3 History of the development of CARVYKTI

3.1 Rationale for the development of CARVYKTI

CARVYKTI is a biepitopic, BCMA-directed, CAR-T cell therapy that has demonstrated deep and durable efficacy in patients with RRMM.[11-13,38-42] BCMA stands out from earlier therapeutic targets as it is selectively expressed by the cell lineage that gives rise to MM, mature B cells and plasma cells, and is upregulated by MM cells.[43-46] BCMA expression by these select cell types may help limit on-target, off-tumor toxicities.

Autologous CAR-T cell therapies are a drug class that gained their first indication in 2017.[47,48] They are immunotherapies that are manufactured by genetically engineering a patient's own T cells to express CARs, which are synthetic antigen-binding receptors that unite key features of T cells with those of antibodies. CAR-T cell therapies combine the effector function of T cells with the ability of antibodies to bind, with high specificity, predefined cell surface molecules without the major histocompatibility complex restriction of T cells.[49-51]

CAR-T cell therapies have the potential for robust effectiveness with a 1-time infusion. Additionally, unlike nontargeted drugs such as chemotherapies, CAR-T therapies can be directed to specifically attack a target commonly expressed on MM cells.

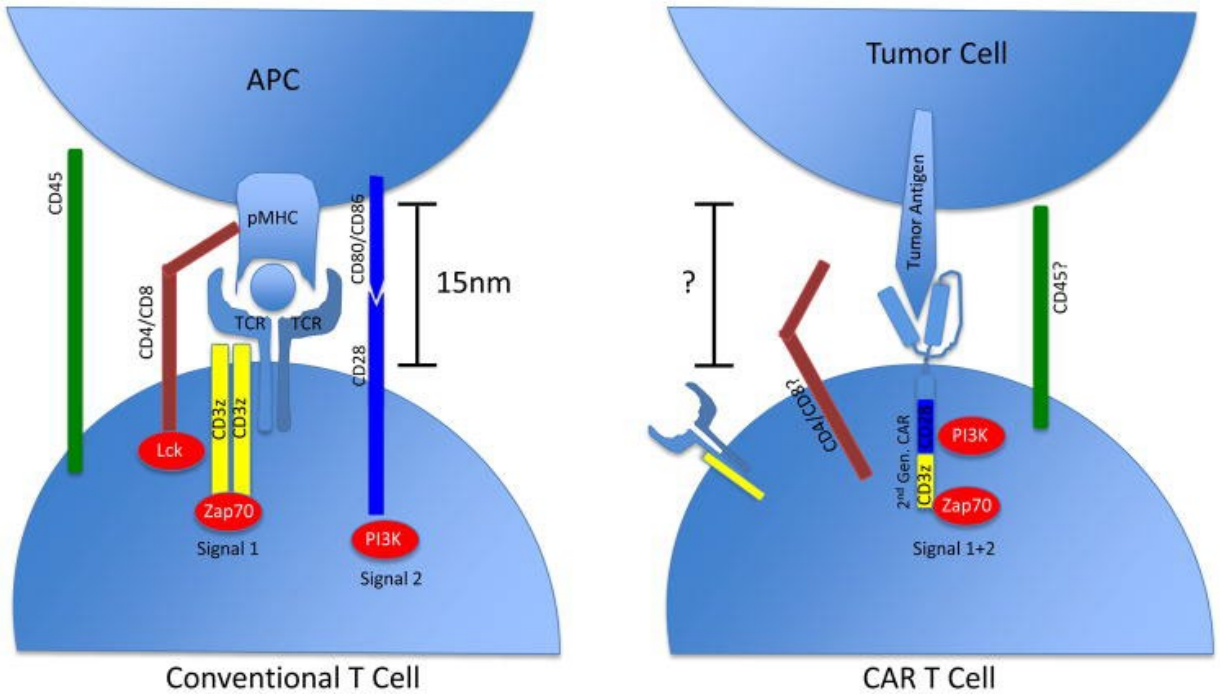

Figure 1: Diagram of conventional T-cell receptor and CAR-T cell receptor (from Srivastava et al. *Trends Immunol*. 2015;36(8):494-502)[51]

3.2 CARVYKTI mechanism of action

CARVYKTI is targeted, via its CAR, to cells with surface expression of BCMA.[38] CAR binding to BCMA activates T-cell programs that mediate killing of recognized cells (ie, MM cells) and T-cell proliferation.[49-51]

