I concur with this review memo. I Wu 2/24/21

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch

BLA NUMBER:	STN # 125736.000
DATE RECEIVED BY CBER[1]:	July 27, 2020
DATE REVIEW COMPLETED:	December 9, 2020; revised December 25, 2020; February 23, 2021
PRODUCT[2]:	Idecabtagene vicleucel (ABECMA®; ide-cel; bb2121)
APPLICANT:	Celgene Corporation
PROPOSED INDICATION:	Treatment of adult patients with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody
PHARM/TOX REVIEWER:	Shana Hardy
PHARM/TOX TEAM LEADER:	Allen Wensky
PHARM/TOX BRANCH CHIEF:	Iwen Wu
PRODUCT (CMC) REVIEWERS:	Anna Kwilas, Jacob Reiser, Jessica Chery
CLINICAL REVIEWERS:	Poornima Sharma, Marc Theoret (CDER/OCE), Bindu Kanapuru (CDER/OCE)
PROJECT MANAGER:	Juliane Carvalho and Colleen Caldwell
DIVISION DIRECTOR:	Tejashri Purohit-Sheth
OFFICE DIRECTOR:	Wilson Bryan

EXECUTIVE SUMMARY:

ABECMA®; (Idecabtagene vicleucel; ide-cel; bb2121) is a cell suspension consisting of autologous human CD3+ T cells that are transduced with a lentiviral vector encoding a chimeric antigen receptor (CAR) that contains an anti-BCMA single-chain variable fragment (scFv) linked to a CD8 hinge and transmembrane domain with a 4-1BB and CD3ζ T cell activating domain.

In vitro co-culture studies of bb2121 and various tumor cell lines demonstrated BCMA-specific cytokine production, proliferation, and cytotoxicity. In vivo proof-of-concept (POC) studies were

also conducted to evaluate the anti-tumor activity of bb2121 in a xenograft murine model of multiple myeloma (MM). In (b) (4) mice bearing subcutaneous BCMA+ (b) (4) human MM xenografts, intravenous administration of bb2121 demonstrated dose-dependent anti-tumor activity and improved survival compared to control mice.

In vivo distribution of bb2121 was observed in the perfused organs including the lungs, blood, bone marrow, liver and spleen in (b) (4) mice. A biphasic peak expansion of bb2121 cells was observed on Days 2 and 11 in the peripheral blood and Days 8 and 15 in analyzed tissues in tumor-bearing mice. No bb2121-related adverse findings were reported in these studies.

No traditional genotoxicity assays and carcinogenicity assessments were performed for bb2121. The safety of bb2121 was assessed by evaluating the integration profile of the lentiviral vector. Integration site analysis was performed for 20 clinical drug product lots. The resulting data showed that the lentiviral vector does not preferentially integrate in or near genes of concern for oncogenic transformation and is consistent with other similar vectors. Additionally, an IL-2-independent growth assay of bb2121 generated from five patient donors and two healthy donors showed no signs of uncontrolled cellular proliferation.

No animal reproductive and developmental toxicity studies were conducted for bb2121 which is acceptable based on the product characteristics.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION[3]:
There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of bb2121. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry[4]:
Idecabtagene vicleucel (ide-cel, bb2121) consists of autologous CD3+ T cells that are transduced using a lentiviral vector to express a BCMA-directed chimeric antigen receptor (CAR). The anti-BCMA CAR construct is comprised of: 1) a single-chain variable fragment (scFv) binding domain derived from a murine BCMA-specific monoclonal antibody (mAb, (b) (4)), 2) human CD8α hinge and transmembrane domain, 3) CD137 (4-1BB) signaling domain, and 4) CD3ζ activation domain (Figure 1).

After lentiviral transduction, the T cells are expanded, washed, harvested, formulated into a cell suspension and cryopreserved in a solution containing Plasma-Lyte A and CryoStor® CS10, resulting in a final DMSO concentration of 5%. A single dose of ide-cel contains a cell suspension of (b) (4) $\times 10^6$ CAR+ T cells in one or more infusion bags.

