Idecabtagene vicleucel (ide-cel, bb2121, Abecma; Bristol Myers Squibb)
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Objectives	Assess the efficacy and safety of ide-cel in patients with triple-class-exposed relapsed and refractory myeloma.
Methods	Single-group, phase 2, open-label, multicenter, multinational trial Inclusion Criteria - ≥18 years, had received at least three previous regimens for multiple myeloma (including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody), had disease that was refractory to their last regimen, had measurable disease, and had adequate organ function. Exclusion Criteria - CrCl <45 mL/min, alanine aminotransferase >2.5 x ULN, and LVEF <45%, ANC<1000, PLT <50. After lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 consecutive days, patients received 150-450 x 10^6 CAR$^+$ T cells after 2 days of rest. Patients were followed for at least 24 months and then asked to participate in a separate long-term follow-up study.
Endpoints	Primary Endpoint - overall response (ORR, partial response or better) defined according to IMWG Uniform Response Criteria for Multiple Myeloma Secondary Endpoints - complete response or better (CR/sCR, comprising complete and stringent complete responses), time to response and duration of response (DOR), progression-free (PFS) and overall survival (OS), minimal residual disease (MRD), safety, pharmacokinetics, and immunogenicity
Results	Baseline Characteristics ● n=128 ● Median age ~61 years ● 51% of patients had a high tumor burden, 39% had extramedullary disease, 16% had stage III disease at screening according to the revised International Staging System, and 35% had a high-risk cytogenetic abnormality. ● Median of 6 previous anti myeloma regimens and 94% had received previous autologous hematopoietic stem-cell transplants. ● 84% of patients had disease that was triple refractory (to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD-38 antibody), 60% had disease that was penta-exposed (to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab), and 26% had disease that was penta-refractory, according to IMWG criteria and based on the most exposure to individual agents. ● 88% received bridging therapy during manufacturing with a median duration of 15 days. ○ Responses to bridging therapy were observed in 4%. ● Median follow-up of 13.3 months. Efficacy ● ORR: 73% (n=94), [95% CI 66-81, p<0.001] ● CR/sCR: 33% (n=42) ● Median DOR: 10.7 months (19 months for patients with CR or sCR) ● Median PFS: 8.8 months (20.2 months for patients with CR or sCR) ● Estimated median OS: 19.4 months ● 12-month OS: 78% ● MRD-negative status was confirmed in 33 patients (26% of all patients and 42% of those with CR or better.

Dose, x 10^6 CAR^+ T Cells	ORR	CR/sCR	Median DOR	Median PFS
150 (n=4)	50%	25%	Not reported	2.8 months
300 (n=70)	69%	29%	9.9 months	5.8 months
450 (n=54)	82%	39%	11.3 months	12.1 months

Safety

- Adverse events were reported in all patients, with 99% experiencing grade 3 or 4.
- Most common toxicities of any grade
    - Cytopenia's: 97%
        - Neutropenia: 91%
        - Anemia: 70%
        - Thrombocytopenia: 63%
    - **Cytokine Release Syndrome (CRS)**
        - Incidence: 84%
        - Median onset: 1 day
        - Median duration: 5 days
        - Tocilizumab use: 52%
        - Glucocorticoid use: 15%
    - **Neurotoxicity**
        - Incidence:18%
        - Grade $\geq$ 3: 3% (no effects greater than grade 3 occurred)
        - Median onset: 2 days
        - Median duration: 3 days
    - A total of 34% of patients died during the study
        - Most attributed to complications of myeloma progression.

Pharmacokinetics and Immunogenicity

- Maximum CAR^+ T-cell expansion (C_{max}) occurred at a median of 11 days.
- Upper quartiles of exposure were observed more frequently at the 450 x 10^6 dose.
- CAR^+ T cells were detected in 59% of patients at 6 months and 36% of patients at 12 months after infusion.
- Among treated patients, 5 were positive for antidrug antibodies before infusion. After infusion, antidrug antibodies were not detected earlier than 3 months; thereafter the percentage of antidrug antibody-positive patients increased from 21% at month 3 to 65% at month 12.
    - Exposure variables or the incidence of response or of complete response or better were not affected by positivity for anti-drug antibodies before or after infusion.
- Levels of proinflammatory markers including cytokines, ferritin, and C-reactive protein, increased early after ide-cel infusion and decreased by 1 month, with peak levels higher in patients having cytokine release syndrome of grade 3 or higher.
- At baseline, 98% of tumor samples expressed BCMA, with most having at least 50% BCMA-positive plasma cells, and all patients having detectable levels of sBCMA. At disease progression, 97% had rising sBCMA levels consistent with progression of BCMA-expressing myeloma, 94% retained BCMA-expressing tumor cells in bone marrow.

Conclusion

Treatment with ide-cel resulted in frequent and deep responses in patients with triple-class-exposed relapsed and refractory myeloma in the pivotal phase 2 KarMMA study. Observed toxic effects were consistent with previous reports. Results support substantial antitumor activity for ide-cel across a target dose range of 150 x 10^6 to 450 x 10^6 CAR^+ T cells. The 450 x10^6 dose appeared to be more effective than other doses.