IDECABTAGENE VICLEUCEL (IDE-CEL; BB2121), A BCMA-TARGETED CAR T CELL THERAPY, IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA: INITIAL KARMMA RESULTS

Author(s): Jesus San Miguel, Nina Shah, Albert Oriol, Philippe Moreau, Ibrahim Yakoub-Agha, Michel Delforge, Deepu Madduri, Ankit Kansagra, Hermann Einsele, Hartmut Goldschmidt, Katja Weisel, Michele Cavo, Donna Reece, Alessandro Rambaldi, Paula Rodríguez-Otero, Fabio Petrocca, Jamie Connarn, Julie Wang, Liping Huang, Timothy B. Campbell, Kristen Hege, Nikhil Munshi

Background

Triple-class exposed patients (pts) with relapsed and refractory multiple myeloma (RRMM) who progress on immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) have poor outcomes. In the phase I CRB-401 study, idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T cell therapy, showed promising tolerability and efficacy in relapsed or refractory multiple myeloma pts with ≥3 prior lines of therapy including an IMiD and a PI, or who were refractory to both drug classes (*N Engl J Med.* 2019;380:1726-1737).

Aims

To report primary efficacy and safety data from the pivotal phase II KarMMa trial of ide-cel in RRMM (NCT03361748).

Methods

Enrolled pts had ≥3 prior regimens (including an IMiD, a PI, and an anti-CD38 mAb) and were refractory to their last regimen per IMWG criteria. After lymphodepletion with cyclophosphamide 300 mg/m^2 plus fludarabine 30 mg/m^2 x 3 d, pts received 150—450 $\times$ 10^6 CAR+ T cells (target dose levels). The primary endpoint was overall response rate (ORR). Secondary endpoints included complete response (CR) rate, duration of response (DOR), and progression-free survival (PFS).

Results

Of 140 pts enrolled in KarMMa, 128 received ide-cel infusion. The median age was 61 y, and the median number of prior regimens was 6 (range, 3-16); 84% were triple- and 26% were penta-refractory. Most pts (88%) received bridging therapy prior to lymphodepletion. With a median follow-up duration of 11.3 mo at the data cutoff for the primary analyses (16 October 2019), 70 pts (55%) were still ongoing in the primary study and 5 (4%) had entered a long-term follow-up study. The most common reason for discontinuation was death or pt withdrawal after disease progression (n=55). Clinically meaningful efficacy was observed at each of the 3 target doses explored and generally increased with dose (**Table**). ORR was 73% across all dose levels and 81% in pts who received 450 $\times$ 10^6 CAR+ T cells. Across doses, the CR rate was 31%, median time to response was 1.0 mo (range, 0.5-8.8), and median DOR was 10.6 mo (95% CI, 9.0-11.3). With a

median follow-up duration of 10.2 mo, median PFS was 8.6 mo (95% CI, 5.6-11.3) for the overall pt population and 11.3 mo (95% CI, 8.8-12.4) for the 54 pts who received 450 $\times$ 10^6 CAR+ T cells. Response rates were consistent (ORR $\geq$50%) in most subgroups examined, including older and historically difficult-to-treat pts (penta-refractory, high tumor burden, extramedullary disease, etc). The most common adverse events (AEs) of special interest were cytopenias (97%), cytokine release syndrome (CRS; 84%), and infections (69%). CRS was mostly grade 1/2; 5 pts (4%) had grade 3, 1 had grade 4, and 1 had grade 5 (at 300 $\times$ 10^6). Neurotoxicity developed in 23 pts (18%); 4 pts (3%) had grade 3 and none had grade $\geq$4. Four grade 5 ide-cel–related AEs occurred (bronchopulmonary aspergillosis, pneumonia cytomegaloviral, gastrointestinal hemorrhage, and CRS). Median peak CAR+ T cell expansion occurred at 11 d. Expansion was higher in responders, and expansion parameters (AUC_{0-28d}, C_{max}) increased with higher dose, with substantial exposure overlap across doses. Durable persistence was observed, with CAR+ T cells detected in 29 of 49 (59%) and 4 of 11 pts (36%) at 6 and 12 mo postinfusion, respectively.

Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Total (N=128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	19 (35)	40 (31)
DOR*, median, mo	†	9.9	11.3	10.6
PFS*, median, mo	†	5.8	11.3	8.6
CRS‡				
Overall, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Grade ≥3, n (%)	0	4 (6)	3 (6)	7 (5)
Onset / duration, median, d	7 / 5	2 / 4	1 / 7	1 / 5
NT§				
Overall, n (%)	0	12 (17)	11 (20)	23 (18)
Grade ≥3, n (%)	0	1 (1)	3 (6)	4 (3)
Onset / duration, median, d	NA	3 / 3	2 / 5	2 / 3

CRS, cytokine release syndrome; CR, complete response; DOR, duration of response; NT, investigator identified neurotoxicity; ORR, overall response rate; PFS, progression-free survival; sCR, stringent CR.
*Kaplan-Meier estimate.
†Not reported due to small n.
‡Graded per Lee et al. *Blood* 2014;124:188-195.
§Graded per CTCAE v4.03 criteria.

Conclusion

In the KarMMa trial, ide-cel demonstrated deep, durable responses in heavily pretreated RRMM pts. Efficacy and safety results reflected prior reports and support a favorable clinical benefit-risk profile of ide-cel across the target dose levels.

Session topic: 14. Myeloma and other monoclonal gammopathies - Clinical

Keyword(s): CAR-T, Myeloma, Refractory, Relapse