(b) (4)

Source: Module 2.6.1, page 4

Abbreviations

41BB	CD137; member of the TNF-receptor superfamily
bb2121	Idecabtagene vicleucel
BCMA	B cell maturation antigen
BD	biodistribution
BL	Burkitt's lymphoma
CAR	chimeric antigen receptor
CD	cluster of differentiation
CRS	cytokine release syndrome
(b) (4)	
FFPE	formalin-fixed paraffin-embedded
GLP	Good Laboratory Practice
HC	high confidence
HED	human equivalent dose
HL	Hodgkin Lymphoma
ide-cel	Idecabtagene vicleucel, bb2121
IFNγ	interferon gamma
(b) (4)	
IL-2	interleukin 2
IS	insertion site
ISA	insertion site analysis
IV	intravenous
MED	minimum effective dose
MM	multiple myeloma
NHL	non-Hodgkin lymphoma
NOD	non-obese diabetic
(b) (4)	
PB	PB
PBMC	peripheral blood mononuclear cell
(b) (4)	
PD	pharmacodynamics
PDL	population doubling level
PK	pharmacokinetics
(b) (4)	
(b) (4)	
sBCMA	soluble BCMA

scFv	single-chain variable fragment
SCID	severe combined immune deficient
SIN	self-inactivating
TLS	tumor lysis syndrome
TSS	transcription start site
VCN	vector copy number
WT HIV	wild-type human immunodeficiency virus

Related File(s):

IND #16664; Celgene Corp; Autologous Peripheral Blood Mononuclear Cells (PBMCs) Transduced with Anti-BCMA02 CAR Lentiviral Vector Expressing Chimeric Antigen Receptor to Human B Cell Maturation Antigen (Anti-BCMA CAR; bb2121) for BCMA-expressing refractory/relapsed multiple myeloma; ACTIVE

IND #22482; Celgene Corp; Autologous T-cells Transduced With Anti-BCMA02 CAR LVV Expressing Chimeric Antigen Receptor to Human B-Cell Maturation Antigen (ide-cel, bb2121), in combination with Iberdomide (CC-220), or BMS-986-405 (JSMD194), or a standard triplet regimen of either Daratumumab (DARA) Pomalidomide (POM) and Dexamethasone (DPd), or Pomalidomide (POM), Bortezomib (BTZ) and Dexamethasone (PVd) for adult patients with relapsed/refractory multiple myeloma; ACTIVE

Table of Contents

INTRODUCTION

Multiple myeloma (MM) is the second most common hematological malignancy characterized by uncontrolled proliferation of monoclonal plasma cells in the bone marrow.[1] Clinical consequences associated with MM include severe bone pain, renal insufficiency, dramatic bone loss, lytic bone lesions, and pathologic fractures that decrease the quality of life and impact survival of individuals diagnosed with MM.[2] The disease trajectory varies for each patient; however, relapse frequently occurs, and patients can become refractory to standard treatments.[3]

BCMA is a cell surface tumor necrosis factor protein receptor (TNFRSF17) expressed on normal and malignant plasma cells. It is involved in the regulation of B-cell maturation and differentiation into plasma cells. BCMA ligands include B cell activating factor (BAFF) and A proliferation-induced ligand (APRIL). BAFF is primarily secreted by cells of B cell lineage, while APRIL is secreted by several cell types, including monocytes, macrophages, dendritic cells and T cells. Collectively, BCMA and BAFF/APRIL function to promote the survival and homeostasis of plasma cells.[4] BCMA is highly expressed on malignant plasma cells from all relapsed or newly diagnosed MM patients and is believed to contribute to the survival of MM cancer cells. Notably, BCMA is reported to have a restricted expression profile, with expression primarily limited to plasma cells and absent in normal non-hematopoietic cells, hematopoietic stem cells, and naïve B-cells.[5,6]

