

CARVYKTI® (ciltacabtagene autoleucel) US Prix Galien submission. [June 16, 2023]

4 Innovation

4.1 CARVYKTI®: Breakthrough Therapy Designation

In December 2019, CARVYKTI received Breakthrough Therapy Designation in the USA. The FDA grants this status to expedite the development and review of drugs that are intended to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on clinically significant endpoints.⁶⁸

Similarly, in the EU, the European Medicines Agency (EMA) granted CARVYKTI Priority Medicines (PRIME) Designation in April 2019. PRIME designation is granted early in drug development with the goal of optimizing and facilitating the development and evaluation of innovative advances that could address high unmet medical needs. Further validating its potential, the EMA announced accelerated assessment for CARVYKTI. The EMA's Committee for Medicinal Products for Human Use grants the accelerated assessment to innovative treatments expected to be of high public health interest.⁶⁹

4.2 CARVYKTI® has a differentiated CAR

CARVYKTI is a highly effective BCMA-directed CAR-T cell therapy that expresses a structurally differentiated CAR compared with other CAR-T cell therapies for hematologic malignancies, including MM. Other commercially available CAR-T therapies use CARs with 1 antigen-binding domain.⁷⁰⁻⁷⁴ By contrast, the CARVYKTI CAR contains 2 different BCMA-directed single-domain llama antibodies that were designed to confer avidity.⁴³

4.3 CARVYKTI's® differentiated clinical benefit in heavily pre-treated RRMM

CARVYKTI is an effective BCMA-directed CAR-T cell therapy bringing new hope to an MM patient population that has historically faced challenges on SOC treatments. By providing such long-lasting clinical benefit through only one CAR-T cell treatment infusion, CARVYKTI can simultaneously improve patient-reported outcomes, including those related to overall health, MM symptoms, and perspectives about the future. Moreover, the latest long-term data raises the possibility that CARVYKTI could redefine MM's status of being an incurable disease and instead suggest a cure in a subset of these patients.

The long-standing hopelessness of MM is illustrated by real-world studies that found that less than one-third of heavily pre-treated patients have any response to treatment with SOC regimens and that half of patients have a progression-free survival of less than 5 months.^{8,9} A single infusion of CARVYKTI led to a complete response or better in the majority of patients (82.5%) in this population, with nearly all the patients (98%) experiencing a treatment response.⁴⁸ Moreover, half of the patients in CARTITUDE-1 were alive and free of disease progression for nearly 3 years.¹⁶ Together, the high response rate and long progression-free survival in CARTITUDE-1, plus the observation that 16% of patients in LEGEND-2 remained disease free for 5 or more years after infusion,⁴⁶ suggest that CARVYKTI may be able to cure some patients with heavily pre-treated RRMM.

The potential for CARVYKTI is further supported by indirect treatment comparisons indicating that it significantly prolonged progression-free survival and overall survival compared with other

CARVYKTI® (ciltacabtagene autoleucel) US Prix Galien submission. [June 16, 2023]

treatments for heavily pre-treated RRMM.^{65,75-78} For example, one indirect comparison of outcomes in CARTITUDE-1 with those in LocoMMotion (a prospective real-world study designed to match CARTITUDE-1) found that CARVYKTI reduced the risk of progression or death vs SOC regimens by 85% and lowered the risk of death by 80%.⁷⁷ In addition, data from a matching-adjusted indirect comparison of outcomes in CARTITUDE-1 vs the registrational trial of idecabtagene vicleucel found that CARVYKTI decreased the risk of progression or death by 62% and reduced the risk of death by 57%.⁷⁸ In the absence of randomized, head-to-head trials, these data provide high-quality evidence to inform comparative efficacy of CARVYKTI versus real-world SOC treatments and versus the only other CAR-T therapy currently available for RRMM.

Alongside the clinical benefit, patients reported clinically meaningful reductions in pain and fatigue by day 100 after treatment; patients were also significantly more optimistic about the future.⁶⁷ Notably, patients attributed improvements in quality of life to the treatment-free period afforded by CARVYKTI, citing benefits of more independence, better social functioning, and the opportunity to go back to work.¹²