CARVYKTI expresses a structurally differentiated CAR that features 2 different extracellular, single-domain llama antibodies that were designed to optimize engagement with BCMA. The CAR also possesses a 4-1BB costimulatory domain and a CD3ζ signaling domain for optimized T-cell activation and proliferation, and a CD8α hinge domain that connects the antigen-binding domain with the costimulatory and signaling domains.[38,52] 4-1BB is also associated with stimulating the generation and proliferation of CD8+ central memory T cells, supported by data showing enrichment of this cell type in the CARVYKTI drug product.[52-56]

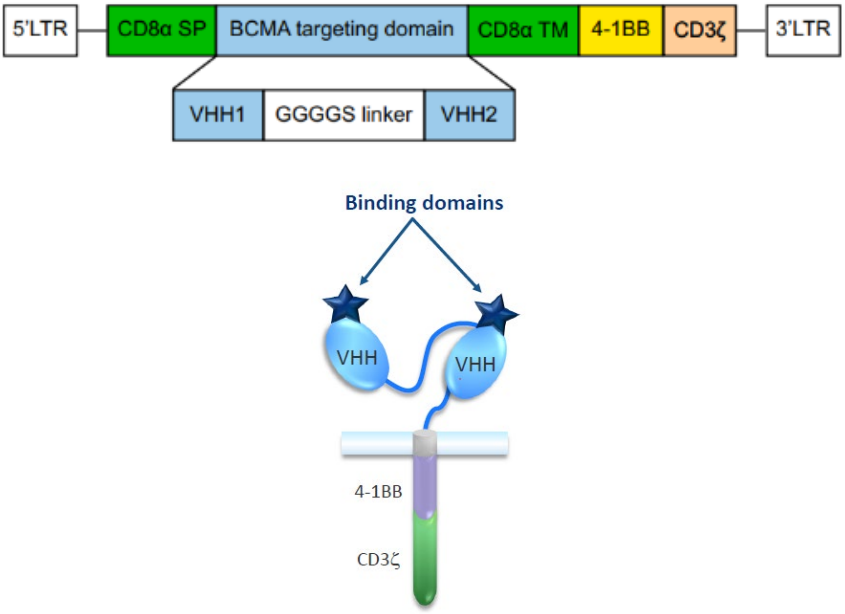

Figure 2: Structure of the CARVYKTI CAR[38,54]

3.3 CARVYKTI clinical development

3.3.1 First-in-human CARVYKTI data

The first clinical data for CARVYKTI were generated in the LEGEND-2 trial (NCT03090659) with LCAR-B38M CAR-T cells. LCAR-B38M is the same CAR construct expressed by CARVYKTI. The phase 1, investigator-initiated study was conducted at 4 institutions in China and evaluated LCAR-B38M CAR-T cells in 74 patients with heavily pretreated RRMM.[38-40]

Data from LEGEND-2 showed high response rates, deep and durable responses, and long-term survival outcomes in patients with heavily pretreated RRMM. In this study, 88% of patients responded to LCAR-B38M CAR-T cells (73% experienced a complete response), and 50% of patients continued to respond to treatment for nearly 2 years. Median progression-free survival

time was 18 months, and 16% of patients remained free of disease after 5 or more years of follow-up. The median overall survival was 55.8 months.[40,41]

3.3.2 CARVYKTI registrational trial data

Following the promising results from LEGEND-2, the phase 1b/2 CARTITUDE-1 trial (NCT03548207)–which served as the basis of United States Food and Drug Administration (FDA) approval of CARVYKTI–was initiated. CARTITUDE-1 enrolled 97 patients in the United States who had received at least 3 prior lines of therapy (median, 6 lines) including a PI, an IMiD, and an anti-CD38 antibody; 88% of patients were refractory to drugs from all 3 of these drug classes at baseline.[11]

Results from the pivotal US cohort of CARTITUDE-1 confirmed the robust efficacy observed in LEGEND-2. In the US cohort, 98% of patients had a treatment response, including 82% who experienced a stringent complete response. Moreover, 92% of patients with evaluable bone marrow samples achieved MRD negativity (10^{-5} sensitivity),[12] which is a predictor of prolonged survival outcomes.[57,58] Additionally, efficacy results at 2 years post CARVYKTI were similar in most patient subgroups, including elderly patients.[59] Longer follow-up revealed that the median duration of response was 33.9 months and median progression-free survival was 34.9 months; median overall survival had not been reached at a median follow-up of 33.4 months.[42] In the most recent analysis, at a median follow-up of 61.3 months, the median overall survival was 60.7 months (95% CI, 41.9–not estimable). Thirty-two (33%) patients remained alive and progression free without further antimyeloma treatment for ≥5 years after CARVYKTI. At a single center, 12 patients in stringent complete response underwent serial MRD and positron emission tomography/computed tomography assessments, and all (100%) were both MRD negative (at least 10^{-5} threshold; 11/12 were MRD negative at 10^{-6} threshold) and imaging-negative at year 5 or later after a single CARVYKTI infusion.[15]