The bb2121 anti-BCMA CAR T cell product is intended to target BCMA-expressing tumor cells. The purported mechanism of action for anti-tumor activity of bb2121 is that once bb2121 binds

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[1] Rajkumar, S. V., Dimopoulos, M. A., Palumbo, A., Blade, J., Merlini, G., Mateos, M. V., Kumar, S., Hillengass, J., Kastritis, E., Richardson, P., Landgren, O., Paiva, B., Dispenzieri, A., Weiss, B., LeLeu, X., Zweegman, S., Lonial, S., Rosinol, L., Zamagni, E., Jagannath, S., … Miguel, J. F. (2014). International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet. Oncology, 15(12), e538–e548.

[2] Esteve, F. R., & Roodman, G. D. (2007). Pathophysiology of myeloma bone disease. Best practice & research. Clinical haematology, 20(4), 613–624.

[3] Bazarbachi, A. H., Al Hamed, R., Malard, F., Harousseau, J. L., & Mohty, M. (2019). Relapsed refractory multiple myeloma: a comprehensive overview. Leukemia, 33(10), 2343–2357.

[4] Rickert, R. C., Jellusova, J., & Miletic, A. V. (2011). Signaling by the tumor necrosis factor receptor superfamily in B-cell biology and disease. Immunological reviews, 244(1), 115–133.

[5] Tai, Y. T., Mayes, P. A., Acharya, C., Zhong, M. Y., Cea, M., Cagnetta, A., Craigen, J., Yates, J., Gliddon, L., Fieles, W., Hoang, B., Tunstead, J., Christie, A. L., Kung, A. L., Richardson, P., Munshi, N. C., & Anderson, K. C. (2014). Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood, 123(20), 3128–3138. https://doi.org/10.1182/blood-2013-10-535088

[6] Carpenter, R. O., Evbuomwan, M. O., Pittaluga, S., Rose, J. J., Raffeld, M., Yang, S., Gress, R. E., Hakim, F. T., & Kochenderfer, J. N. (2013). B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clinical cancer research : an official journal of the American Association for Cancer Research, 19(8), 2048–2060.

to its cognate antigen, it becomes activated, proliferates, and subsequently exerts cytotoxic effects against BCMA-expressing cells.

NONCLINICAL STUDIES

The following bb2121 test article lots were used for the nonclinical studies submitted in the BLA:

Study Number	CAR T Cell Product Experiment No.*
1	N/A
2	TC14028
3	N/A
4	N/A
5	TC14028
6	TC14094
7	TC14094
8	TC14094
9	TC14094
10	TC14094
Study Number	**bb2121 Drug Product Lot No.**
11	(b) (4)
12	(b) (4)

***Lot Nos. were not assigned for CAR T cells assessed in nonclinical studies #1-8; they were manufactured under Experiment Nos.**

Reviewer's comment: *The release criteria for bb2121 clinical lots include ≥ 95% CD45+ CD3+ T cells, ≥ 78% viability, and ≥18% CAR+ T cells. According to the certificates of testing (COTs) included in the study reports, those specifications were met for the nonclinical experiment batches.*

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies[5]

The following pharmacology studies were conducted to support the rationale for the administration of bb2121 for the proposed clinical indication.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	Evaluation of the In Vitro Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells	B4-15-131
2	An (b) (4) Survey of BCMA Expression on Human Multiple Myeloma and Lymphoma Tumor Cell Lines and Primary Human Multiple Myeloma and Lymphoma Tumor Biopsies	B4-15-121
3	Evaluation of Unintended (Off-target) Binding of Anti-BCMA Antibodies on (b) (4) Expressing BCMA-related and Non-BCMA-related Human Proteins	B4-15-137
4	A Tissue Cross-reactivity Study of Goat Polyclonal Anti-human BCMA Antibody (b) (4) of Normal Human Tissues	B4-15-097 (20071647)

