4 Innovation

4.1 CARVYKTI: Breakthrough Therapy designation

In December 2019, CARVYKTI received Breakthrough Therapy designation in the United States. 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.[67]

Similarly, in the European Union, 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 Committee for Medicinal Products for Human Use grants the accelerated assessment to innovative treatments expected to be of high public health interest.[68]

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.[69-73] By contrast, the CARVYKTI CAR contains 2 different BCMA-directed, single-domain llama antibodies that were designed to confer avidity.[38]

4.3 Differentiated clinical benefit of CARVYKTI in RRMM

CARVYKTI is an effective BCMA-directed CAR-T cell therapy that offers renewed hope to patients with MM who have historically struggled with standard therapies. Until recently, heavily pretreated patients with RRMM had a dismal prognosis, which is illustrated by real-world studies that found that less than one-third of heavily pretreated patients have any response to SOC regimens, and that half of patients have a progression-free survival of less than 5 months.[74,75]

In CARTITUDE-1, a single infusion of CARVYKTI led to a complete response or better in the majority of heavily pretreated patients (83%), with nearly all (98%) the patients experiencing a treatment response.[12] Moreover, half of the patients in CARTITUDE-1 were alive and free of disease progression for nearly 3 years.[42] Longer follow-up showed that patients in CARTITUDE-1 had a median overall survival of 5 years, and one-third (33%) of patients remained progression-free for at least 5 years after a single CARVYKTI infusion, without maintenance or subsequent therapy, possibly setting a new benchmark for this patient population.[15]

The goal of newer MM therapies is to extend survival in a greater proportion of patients, and achieving this requires the use of these therapies earlier in the treatment paradigm, while patients remain eligible–especially since patient attrition rises with each successive line of therapy[76]. 30-month survival outcomes in CARTITUDE-4 (1–3 prior lines of therapy) with those of CARTITUDE-1 (≥3 prior lines) showed that CARVYKTI use in earlier lines resulted in numerically higher rates of overall survival (84% vs 68%, respectively) and progression-free survival (68% vs 54%, respectively).[61] Corresponding with the increased rates of survival, higher rates of MRD negativity were observed in CARTITUDE-4 than in CARTITUDE-1 (73% vs 59%

for MRD 10^{-5} and 68% vs 40% for MRD 10^{-6}, respectively).[77] Use of CARVYKTI in earlier lines of therapy also offers greater availability of effective bridging therapy, allowing further optimization of the effector to target ratio, and the likelihood of patients having fitter, better quality immune T cells. These have been shown to be key covariates of longer progression-free survival in CARTITUDE-1. Furthermore, CARVYKTI is given as a single infusion, and therefore offers a treatment-free interval after the initial infusion.

The potential of CARVYKTI to change the treatment paradigm is further supported by the first phase 3 study of patients with MM as early as after first relapse (CARTITUDE-4). As in CARTITUDE-1, almost all patients in CARTITUDE-4 who received CARVYKTI as study treatment (n=176) had a response.[13,78] Among all randomized patients in CARTITUDE-4, compared to SOC (n=211; PVd or DPd), CARVYKTI (n=208) significantly lowered the risk of disease progression or death (70% reduction).[61] The progression-free survival benefit of CARVYKTI over SOC was also strong across prespecified subgroup analyses and in post hoc analyses conducted in high-risk subgroups. The strong progression-free survival benefit and high rates of deep response in all populations, including high-risk groups, shows the potential of CARVYKTI to become an SOC treatment earlier in disease progression.[13,61,79]

In addition to providing long-lasting clinical benefit through a single CAR-T cell infusion, CARVYKTI has demonstrated improvements in patient-reported outcomes, including those related to health-related quality of life (HRQoL) and MM-related symptoms, in heavily pretreated patients and in those at earlier stages of the treatment journey.[64,65] Notably, patients attributed improvements in HRQoL to the treatment-free period afforded by CARVYTKI, citing benefits of more independence, better social functioning, and the opportunity to return to work.[66]

In patients with 1–3 prior lines of therapy in CARTITUDE-4, CARVYKTI also delayed the time to sustained symptom worsening vs SOC (median, 23.7 months vs 18.9 months, respectively).[64]

