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Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma: Updated Results from Phase 1 CRB-401 Study

Yi Lin, MD, PhD[1], *Noopur S. Raje, MD*[2], *Jesus G. Berdeja, MD*[3], *David S. Siegel, MD*[4], *Sundar Jagannath, MD*[5], *Deepu Madduri, MD*[5]*, *Michaela Liedtke, MD*[6], *Jacalyn Rosenblatt, MD*[7], *Marcela V. Maus, MD, PhD*[2], *Monica Massaro, MPH*[8]*, *Fabio Petrocca, MD*[9]*, *Andrea Caia, MS*[10]*, *Zhihong Yang, PhD*[10]*, *Timothy B. Campbell, MD, PhD*[10]*, *Kristen Hege, MD*[10], *Nikhil C. Munshi, MD*[11] *and James N. Kochenderfer, MD*[12]

[1]Mayo Clinic, Rochester, MN
[2]Massachusetts General Hospital Cancer Center, Boston, MA
[3]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN
[4]Hackensack University Medical Center, Hackensack, NJ
[5]Mount Sinai Medical Center, New York, NY
[6]Stanford University Medical Center, Stanford, CA
[7]Beth Israel Deaconess Medical Center, Boston, MA
[8]bluebird bio, Inc., Cambridge, MA
[9]bluebird bio, Cambridge, MA
[10]Bristol Myers Squibb, Princeton, NJ
[11]Dana-Farber Cancer Institute, Boston, MA
[12]Surgery Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD

*signifies non-member of ASH

Background: Ide-cel, a BCMA-directed CAR T cell therapy, showed tolerability and promising efficacy in patients with relapsed and/or refractory multiple myeloma (RRMM) in the first-in-human phase 1 CRB-401 study (Raje et al. *N Engl J Med.* 2019;380:1726) and the pivotal phase 2 KarMMa study (Munshi et al. *J Clin Oncol.* 2020;38[suppl, abstr]:8503). Ide-cel demonstrated a favorable benefit-risk profile with an overall response rate (ORR) of 85%, a complete response (CR) rate of 45%, and a median progression-free survival (PFS) of 11.8 months in the first 33 patients treated in CRB-401. Reported here are updated safety and efficacy results for 62 patients who received ide-cel in the ongoing CRB-401 study.

Methods: CRB-401 (NCT02658929) is a 2-part, phase 1 dose-escalation and -expansion study. The expansion phase enrolled patients who had received ≥3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody, and were refractory to their last line of therapy. Eligibility criteria for the dose-escalation phase were described previously (Raje et al. *N Engl J Med.* 2019;380:1726). After lymphodepletion with fludarabine (30 mg/m^2/day) and cyclophosphamide (300 mg/m^2/day) for 3 days followed by 2 days of rest, patients received ide-cel at target doses of 50, 150, 450, or 800 × 10^6 CAR+ T cells in the dose-escalation phase and 150 to 450 × 10^6 CAR+ T cells in the dose-expansion phase. The primary endpoint was safety. Secondary endpoints included tumor response according to the International Myeloma Working Group criteria. Exploratory endpoints included PFS, overall survival (OS), and minimal residual disease (MRD).

Results: As of January 14, 2020, 21 patients had received ide-cel in the dose-escalation phase, and 41 patients received ide-cel in the dose-expansion phase. The median age was 61 years, and 44% of patients had high tumor burden (≥50% bone marrow CD138+ plasma cells). Of the 62 patients, 45% received >6 prior regimens, 90% were daratumumab-exposed, and 77% were daratumumab-refractory. As of the cutoff date, 13 patients were ongoing, and 49 patients had discontinued the study. Reasons for study discontinuation were progressive disease (58%), withdrawal by patients (10%), and death (10%). Based on safety and efficacy in the dose-escalation phase, target dose levels of 150 to 450 × 10^6 CAR+ T cells were selected for the dose-expansion phase. The most frequent adverse events (AEs) were neutropenia (92%), cytokine release syndrome (CRS; 76%), anemia (76%), and thrombocytopenia (74%). The most frequent grade 3/4 AEs were neutropenia (89%), leukopenia (61%), anemia (57%), and thrombocytopenia (57%). Most CRS events were grade 1 or 2 (**Table**). Four patients (7%) had grade 3 CRS; there were no grade >3 CRS events. The incidence of CRS generally increased with target dose level. Neurologic toxicity (NT; clustered term) occurred in 27 patients (44%) and was primarily grade 1/2 with 1 patient having grade 3 and 1 patient having grade 4 NT. Among all 62 patients in the dose-escalation and -expansion phases, the ORR was 76%, including 24 patients (39%) with a CR or better and 40 patients (65%) with a very good partial response or better. The median duration of response was 10.3 months. Of 37 responders evaluable for MRD, 30 were MRD negative (≤10^{-4} nucleated cells) at 1 or more time point, and 7 responders were MRD positive. With a median