In Vivo Studies

***In Vivo* Studies in Tumor Xenograft Animal Models**

Study Number	Study Title / Publication Citation	Report Number
5	Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts	B4-14-011
6	Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with Large BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts	B4-14-043
7	Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts	B4-14-047
8	Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+/CD19+ (b) (4) Human Burkitt's Lymphoma Systemic Xenografts	B4-14-050
9	Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+/CD19+ (b) (4) Human Burkitt's Lymphoma Systemic Xenografts	B4-14-065

Overview of Pharmacology Studies

Overview of In Vitro Studies

Study #1: Evaluation of the In Vitro Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells (Study Report #B4-15-131)

This report included a series of in vitro pharmacology experiments to evaluate 1) the surface expression of anti-BCMA CARs on bb2121, 2) correlation of tumor cell line expression of BCMA mRNA and receptor density with bb2121 secretion of IFNɣ, 3) bb2121 BCMA-specific cytokine secretion, 4) bb2121 BCMA-specific cytotoxicity, 5) bb2121 BCMA-specific proliferation, and 6) BCMA mRNA expression in primary human tissues and lymphomas. These assessments are summarized below.

1. **Anti-BCMA CAR Expression**: Anti-BCMA CAR expression in bb2121 was evaluated after transduction of healthy donor T cells with the BCMA02 lentiviral vector (clinical construct). The anti-BCMA CAR was detected by (b) (4) . Expression was observed on >50% of bb2121 cells.

2. **BCMA expression/ bb2121 activity correlation**: To correlate BCMA expression with bb2121 activity, various MM and lymphoma cell lines were tested for BCMA expression and receptor density via (b) (4) , respectively. This was followed by producing bb2121 from 3 healthy donors, co-incubating them with the selected cell lines, and assessing activation of bb2121 by measuring IFNɣ secretion by (b) (4).

   BCMA expression was observed in the following cell lines, (b) (4) (12590 receptors/cell), (b) (4) (3173 receptors/cell), (b) (4) (222 receptors/cell), (b) (4) (1219 receptors/cell), (b) (4) (1173 receptors/cell), and (b) (4) (1713 receptors/cell). BCMA expression was absent in (b) (4) cells were also transduced to express BCMA at low and high densities, and the cell lines are designated as (b) (4) BCMA (16) and (b) (4) BCMA (B5), respectively. BCMA expression was confirmed in the engineered lines, with 5061 receptors/cell in (b) (4) BCMA (16) and 76942 receptors/cell in (b) (4) BCMA (B5). BCMA mRNA expression levels were consistent with f(b) (4) BCMA receptor densities.

   bb2121 activation was observed in all cell lines expressing BCMA. This activation was correlated to BCMA mRNA expression and receptor density (i.e., in order of greatest IFNɣ secretion: (b) (4) .

3. **bb2121 activation against CLL Patient PBMCs**: The activity of bb2121 was also evaluated against (b) (4) cells expressing variable amounts of BCMA ((b) (4) -BCMA+) and PBMCs collected from healthy subjects and chronic lymphocytic leukemia (CLL) patients, with or without BCMA expression. Activation was confirmed by measuring the secretion of IFNɣ.

   The results showed bb2121 activation against BCMA+ cells (i.e., (b) (4) -BCMA+ , (b) (4) , and CLL-BCMA+ PBMCs). The highest levels of IFNɣ release were observed against (b) (4) -BCMA (B5), which expresses BCMA at the highest density of all the cell lines tested. bb2121 secreted IFNɣ at similar levels against (b) (4) and CLL-BCMA+ PBMCs. There were no detectable amounts of IFNɣ secreted by bb2121 co-cultured with healthy PBMCs or CLL-BCMA- cells.