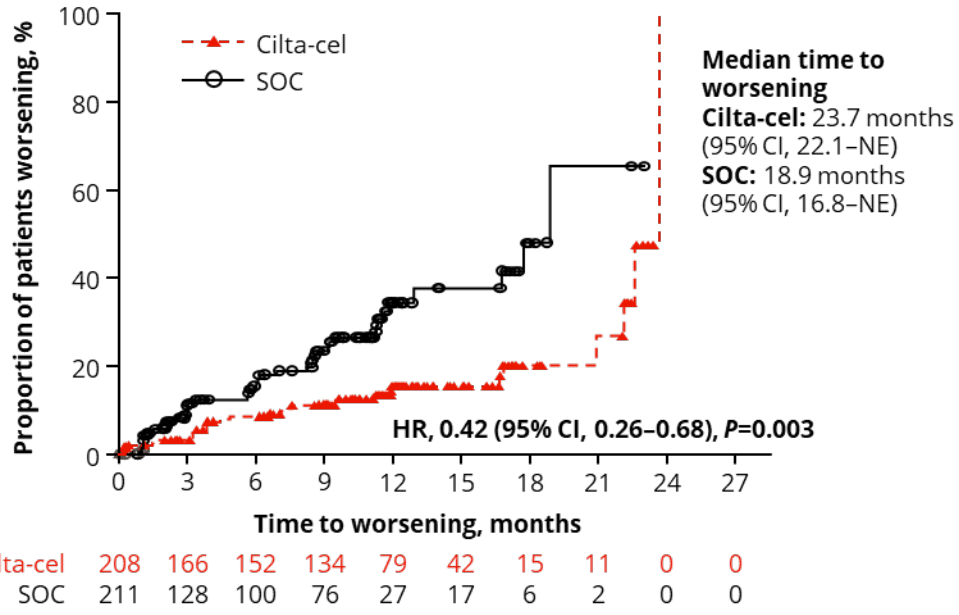

Figure 9: Time to symptom worsening with CARVYKTI vs SOC in CARTITUDE-4[64]

The efficacy and HRQoL improvements from baseline with CARVYKTI in CARTITUDE-1, the significant overall survival and progression-free survival benefit and greater improvements in HRQoL with CARVYKTI over SOC in CARTITUDE-4,[13,61,64] and the potential treatment-free period afforded by a 1-time infusion of CARVYKTI highlight the potential of CARVYKTI to be a new SOC treatment for lenalidomide-refractory MM as early as after first relapse.

4.4 Ongoing innovation in the CARVYKTI clinical development program

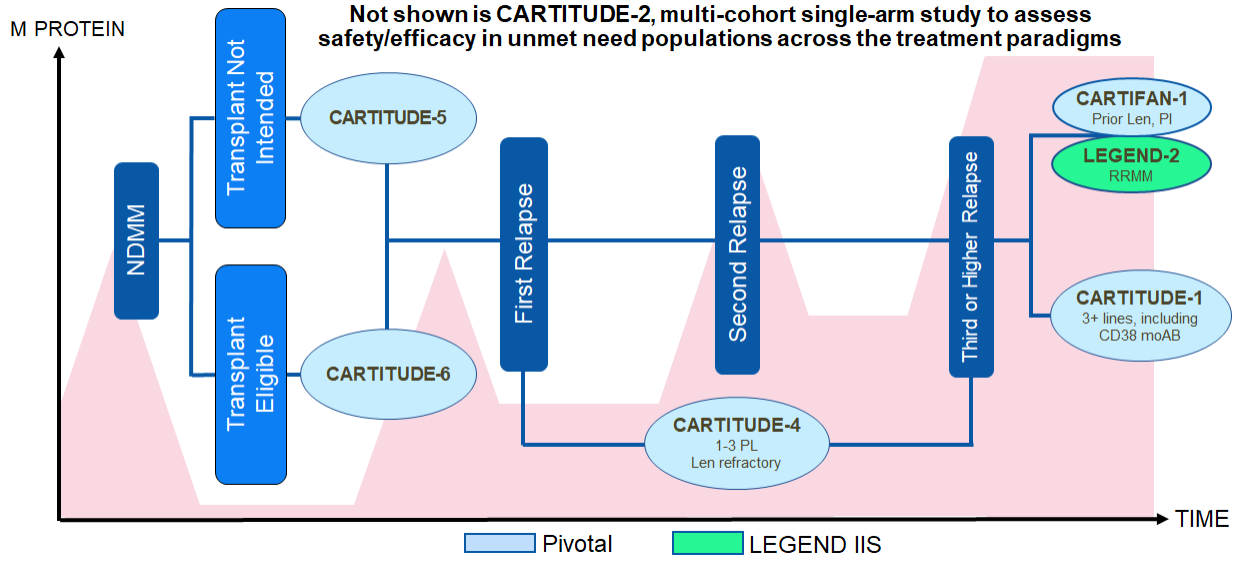

Figure 10: CARVYKTI clinical development plan

Backed by a foundation of robust efficacy in patients with RRMM as early as first relapse, the CARVYKTI clinical development plan comprises studies spanning the MM treatment continuum, including the earliest stages of disease. CARTITUDE-2 (NCT04133636) is a multicohort, phase 2 trial of CARVYKTI in a range of MM populations, including patients who had a suboptimal response to frontline autologous stem cell transplant (ASCT). CARTITUDE-5 (NCT04923893) and CARTITUDE-6 (NCT05257083) are ongoing phase 3 studies of CARVYKTI as frontline treatment in different populations of patients with newly diagnosed MM (NDMM).