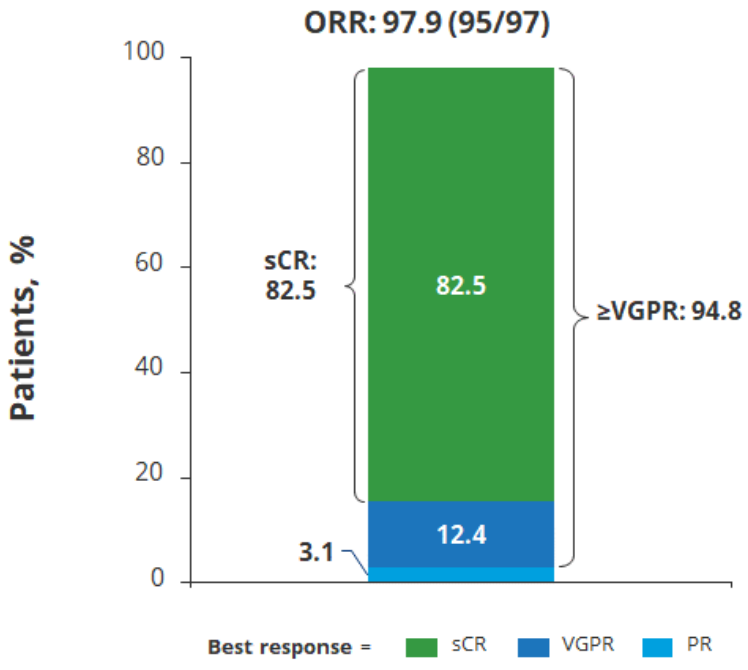

Figure 3: CARVYKTI treatment response rates in CARTITUDE-1 at 27.7-month follow-up[12]

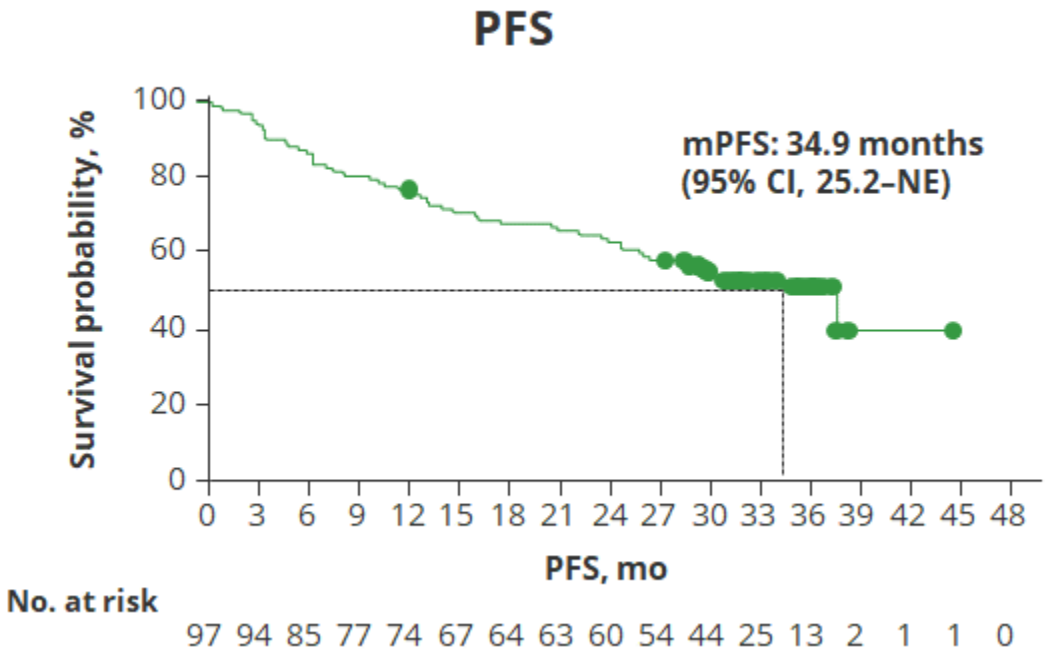

Figure 4: Progression-free survival in CARTITUDE-1 at median 33.4-month follow-up[42]

