Division Director Memo
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapies

APPLICATION:	BLA 125736	**TRADE NAME:**	ABECMA
APPLICANT/SPONSOR:	Celgene Corporation, a Bristol-Myers Squibb Company	**ESTABLISHED NAME:**	idecabtagene vicleucel)
SUBMISSION DATE	7/27/20		
PDUFA DATE	3/26/21	**PRODUCT CLASS:**	B-cell maturation antigen (BCMA)- directed, genetically modified autologous T cell immunotherapy
REVIEW DATE:	3/26/21	**ROUTE:**	Intravenous infusion

INDICATION: for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Review Team (for comprehensive review team members from other offices, please see SBRA)

Clinical: Drs. Poornima Sharma and Bindu Kanapuru (OCE); **Statistical:** Dr. Mary Lin; **Pharm/Tox**: Dr. Shana Hardy; **Clin Pharm**: Dr. Xiaofei Wang; **CMC**: Drs. Anna Kwilas, Jakob Chery, and Bo Liang

REVIEW SUMMARY:

Celgene Corporation submitted this original BLA to seek marketing approval for ABECMA, a BCMA- directed, genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory (R/R) multiple myeloma after at least three or more lines of therapy.

The primary evidence of effectiveness and safety to support this application is generated from Study BB2121-MM001, a Phase 2, single-arm, open-label multicenter study in adults with relapsed or refractory (R/R) multiple myeloma after three or more lines of prior therapy to include an immunomodulatory drug (IMiD), proteasome inhibitor and an anti-CD38 antibody. Of the 135 subjects who underwent leukapheresis, 127 received ABECMA in three dose cohorts ranging from 150×10^6 and 450×10^6, and these subjects comprised the safety analysis set. Of the 127 treated subjects, 100 were treated with ABECMA in the 300×10^6 and 450×10^6 dose range, and were considered efficacy-evaluable, comprising the primary efficacy analysis set. The pre-specified primary efficacy endpoint was objective response rate (ORR), which included stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) as determined by an Independent Response Committee (IRC). Key secondary efficacy endpoints included duration of response (DOR) and minimal residual disease (MRD) negativity.

The IRC assessed the ORR as 72% (95% CI: 62%, 81%), sCR as 28% (95% CI: 19%, 38%), VGPR as 25% (95% CI: 17%, 35%) and PR as 19% (95% CI: 12%, 18%), with a median duration of response (DOR) of 11 months. The DOR was estimated to be higher in patients with a sCR (estimated to be 19 months). The MRD negativity rate was 21% (95% CI: 13%, 30%) in all efficacy evaluable subjects and 75% (95% CI: 55%, 89%) in patients achieving sCR, Of the efficacy evaluable population, 88% had received 4 or more prior lines of therapy.

With respect to safety, serious adverse reactions associated with ABECMA included cytokine release syndrome, neurologic toxicity, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged cytopenias, infections, and hypogammaglobulinemia. Cytokine release syndrome (CRS) and neurologic toxicity were reported in 85% and 28% of subjects, respectively. Grade 3 and higher CRS and neurotoxicity were reported in 9% and 4% of subjects, respectively. Other common adverse reactions occurring at an incidence of ≥ 20%, included, fatigue, musculoskeletal pain, diarrhea, upper respiratory tract infection, nausea, encephalopathy, edema, pyrexia, cough, headache, and decreased appetite.

I conclude that the Applicant has provided substantial evidence of effectiveness and safety from an adequate and well controlled study as well as confirmatory evidence from nonclinical studies to support an indication for the treatment of adults with relapsed/refractory multiple myeloma after 4 or more prior lines of therapy (including an IMiD, proteasome inhibitor, and anti-CD 38 antibody). Although the Applicant proposed an indication in adults with R/R multiple

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myeloma after 3 or more prior lines of therapy, as 88% of the subjects had received 4 or more prior lines of therapy, the data support a regular approval in patients who received 4 or more prior lines of therapy. The benefit/risk profile is favorable with implementation of a REMS for the serious life-threatening risks of CRS and neurotoxicity. I concur with the review team's, to include OCE's, recommendation of Approval with a Risk Mitigation and Evaluation Strategy (REMS) and a PMR for a postmarketing observational study to assess long-term toxicities of ABECMA, particularly secondary malignancies.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION

X	**APPROVAL**		**COMPLETE RESPONSE**		

Tejashri Purohit-Sheth, M.D.
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