients with RRMM in the phase 1b/2 CARTITUDE-1 trial,[11,12] and significantly prolonged progression-free survival and overall survival in patients with lenalidomide-refractory MM after 1–3 prior lines of therapy in the phase 3 CARTITUDE-4 trial.[13,14] Long-term follow-up of the pivotal CARTITUDE-1 study in heavily pretreated RRMM (97% daratumumab refractory) confirmed that one-third (33%) of patients remained in remission for ≥5 years after a single CARVYKTI infusion without maintenance or subsequent therapy. Of these progression-free patients, 12 from a single center with serial minimal residual disease (MRD) assessments were all MRD- and imaging-negative at year 5 or later after CARVYKTI without additional therapy, showing profound long-term remission.[15] These results, combined with the median overall survival of 5 years seen in this study, are remarkable given the historically dismal prognosis for this population with a median overall survival of ~1 year.[9,10,16] No therapies currently approved for the treatment of triple-class exposed/refractory RRMM achieved similar outcomes; moreover, existing regimens typically require ongoing therapy and are often associated with relapse. These data from CARTITUDE-1 represent the longest study follow-up after any CAR-T cell therapy in MM, with a third of patients remaining treatment and progression free for at least 5 years after a single CARVYKTI infusion. Additionally, the potential for long-term remission was not limited to patients with standard-risk disease; patients with high-risk cytogenetics and those with extramedullary plasmacytomas were equally likely to be progression free.[15]

2.2 MM treatment landscape before CARVYKTI

Many therapeutic agents that were 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.[17] The primary IMiDs deployed to treat MM are thalidomide, lenalidomide, and pomalidomide.[18] Thalidomide and lenalidomide were first indicated for MM in the United States in 2006,[19,20] and pomalidomide was initially authorized in 2013.[21]

- PIs are small molecules that inhibit component(s) of the proteasome, intracellular machinery that degrades proteins.[22] This class includes bortezomib, carfilzomib, and ixazomib. In 2003, bortezomib was the first PI to be approved for MM in the United States,[22] followed by carfilzomib and ixazomib in 2012 and 2015, respectively.[23,24]

- Anti-CD38 antibodies are monoclonal antibodies that bind CD38, a membrane protein present on immune cells, including B cells, and upregulated on MM cells.[25,26] Both daratumumab and isatuximab are anti-CD38 antibodies approved in the United States to treat MM. Daratumumab was initially approved in 2015[27] and isatuximab in 2020.[28]

2.2.1 Standard-of-care (SOC) treatments for early RRMM

Most IMiDs, PIs, and anti-CD38 antibodies were initially indicated for the treatment of RRMM.[19-24,27,28] They are being used with increasing frequency at earlier stages in the patient treatment journey, including in the frontline setting; notably, lenalidomide is often used in the earliest lines of therapy and is also a mainstay of maintenance regimens.[18,29,30] Second-line to fourth-line treatments of RRMM are commonly triplet combinations of IMiDs, PIs, and anti-CD38 antibodies, and nearly all of the regimens recommended by the National Comprehensive Cancer Network include a representative of 1 or more of these drug classes.[18]

Unfortunately, MM is becoming nonresponsive to lenalidomide earlier in the treatment journey, including in the second-line setting, because of its widespread use in early lines of therapy.[29] Because other IMiDs, as well as PIs and anti-CD38 antibodies, are also being administered in 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.

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, and dexamethasone; and isatuximab, carfilzomib, and dexamethasone. However, patients with lenalidomide-refractory MM continue to have a poor prognosis.[31]

2.2.2 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, BCMA, and G protein–coupled receptor class C group 5 member D, and the new treatment modalities were antibody-drug conjugates, bispecific antibodies, and CAR-T cell therapies.[32-37] These recently developed therapies are primarily used in later lines of treatment,[18] 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.