

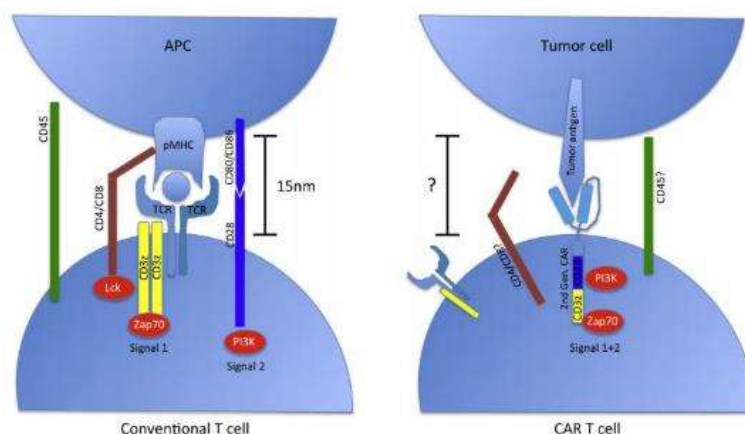
## 3 History of the development of CARVYKTI®

### 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 heavily pre-treated RRMM.<sup>16,43-48</sup> BCMA, a new drug target, stands out from prior 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.<sup>49-52</sup> Lack of BCMA expression in other bone marrow populations may help limit on-target off-tumor toxicities.

CAR-T cell therapies are a new drug class that gained their first indication in 2017.<sup>53,54</sup> 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, pre-defined cell surface molecules without the major histocompatibility complex restriction of T cells.<sup>55-57</sup>

CAR-T cell therapies have the potential for robust effectiveness with 1 treatment infusion. Additionally, unlike non-targeted drugs such as chemotherapies, CAR-Ts can be directed to specifically attack malignant cells.



**FIGURE 1: Diagram of conventional T-cell receptor and CAR-T cell receptor<sup>57</sup>**

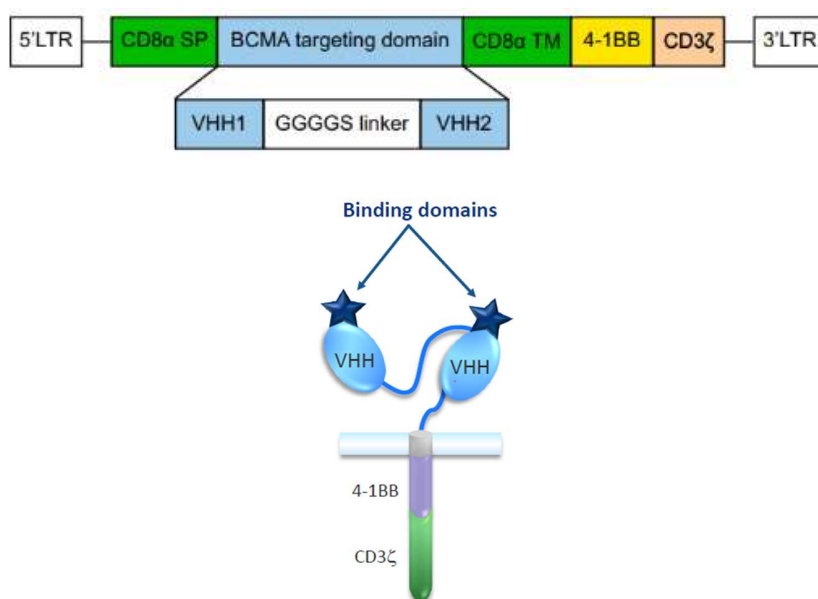
### 3.2 CARVYKTI® mechanism of action

CARVYKTI is targeted, via its CAR, to cells with surface expression of BCMA.<sup>43</sup> CAR binding to BCMA activates T-cell programs that mediate killing of recognized cells (ie, MM cells) and T-cell proliferation.<sup>55-57</sup>

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 co-stimulatory and signaling domains.<sup>43,58</sup> 4-1BB is also associated with stimulating the generation and proliferation of CD8+ central memory T cells,

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supported by data showing enrichment of this cell type in the CARVYKTI drug product – and may improve the persistence of CAR-T cells after administration to patients.<sup>58-61</sup>



**Figure 2. Structure of the CARVYKTI CAR<sup>43,60</sup>**

### 3.3 3.3 CARVYKTI clinical development

#### 3.3.1 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 patients with heavily pre-treated RRMM (N=74).<sup>43-45</sup>