4.4 Ongoing innovation in the CARVYKTI clinical development program

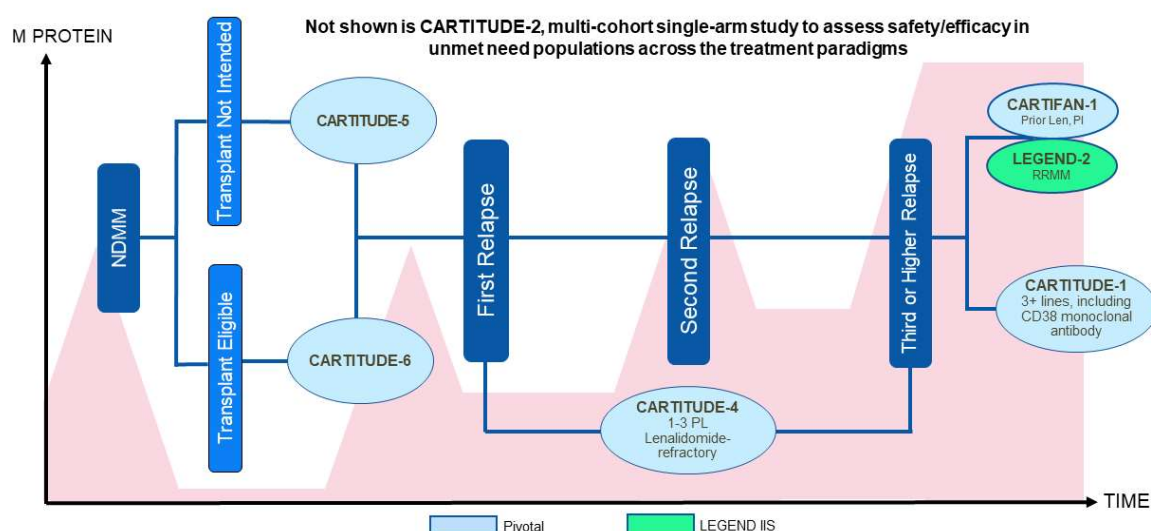


FIGURE 6: CARVYKTI clinical development plan

Backed by a foundation of significant effectiveness in patients with heavily pretreated RRMM, the CARVYKTI clinical development plan comprises studies spanning the MM treatment continuum, where the cell therapy is continuing to provide robust clinical benefit: CARTITUDE-4 (NCT04181827) a phase 3 study of CARVYKTI after 1–3 prior lines of therapy; CARTITUDE-5 (NCT04923893) and CARTITUDE-6 (NCT05257083), phase 3 studies of CARVYKTI as first-line treatment in different populations of patients with newly diagnosed MM (NDMM); and CARTITUDE-2 (NCT04133636), a multicohort, phase 2 trial of CARVYKTI in a range of MM populations, including those who previously received a BCMA-directed therapy and those considered to have functionally high-risk disease at first relapse.

CARVYKTI® (ciltacabtagene autoleucel) US Prix Galien submission. [June 16, 2023]

4.4.1 CARVYKTI® in NDMM

As indicated above, the CARVYKTI clinical development plan includes several trials in patients with NDMM, reflecting the goal of transforming the patient treatment journey from diagnosis. CARTITUDE-5 is an ongoing phase 3 study of CARVYKTI vs current frontline SOC in patients with NDMM for whom autologous stem cell transplantation (ASCT) is not intended to be the first-line treatment. CARTITUDE-6 is a phase 3 trial which will enroll patients with NDMM and evaluate CARVYKTI vs ASCT, which is the gold standard for first line treatment in fit patients.⁷⁹

4.4.2 CARVYKTI® in early lines of RRMM treatment

Emerging data have shown that CARVYKTI can improve clinical outcomes, including treatment response and progression-free survival, in patients as early as after the first MM relapse. It is on the threshold of bringing the effectiveness it demonstrated in heavily pre-treated RRMM to patients at earlier stages of the RRMM treatment landscape.

Data from the phase 3 randomized CARTITUDE-4 trial showed that CARVYKTI is superior to established SOC regimens (pomalidomide, bortezomib, and dexamethasone or daratumumab, pomalidomide, and dexamethasone) in prolonging progression-free survival in patients with lenalidomide-refractory RRMM after 1–3 prior lines of therapy, including a PI and an IMiD. CARVYKTI reduced the risk of disease progression or death by 74%. At median 15.9-month follow-up, median progression-free survival was not reached with CARVYKTI and was 11.8 months with SOC. CARVYKTI led to similar reductions in the risk of disease progression or death in all subgroups analyzed, including those with high-risk disease features.^{80,81}

In this population, CARVYKTI also showed an exceptionally high response rates of 84.6%, including a 73.1% complete response rate or better. Among the patients who received CARVYKTI as study treatment, response rates were 99.4% and 86.4% achieved a complete response; the median duration of response has not been reached.^{80,81}