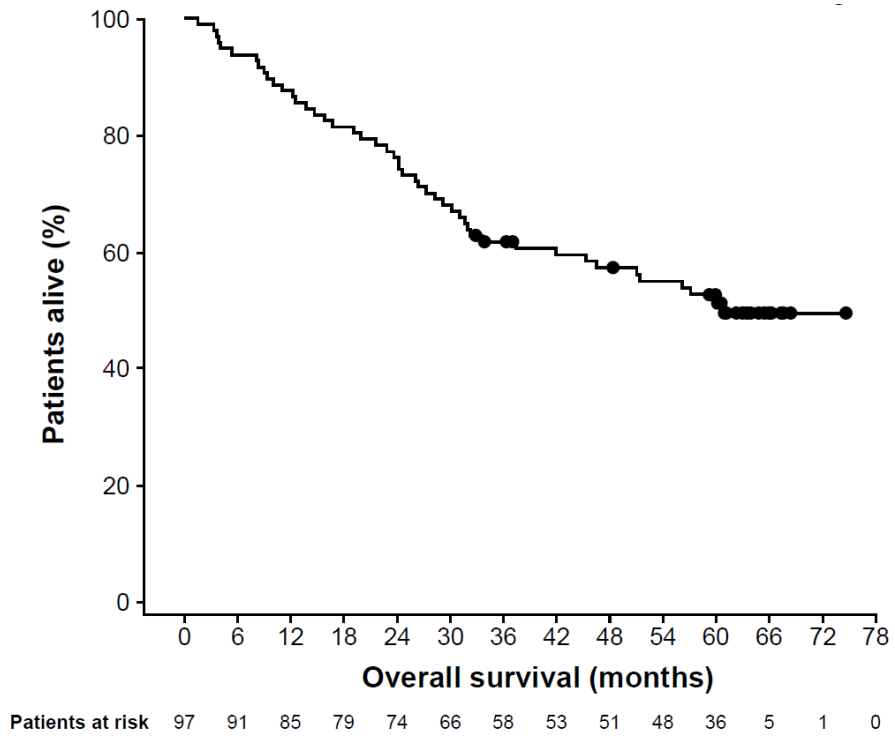

Figure 5: Overall survival in CARTITUDE-1 at median 61.3-month median follow-up

Complementing the high efficacy of CARVYKTI in CARTITUDE-1 was a safety profile generally consistent with that of other CAR-T cell therapies.[11,12]

CARVYKTI also showed high efficacy and a manageable safety profile in the phase 3 randomized CARTITUDE-4 trial (NCT04181827) in patients with lenalidomide-refractory relapsed MM who were at earlier stages of their treatment journey (1–3 prior lines). This study was the basis for US and European approval of CARVYKTI label extensions to include treatment of lenalidomide-refractory MM after at least 1 prior line of therapy, including a PI and an IMiD.[60] CARTITUDE-4 showed that CARVYKTI is superior to established SOC regimens (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]) in prolonging overall survival and progression-free survival. CARVYKTI significantly improved overall survival compared with SOC, with a 45% reduction in the risk of death (HR, 0.55 [95% CI, 0.39–0.79]; *P*=0.0009). The 30-month overall survival rate was 76.4% for CARVYKTI (n=208) vs 63.8% for SOC (n=211); and at a median follow-up of 33.6 months, median overall survival had not been reached. CARVYKTI reduced the risk of disease progression or death vs SOC by ~70% (HR, 0.29 [95% CI, 0.22–0.39]; *P*<0.0001) and median progression-free survival was not reached.[61] Additionally, CARVYKTI showed consistent overall survival and progression-free survival benefits vs SOC across prespecified subgroup analyses, including patients with standard- and high-risk cytogenetics, extramedullary disease, and 1 prior line of therapy and beyond, suggesting that CARVYKTI may overcome the poor prognosis associated with these high-risk features.[61,62] CARVYKTI is the first and only CAR-T cell therapy to significantly extend overall survival vs SOC for patients with MM as early as second-line.