Data from LEGEND-2 showed high response rates, deep and durable responses, and long-term survival outcomes in patients with heavily pretreated RRMM. 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 remain disease-free after 5 or more years of follow-up; median overall survival was 55.8 months.<sup>45,46</sup>

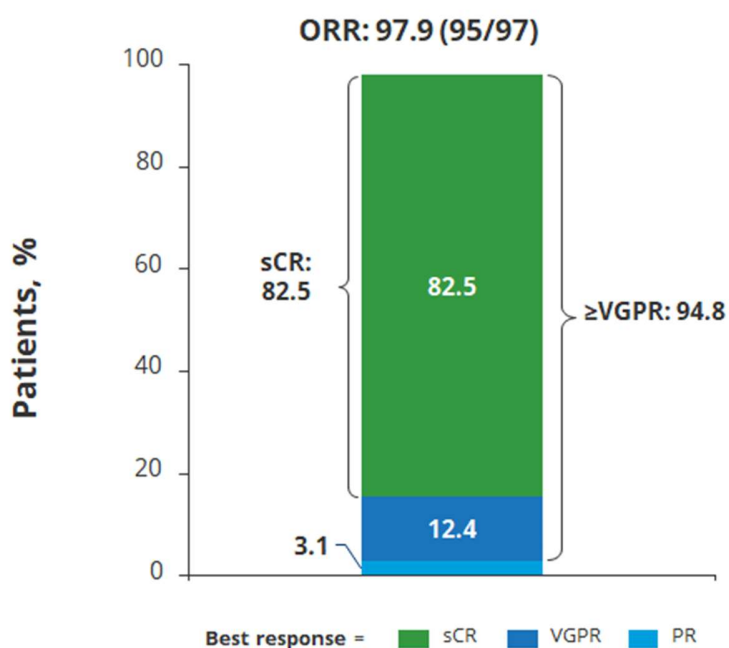
#### 3.3.2 CARVYKTI® registrational trial data

Following the promising results from LEGEND-2, the phase 1b/2 CARTITUDE-1 trial, the basis for the US Food and Drug Administration's (FDA's) approval of CARVYKTI was initiated. CARTITUDE-1 enrolled 97 patients in the USA who had received at least 3 prior lines of therapy

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(median, 6 lines) including a PI, an IMiD, and an anti-CD38 antibody; 88% of patients were refractory to drugs from all three of these drug classes at baseline.<sup>47</sup>

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. In addition, 92% of patients with evaluable bone marrow samples achieved minimal residual disease negativity ( $10^{-5}$  sensitivity),<sup>48</sup> which is a predictor of prolonged survival outcomes.<sup>62,63</sup> Additionally, efficacy results at 2 years post CARVYKTI were similar in most patient subgroups, including elderly patients.<sup>64</sup> 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.<sup>16</sup> Notably, the median progression-free survival in CARTITUDE-1 is longer than the median progression-free survival of less than 6 months that was observed in prospective and retrospective real-world analyses of RRMM treated with standard of care therapies; these studies from 2018 and 2021 included heavily pretreated patients previously exposed to a PI, an IMiD, and an anti-CD38 antibody.<sup>8,9,65</sup>