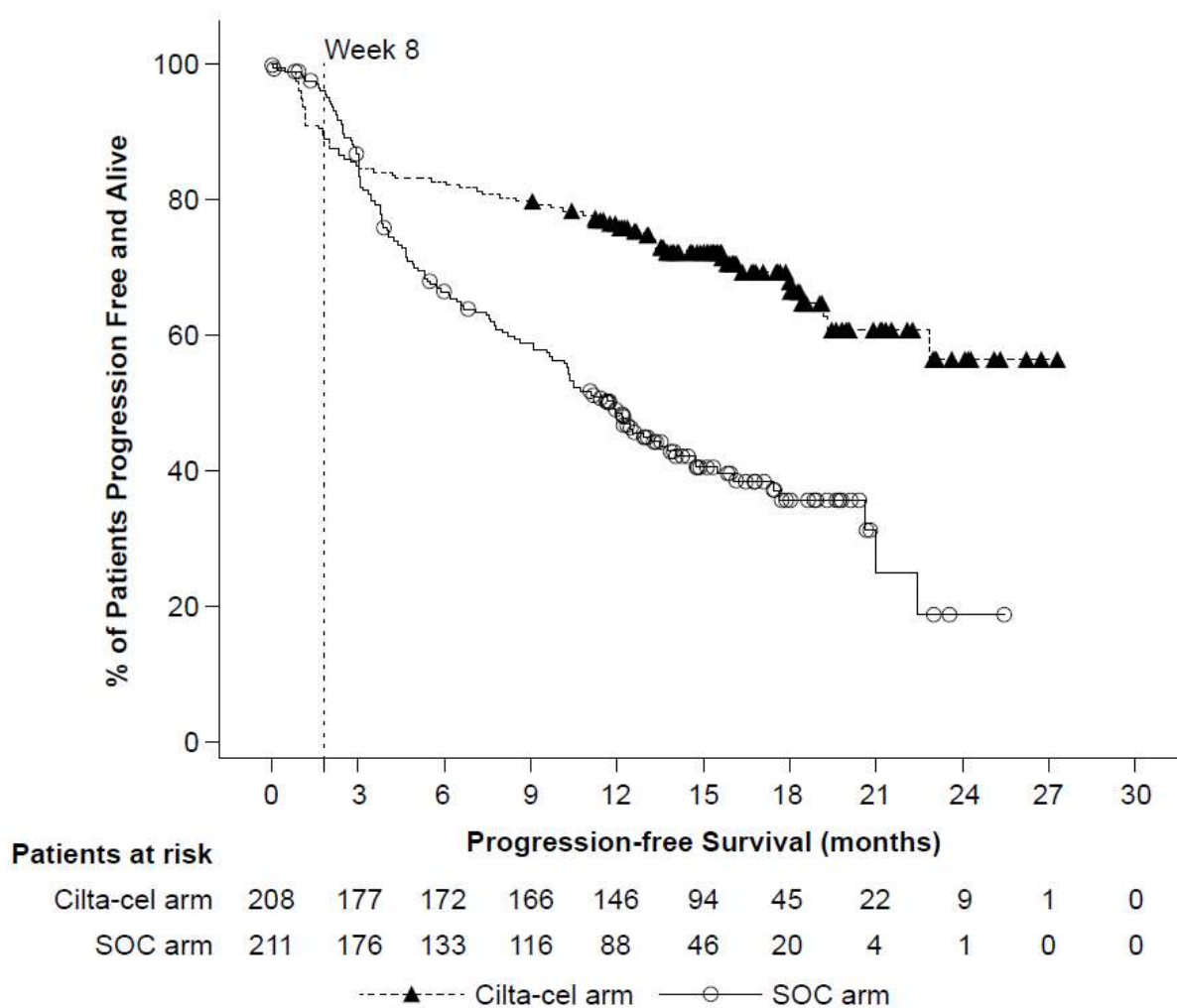


FIGURE 7: Progression-free survival in CARTITUDE-4⁸¹

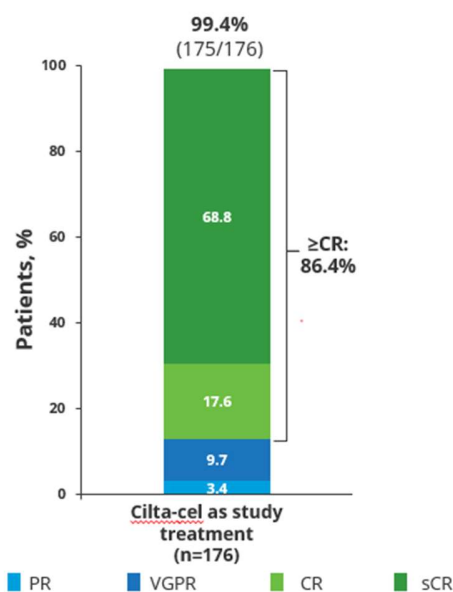


FIGURE 8: Overall response rate in patients infused with CARVYKTI as study treatment in CARTITUDE-4^{80,81}