4.4.1 CARVYKTI in patients with NDMM, including those with suboptimal response to frontline ASCT

As indicated above, the CARVYKTI clinical development plan includes trials in patients with NDMM, including those who had suboptimal response to frontline ASCT, underscoring the goal of transforming the patient treatment journey from the point of diagnosis.

CARTITUDE-2 Cohort D is evaluating CARVYKTI in patients who had suboptimal response (ie, did not achieve complete response or better) to frontline ASCT. Adverse events in CARTITUDE-2 Cohort D were consistent with the known safety profile of CARVYKTI and at median follow-up of 22 months, 16 (94%) of 17 patients treated with CARVYKTI had a complete response or better.[80] The 18-month duration of response rate was 93%, and 18-month progression-free survival and overall survival rates were 94%.

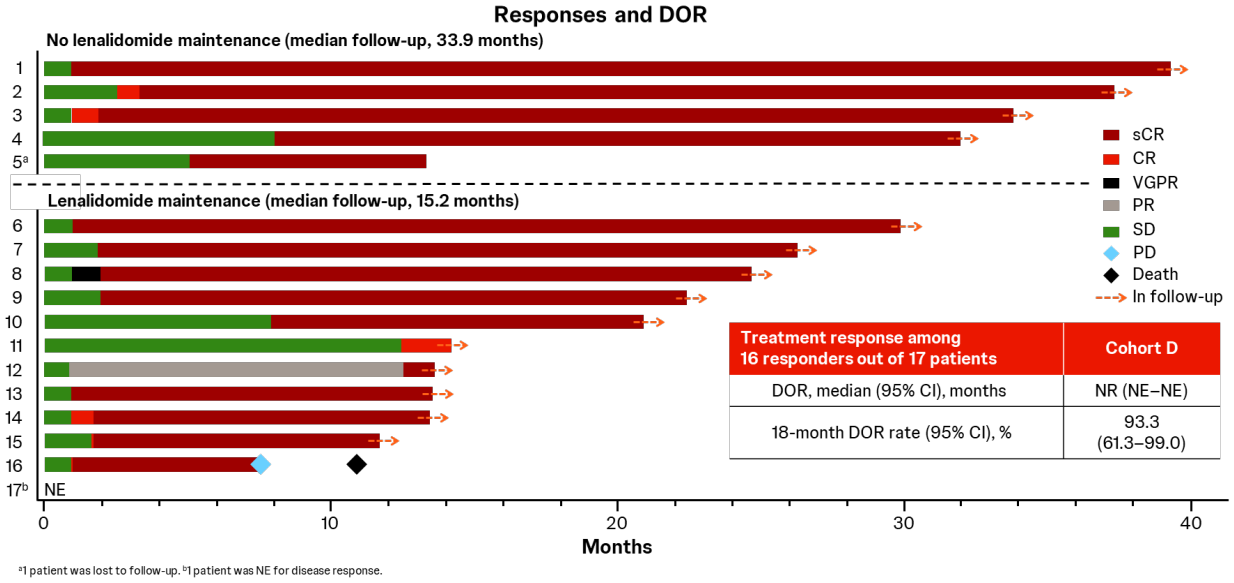

Figure 11: Responses to CARVYKTI in patients who had suboptimal response to frontline ASCT in CARTITUDE-2 Cohort D[80]