**FIGURE 3: Ciltacabtagene autoleucel treatment response rates in CARTITUDE-1 at 27.7-month follow-up<sup>48</sup>**

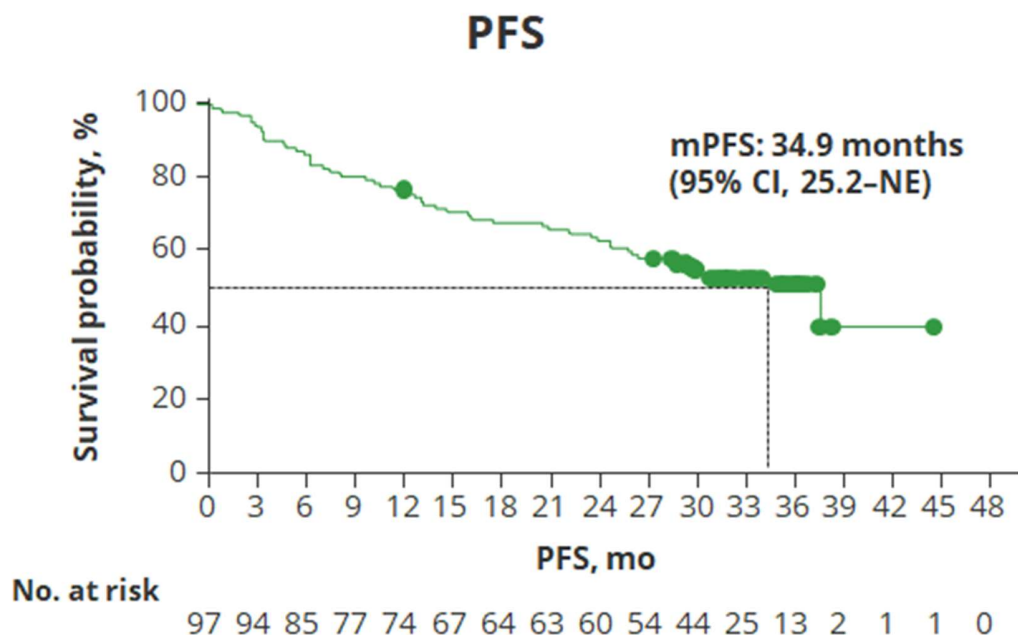


FIGURE 4: Progression-free survival in CARTITUDE-1 at median 33.4-month follow-up<sup>16</sup>

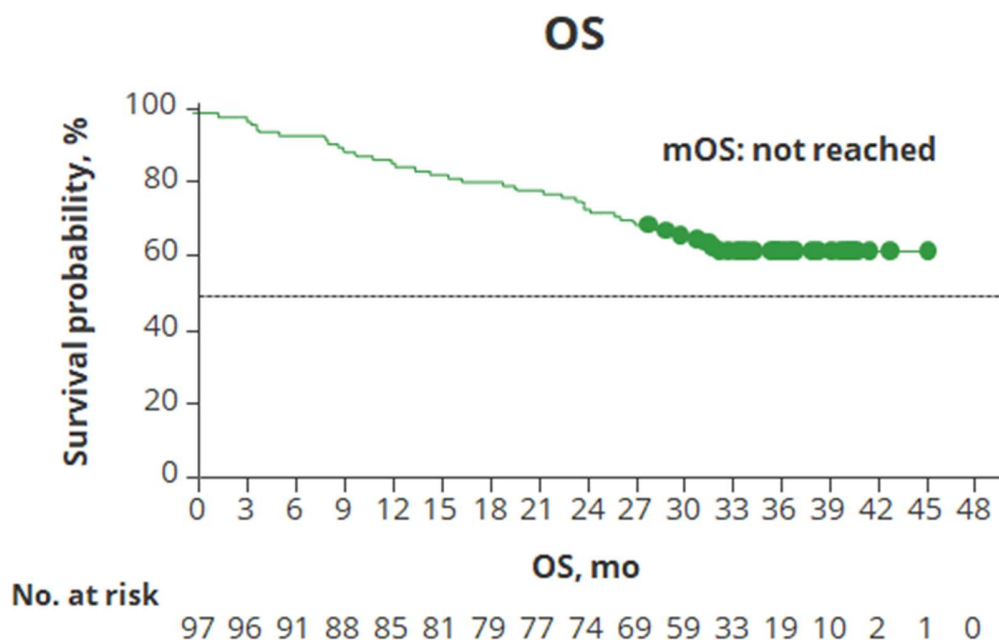


FIGURE 5: Overall survival in CARTITUDE-1 at median 33.4-month follow-up<sup>16</sup>

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CARTIFAN-1 (NCT03758417), a phase 2 study of CARVYKTI conducted in China, corroborated these data in patients with a median of 4 prior lines of therapy. 79% of patients achieved a stringent complete response; median duration of response, median progression-free survival, and median overall survival had not been reached at a median 26-month follow-up.<sup>66</sup>

Complementing the high response rates of CARVYKTI in CARTITUDE-1 was a safety profile generally consistent with that of other CAR-T cell therapies.<sup>47,48</sup>

Beyond the clinical benefit shown in CARTITUDE-1, patient-reported outcomes indicated that CARVYKTI led to better perspectives about the future and improved overall quality of life, including improvements in physical function and reductions in pain and fatigue. Among the factors associated with improved quality of life was CARVYKTI being a single infusion.<sup>12,67</sup> This, combined with the prolonged progression-free survival, enables patients to benefit from a potentially treatment-free period after CARVYKTI infusion.