4. **bb2121 BCMA-specific cytotoxicity**: BCMA positive tumor cells lines were co-cultured with bb2121 or negative control anti-CD19 CAR T cells at varying effector-to-target (E:T) cell ratios of 0.3:1, 1:1, 3:1, and 10:1 for 4 hours. bb2121 cytotoxicity was observed against BCMA positive cells. Little to no cytotoxicity was observed against

BCMA-negative cells. CD19 CAR T cells exhibited little to no cytolysis against any of the tumor cells.

Reviewer comment*: Although the sponsor reports to have tested bb2121 cytolysis against BCMA-negative tumor cells lines in the description of their study design, the data was not provided in the study report.*

5. **bb2121 BCMA-specific proliferation:** bb2121 proliferation was assessed following co-culture with (b) (4) cells with and without BCMA expression. T cell proliferation was quantified via (b) (4) by measuring the (b) (4) . T cell proliferation was only observed against (b) (4)-expressing BCMA cells.

6. **BCMA mRNA expression in primary human tissues and lymphomas:** BCMA mRNA expression was evaluated in 42 primary lymphomas and 6 normal tissues (i.e., lymph node, spleen) or inflamed tissue controls (i.e., colitis, pancreatic adenocarcinoma, lymph node granuloma). Forty-five per cent (45%) of the lymphoma samples expressed substantial levels of BCMA mRNA, of which 91% were NHL and 5% Hodgkin Lymphoma (HL); 78% of the remaining lymphoma samples expressing lower levels of BCMA mRNA with 55% NHL and 22% HL. 83% of HL samples did not express significant levels of BCMA. In non-lymphoma tissues, BCMA expression was only observed in healthy tissues enriched with plasma cells (i.e., spleen tissue and ulcerative colitis), likely due to BCMA+ plasma cells being present in these tissues.

Study #2: An (b) (4) Survey of BCMA Expression on Human Multiple Myeloma and Lymphoma Tumor Cell Lines and Primary Human Multiple Myeloma and Lymphoma Tumor Biopsies (Study Report #B4-15-121)

(b) (4) of BCMA was conducted on MM and lymphoma (HL and NHL) tumor cell lines tested in Study Report #B4-15-131 and patient tissue biopsies. Control cells included (b) (4) BCMA (16), and (b) (4) BCMA (B5). BCMA (b) (4) was observed in MM and lymphoma cell lines reported to express BCMA receptor protein, consistent with results form Study Report #B4-15-131, and absent in BCMA- tumor cell lines, with the exception of the (b) (4) cell line. The (b) (4) cell line exhibited low receptor density by (b) (4) but (b) (4) negative for BCMA (b) (4) by (b) (4). BCMA expression has been reported on some lymphoma cell lines, including (b) (4) cells by other investigators.[7,8]

[7] Coquery, C. M., & Erickson, L. D. (2012). Regulatory roles of the tumor necrosis factor receptor BCMA. Critical reviews in immunology, 32(4), 287–305.

[8] Rennert, P., Schneider, P., Cachero, T. G., Thompson, J., Trabach, L., Hertig, S., Holler, N., Qian, F., Mullen, C., Strauch, K., Browning, J. L., Ambrose, C., & Tschopp, J. (2000). A soluble form of B cell maturation antigen, a receptor for the tumor necrosis factor family member APRIL, inhibits tumor cell growth. The Journal of experimental medicine, 192(11), 1677–1684.

Regarding the BCMA (b) (4) of MM and lymphoma biopsies, BCMA protein (b) (4) was most prevalent in MM biopsies, in which BCMA (+) cells represented ≥ 50% of tumor tissue area in 41% of MM biopsies. BCMA protein (b) (4) was less prevalent in lymphoma (HL and NHL) biopsies. BCMA (+) cells represented 5% to 50% of tissue in 57% of HL biopsies and in 18% of NHL biopsies, which was inconsistent with BCMA mRNA expression levels assessed in HL and NHL biopsy samples in Study Report #B4-15-131. Per the applicant, BCMA mRNA and protein ((b) (4)) were not directly compared on the same samples. Therefore, the differences in results for mRNA and BCMA expression may represent differences in the samples evaluated and/or differences between mRNA and protein expression within any single sample.