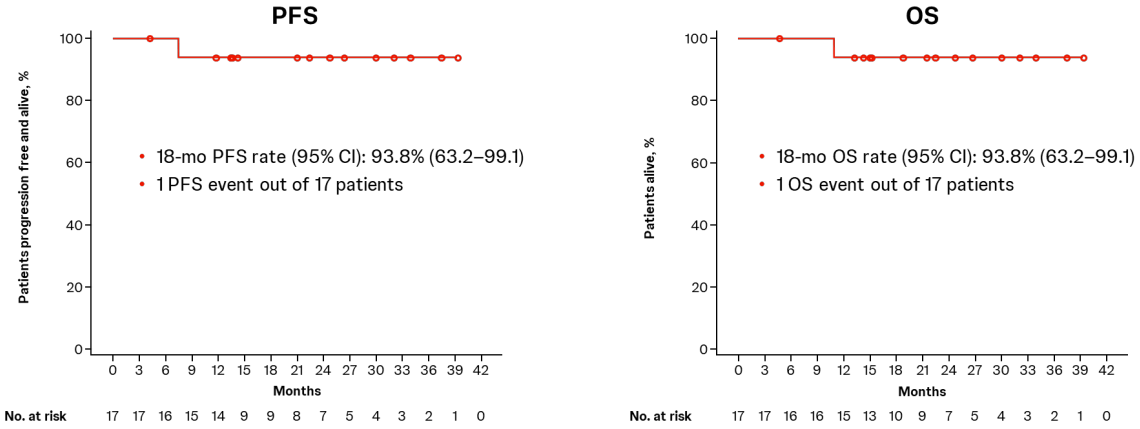

Figure 12: Progression-free survival and overall survival with CARVYKTI in patients who had suboptimal response to frontline ASCT in CARTITUDE-2 Cohort D[80]

CARTITUDE-5 is an ongoing phase 3 study of CARVYKTI vs current frontline SOC in patients with NDMM for whom 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.[81]

5 Conclusions

Despite advancements in the MM therapeutic landscape over the 2 decades preceding the introduction of CARVYKTI, including several in the immediate years prior, improvements in clinical outcomes remained limited for patients with heavily pretreated RRMM. As demonstrated in the LEGEND-2, CARTITUDE-1, and CARTITUDE-4 trials, CARVYKTI offers patients as early as after first relapse, the potential to achieve and maintain a complete response for years. The remarkable outcomes reported in the long-term follow-up from CARTITUDE-1 provide the first evidence of the long-term survival benefit of CARVYKTI in patients suffering from this devastating disease. To date, more than 6,500 patients have been treated with CARVYKTI, both in the clinical trial setting and with commercially available product in the real-world setting.

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, after CARVYKTI[66]

“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, after CARVYKTI[66]

“I’ve been dealing with the, the pain and the nausea from chemo and stuff, and…just 6 months of a break is huge.”

Male patient, after CARVYKTI[66]

“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, after CARVYKTI[66]

“I was fortunate to have cilta-cel in April 2019. That was nearly 5 years ago… cilta-cel gave me back my life and I hope more people will be able to get it earlier so they can have their life back sooner than I did.”

Female patient, after CARVYKTI, as part of public comment for FDA Oncologic Drugs Advisory Committee, March 3, 2024[82]

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

5.2 Quotes from physicians

“The most impressive myeloma abstract at ASCO25. Outstanding long-term efficacy with cilta-cel CAR-T. Five-year survival rate 50%. Five-year PFS rate of 33%. Astounding, given multidrug relapsed refractory setting.”

S Vincent Rajkumar, Mayo Clinic, Minnesota, discussing CARTITUDE-1 data presented at ASCO 2025[83]

“The belle of the ball – long-term follow-up of CARTITUDE-1. One-third remain alive and [without] progression at 5 years. Eleven patients are MRD negative at 10^{-6}”

Rafael Fonseca, Mayo Clinic, Arizona, discussing CARTITUDE-1 data presented at ASCO 2025[83]

“CARTITUDE-1 [follow-up] at #EHA2025. I was even more impressed looking at these results today as I was a week ago and they are still sinking in. One-third are progression free and MRD neg at 5 [years]. Real hope of long-term control for many very RRMM patients.”

Daniel AuClair, Multiple Myeloma Research Foundation, discussing CARTITUDE-1 data presented at EHA 2025[84]

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

Thomas Martin, University of California, San Francisco, discussing CARTITUDE-1 data presented at ASH 2021[85]

“After more than 2 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 release[86]

“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 release[87]

“I'm speaking as a physician taking care of patients every day in clinics. While we've seen an improvement in myeloma outcomes in the last 2 decades, we know that myeloma is a very heterogenous disease, and even in patients who are at their first and second relapses we see very aggressive nature of disease…We have seen so many examples in clinics of patients cycling through available treatments within months, but benefiting tremendously from these

therapies and subsequent lines. I'd like to offer that option to my patients who have that aggressive relapse in early lines who otherwise won't be able to get this therapy."

Saad Z Usmani, Memorial Sloan Kettering Cancer Center, as part of public comment for FDA Oncologic Drugs Advisory Committee, March 15, 2024[88]

"I would like to share with you an example of one such patient I had on CARTITUDE-4. He's a young man in his 40s. I saw him for a transplant consult but he progressed within 2 months of starting frontline therapy with bortezomib, lenalidomide and dexamethasone. We know historically these patients do very poorly. He was randomized to the cilta-cel arm and is in a stringent complete response 3 years later. He's back to work full-time, which for him was very important as he has a young family to support and he's enjoying an excellent quality of life."

Surbhi Sidana, Stanford University, as part of public comment for FDA Oncologic Drugs Advisory Committee, March 15, 2024[88]