follow-up of 14.7 months for all patients in the dose-escalation and dose-expansion phases, median PFS was 8.8 months and median OS was 34.2 months. Overall, a dose-dependent effect was observed on responses and survival outcomes, with greater efficacy reported at ≥150 × 10^6 CAR+ T cells (**Table**).

Conclusions: Ide-cel demonstrated deep and durable responses in heavily-pretreated RRMM patients. Efficacy and safety reflect prior reports and support a favorable clinical benefit-risk profile for ide-cel at target dose levels ≥150 × 10^6 CAR+ T cells.

Target Dose, × 10^6 CAR+ T cells	50 (n=3)	150 (n=18)	450[a] (n=38)	800 (n=3)	Total (N=62)
Safety[b]					
CRS overall, n (%)	2 (67)	7 (39)	35 (92)	3 (100)	47 (76)
Grade ≥3, n (%)	0	0	3 (8)	1 (33)	4 (6)
NT overall,[c] n (%)	0	5 (28)	20 (53)	2 (67)	27 (44)
Grade ≥3, n (%)	0	0	2 (5)	0	2 (3)
Efficacy					
ORR, n (%)	1 (33)	9 (50)	34 (89)	3 (100)	47 (76)
CR rate,[d] n (%)	0	7 (39)	14 (37)	3 (100)	24 (39)
≥VGPR rate, n (%)	0	7 (39)	30 (79)	3 (100)	40 (65)
Median DOR (95% CI),[e,f] mo	1.9 (NE–NE)	13.7 (2.9–39.6)	10.0 (6.3–14.8)	12.9 (10.9–NE)	10.3 (7.7–13.7)
Median PFS (95% CI),[e] mo	2.1 (1.1–2.9)	4.5 (2.0–12.0)	9.0 (7.2–12.2)	13.9 (11.9–NE)	8.8 (5.9–11.9)
Median OS (95% CI),[e] mo	6.0 (5.1–9.3)	NE (10.8–NE)	34.2 (23.2–NE)	21.2 (19.2–NE)	34.2 (19.2–NE)

Data cutoff: January 14, 2020. CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NA, not applicable; NE, not estimable; NT, neurologic toxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

[a]One patient who received 205 × 10^6 CAR+ T cells and 1 who received 305 × 10^6 are included under the 450 × 10^6 target dose.

[b]Adverse events occurring after ide-cel infusion.

[c]NT includes preferred terms from focused Medical Dictionary for Regulatory Activities version 22.0: neurotoxicity, confusional state, insomnia, tremor, gait disturbance, somnolence, delirium, disturbance in attention, lethargy, aphasia, bradyphrenia, brain edema, cognitive disorder, depressed level of consciousness, dysarthria, dysgraphia, hallucination, memory impairment, nystagmus, postural tremor, and sleep disorder. All symptoms of CRS are included.

[d]Defined as the rate of CR or stringent CR.

[e]Kaplan-Meier estimate.

[f]Duration among responders with partial response or better.

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Springer Healthcare Ibérica S.L.
Rosario Pino, 14 - 4ª Planta. 28020 Madrid. Spain
Tel.: +34 91 555 40 62. Fax: +34 91 555 76 89
E-mail: Miguel.Quesada@springer.com
www.springerhealthcare.com
www.springernature.com

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