Study #3: Evaluation of Unintended (Off-target) Binding of Anti-BCMA Antibodies on (b) (4) Expressing BCMA-related and Non-BCMA-related Human Proteins (Study Report #B4-15-137)

The objective of this non-GLP study was to evaluate off-target binding of four anti-human BCMA antibodies to BCMA-related and non-BCMA-related proteins using a (b) (4) of (b) (4) cell lines, each transduced with a vector coding for (b) (4) The proteins expressed in the (b) (4) array included BCMA ((b) (4)), 22 of 29 known related (b) (4) members, and a random selection of 358 other proteins. The anti-human BCMA antibodies (test articles) included 1) a commercially available goat polyclonal immunoglobulin G (IgG) antibody ((b) (4)), a commercially available mouse monoclonal IgG2a antibody (mAb) clone (b) (4) and proprietary mouse IgG1 mAb clones (b) (4) . Control articles included goat IgG control and mouse IgG1 and IgG2a controls. Transgenic protein expression and test article/antibody binding was detected and measured using a (b) (4) .

The results indicated that (b) (4) does not express BCMA or related proteins that could be recognized by any of the test articles used. In the (b) (4) was detected with all of the anti-human BCMA antibodies when co-incubated with BCMA-expressing cells. It was reported that these antibodies did not bind to any of the 22 TNFRSF member proteins or 358 unrelated proteins.

Reviewer's comments:

- *This study was not conducted with the bb2121 scFv clone (b) (4) . Thus, this study does not directly assess the potential cross-reactivity of bb2121 and potential for off-target activity.*

- *The results showed that the anti-BCMA antibodies tested are specific for BCMA and indicates that they do not appear to cross-react with other (b) (4) member proteins.*

Study #4: A Tissue Cross-reactivity Study of Goat Polyclonal Anti-human BCMA Antibody (b) (4) of Normal Human Tissues (Study Report #B4-15-097)

Report Number	B4-15-097
Date Report Signed	13-JULY-2015
Title	A Tissue Cross-reactivity Study of Goat Polyclonal Anti-human BCMA Antibody (b) (4) of Normal Human Tissues
GLP Status	Yes
Testing Facility	(b) (4)
Objective(s)	To evaluate the cross-reactivity of a commercially available human BCMA-directed polyclonal goat IgG antibody (goat anti-BCMA, (b) (4)) against human tissues derived from three separate donors to assess expression and distribution of BCMA.
Test Article(s)	Goat anti-human BCMA (b) (4)
Control Article(s)	Goat anti-chicken IgY (Jackson (b) (4)
Experimental Design	Tissue cross-reactivity was evaluated by (b) (4) and scored by a board-certified pathologist. Positive controls included the BCMA+ (b) (4) MM cell line and human small intestine tissues containing mononuclear cells in the lamina propria (cryosection) positive for BCMA. BCMA- (b) (4) cells served as the negative control. See Table 1 for the tissues assessed.

Table 1: Normal Human Tissues Assessed from Three Separate Donors

Adrenal	Heart	Salivary Gland
Bladder (urinary)	Kidney (glomerulus, tubule)	Skin
Blood Cells [a]	Liver	Spinal Cord
Blood Vessels (endothelium) [b]	Lung	Spleen
Bone Marrow	Lymph Node	Striated Muscle (skeletal)
Brain – cerebellum	Ovary	Testis
Brain – cerebrum (cerebral cortex)	Pancreas	Thymus
Breast	Parathyroid	Thyroid
Colon (large intestine)	Peripheral Nerve	Tonsil
Eye	Pituitary	Ureter
Fallopian Tube	Placenta	Uterus – cervix
Gastrointestinal (GI) Tract [c]	Prostate	Uterus – endometrium

[a] Evaluated from peripheral blood smears.
[b] Evaluated from all tissues where present.
[c] Includes esophagus, small intestine, and stomach (including underlying smooth muscle).