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 (MNT) in patients who received CARVYKTI as study treatment were lower than in the heavily pre-treated 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 for MNT occurred in 1 patient (grade 1) in CARTITUDE-4 and in 6% in CARTITUDE-1.^{47,48,80,81} This suggests improved tolerability when used earlier in treatment. Regulatory applications have been submitted to expand the indication of CARVYKTI to include lenalidomide-refractory patients with 1–3 prior lines of therapy.⁸²⁻⁸⁴

4.4.3 CARVYKTI® after treatment with other BCMA-directed therapies

The aim of CARTITUDE-2 cohort C is to demonstrate if CARVYKTI can still provide clinical benefit to patients who have received other treatments with the same drug target. In a population previously treated with BCMA-directed antibody-drug conjugates or bispecific antibodies, CARVYKTI led to treatment responses in 60% of patients, including a 35% complete response rate. These patients had a median duration of response of 12.3 months and a median progression-free survival of 9.1 months;⁸⁵ these outcomes are better than heavily pre-treated patients receiving SOC in real-world settings.^{8,9}

5 Conclusions

Despite advancements in the MM therapeutic landscape in the two decades before the introduction of CARVYKTI, including several in the immediate years prior, improvements in clinical outcomes for patients with heavily pre-treated RRMM remained limited. As demonstrated in the LEGEND-2 and CARTITUDE-1 trials, CARVYKTI offers patients with RRMM the potential of achieving and maintaining a complete response for multiple years. Moreover, the latest long-term data from these studies raise the possibility that CARVYKTI could change MM's status as an incurable disease and instead suggest a cure in a subset of these patients. Emerging data from CARTITUDE-4 also suggest that CARVYKTI may have the potential to similarly improve the outcomes of patients receiving earlier lines of MM treatment.

The significant efficacy of CARVYKTI in patients with RRMM, along with its delivery in a single infusion has the potential to improve quality of life of patients. These improvements have been observed not only on measures based on MM symptoms but also on those assessing patients' perspectives about their disease and their future.

5.1 Quotes from patients after CARVYKTI®

"I feel more energy to be active... I noticed that after the T-cell treatment, after maybe like a couple of months, my fatigue level has gone down. I'm at a... point now where I can stay up throughout the day."

Male patient, aged 46 years, after CARVYKTI¹²

"It's very, very meaningful to me, and, yes, it's been amazing... And being able to go back to work is very important because, otherwise, I wouldn't be able to continue with everything that I was getting from my work. So it's like a survival saying at this point and being able to continue with my salary and health benefits and all that."

Female patient, aged 52 years, after CARVYKTI¹²

"I've been dealing with the, the pain and the nausea from chemo and stuff, and... just six months of a break is huge."

Male patient, aged 54 years, after CARVYKTI¹²

"It's just amazing to me. My neck doesn't hurt and my back. I had such back issues and that doesn't hurt anymore. So yes. It's amazing."

Female patient, aged 71 years, after CARVYKTI¹²

5.2 Quotes from physicians

"The 2-year progression-free percentage rate [in CARTITUDE-1] was 60.5%. So people are getting two years or more remission durations, so that's great."

Thomas Martin, University of California San Francisco, discussing CARTITUDE-1 data presented at ASH 2021⁸⁶

CARVYKTI® (ciltacabtagene autoleucel) US Prix Galien submission. [June 16, 2023]

“After more than two years of follow-up, cilta-cel continues to provide durable responses for patients with relapsed or refractory multiple myeloma who often have exhausted multiple lines of therapy and face poor prognoses... This population of patients has an unmet need, and it is exciting that we have a treatment option that can keep disease progression at bay.”

Saad Z. Usmani, Memorial Sloan Kettering Cancer Center, in a press release⁸⁷

“The treatment journey for the majority of patients living with multiple myeloma is a relentless cycle of remission and relapse with fewer patients achieving a deep response as they progress through later lines of therapy... This is why I have been really excited about the results from the CARTITUDE-1 study, which has demonstrated that cilta-cel can provide deep and durable responses and long-term treatment-free intervals, even in this heavily pretreated multiple myeloma patient population.”

Sundar Jagannath, the Center of Excellence for Multiple Myeloma and The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai, in a press release⁸⁸