In the 208 patients randomized to the CARVYKTI arm of CARTITUDE-4, CARVYKTI also showed a high response rate of 85%, including a 77% rate of complete response or better.[61] At a median follow-up of 33.6 months, the median duration of response was not reached in the CARVYKTI arm and was 18.7 months in the SOC arm, with a 30-month duration of response rate of 67% for CARVYKTI vs 36% for SOC.[61]

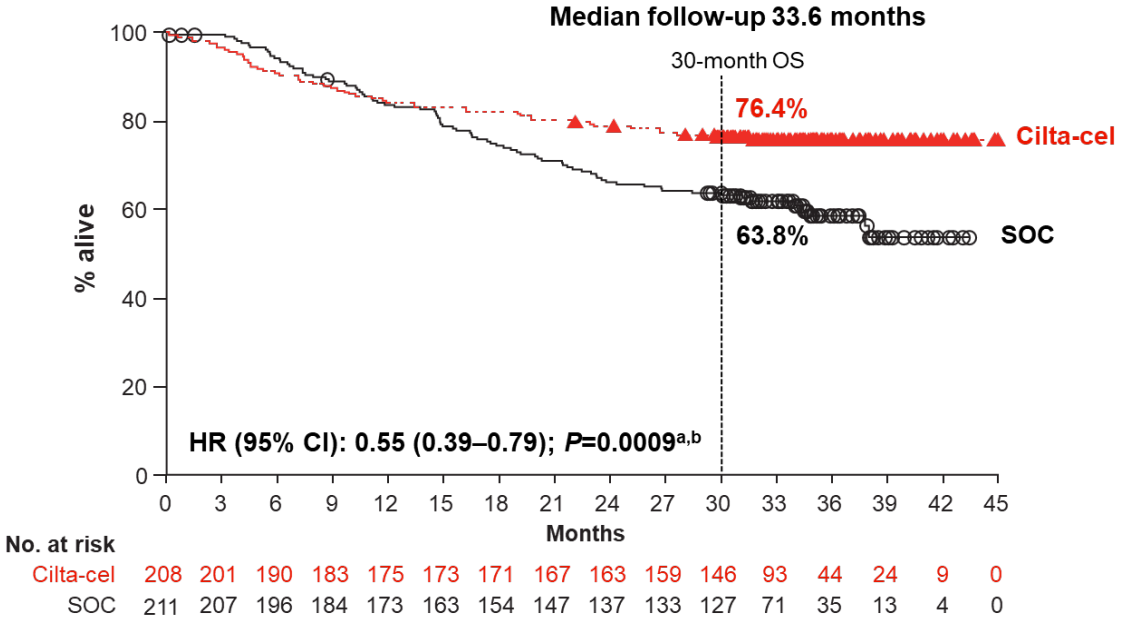

Figure 6: Overall survival at median follow-up of 34 months in CARTITUDE-4[61]

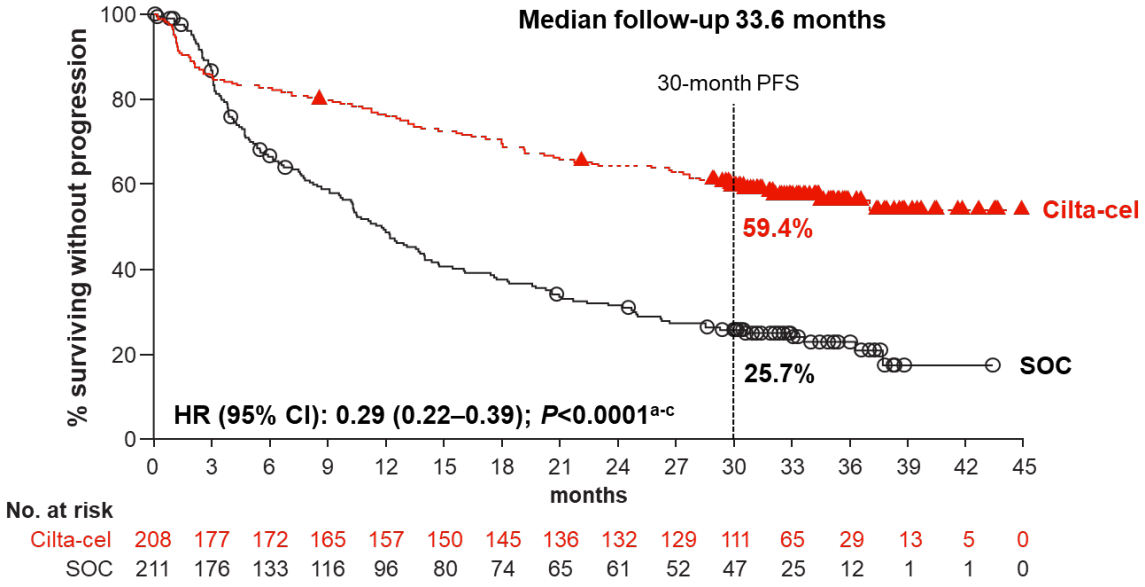

Figure 7: Progression-free survival at median follow-up of 34 months in CARTITUDE-4[61]

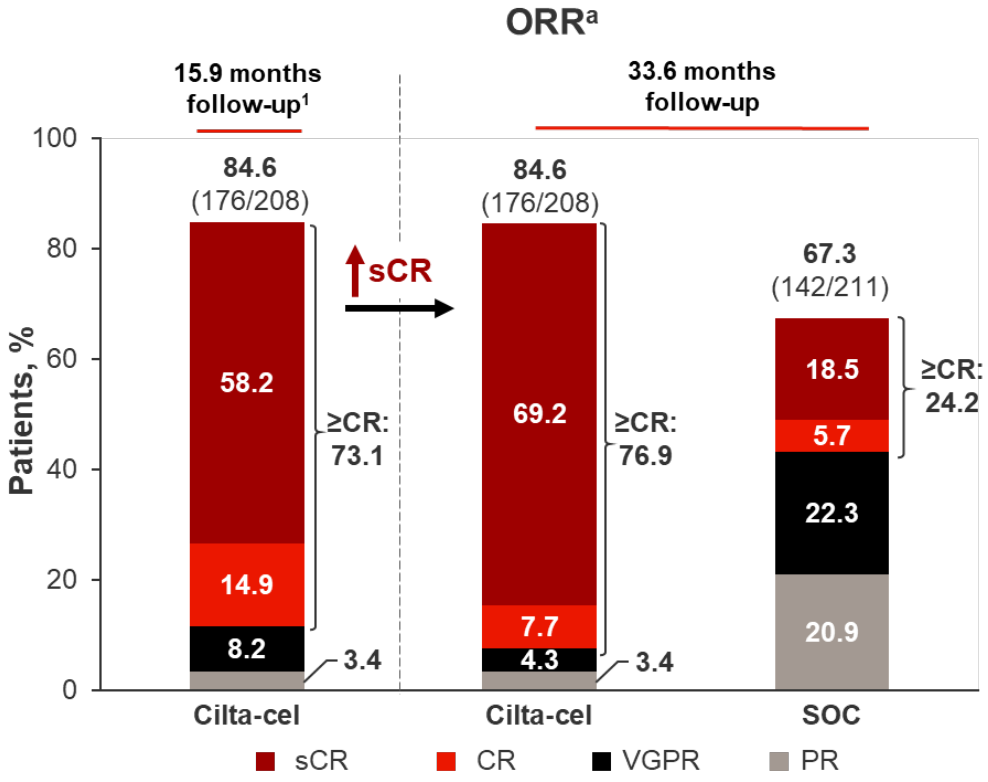

Figure 8: Increased rates of deep responses seen at median follow-up of 34 months with CARVYKTI as study treatment in CARTITUDE-4[61]

CARVYKTI® (ciltacabtagene autoleucel) US Prix Galien submission. [July 11, 2025]

In CARTITUDE-4, rates of any-grade and high-grade (grade 3/4) cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and movement and neurocognitive treatment-emergent adverse events (MNTs) in patients who received CARVYKTI as study treatment were lower than in the heavily pretreated population in CARTITUDE-1. The incidence of CRS in CARTITUDE-4 was 76% (grade 3/4, 1%) vs 95% (grade 3/4, 4%) in CARTITUDE-1; respective rates for ICANS were 5% (grade 3/4, 0%) vs 17% (grade 3/4, 2%); and MNTs occurred in 1 patient (grade 1) in CARTITUDE-4 and in 6% of patients in CARTITUDE-1.[11-13,63] This suggests improved tolerability when used earlier in treatment and continues to support a positive benefit-risk ratio for CARVYKTI in patients with lenalidomide-refractory MM as early as after first relapse.[31]

Beyond the clinical benefit shown in CARTITUDE-4, patient-reported outcomes indicated that CARVYKTI led to improved overall quality of life vs SOC, including improvements in physical function and reductions in pain and fatigue.[64] CARVYKTI treatment also resulted in delayed worsening of MM-related symptoms vs SOC. Studies in patients from CARTITUDE-1 have shown that improvements from baseline in quality of life may be associated with treatment-free periods.[65,66] The expanded indication for CARVYKTI, which is administered as a single infusion, will enable more patients to benefit from a potential treatment-free period earlier in the disease course.