Samples (from at least three separate donors) from each of the above listed tissues were evaluated. After pathology review, it was determined that some of the tissue sample(s) did not contain a sufficient amount of the required tissue for evaluation or were determined to be unsuitable for evaluation due to tissue morphology. Therefore, additional sample(s) of the tissue were stained and evaluated to obtain the required three samples of each tissue.

Source: Module 4.2.3.4.3, B4-15-097, page 12

Key Results:

- Membrane and cytoplasm (b) (4) were observed on (b) (4) tumor cells and resident, migrating, or infiltrating B-cell lineage mononuclear cells in several human tissues including the colon, fallopian tubes, GI-tract tissues (i.e., esophagus, stomach, small intestine), prostate, thymus, and tonsils.

- Rare (b) (4) was also observed in the cytoplasm of spindle cells in one thyroid and two tonsil samples. Per the report, spindle cell (b) (4) was unexpected and may be non-specific.

Reviewer comments:

- *Note, the TCR study was conducted with a commercially available anti-BCMA polyclonal antibody, rather than bb2121 scFv clone* (b) (4) .

- *There have been no reports in the literature regarding BCMA protein expression in spindle cells. Thus, non-specific* (b) (4) *cannot be ruled out.*

- *The report concludes that the BCMA* (b) (4) *is consistent with literature reports of restricted BCMA protein expression in plasma cells. This reviewer concurs with this conclusion.*[9,10]

Overview of In Vivo Studies

***In Vivo* Studies in Xenograft Tumor Animal Models**

Study #5: Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) ***Mice with BCMA+*** (b) (4) ***Human Multiple Myeloma Subcutaneous Xenografts (Study Report #B4-14-011)***

Report Number	B4-14-011
Date Report Signed	26-AUG-2015
Title	Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+ (b) (4) Human Multiple Myeloma Subcutaneous Xenografts
GLP Status	No

[9] Tai, Y. T., Mayes, P. A., Acharya, C., Zhong, M. Y., Cea, M., Cagnetta, A., Craigen, J., Yates, J., Gliddon, L., Fieles, W., Hoang, B., Tunstead, J., Christie, A. L., Kung, A. L., Richardson, P., Munshi, N. C., & Anderson, K. C. (2014). Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood, 123(20), 3128–3138.

[10] Bu, D. X., Singh, R., Choi, E. E., Ruella, M., Nunez-Cruz, S., Mansfield, K. G., Bennett, P., Barton, N., Wu, Q., Zhang, J., Wang, Y., Wei, L., Cogan, S., Ezell, T., Joshi, S., Latimer, K. J., Granda, B., Tschantz, W. R., Young, R. M., Huet, H. A., … Milone, M. C. (2018). Pre-clinical validation of B cell maturation antigen (BCMA) as a target for T cell immunotherapy of multiple myeloma. Oncotarget, 9(40), 25764–25780.

<table>
<tr><td colspan="2">Testing Facility</td><td>(b) (4)
Study Reference No.: (b) (4)</td></tr>
<tr><td colspan="2">Objective(s)</td><td>To evaluate the activity of bb2121 in (b) (4) mice with BCMA+ (b) (4) human MM subcutaneous (SC) xenografts.</td></tr>
<tr><td rowspan="6">Study Animals</td><td>Strain/Breed</td><td>(b) (4)</td></tr>
<tr><td>Species</td><td>Mouse (Mus musculus)</td></tr>
<tr><td>Age</td><td>5 weeks</td></tr>
<tr><td>Body Weight</td><td>19.5 g</td></tr>
<tr><td>#/sex/group</td><td>10/f/group</td></tr>
<tr><td>Total #</td><td>70</td></tr>
<tr><td colspan="2">Test Article(s)</td><td>bb2121</td></tr>
<tr><td colspan="2">Control Article(s)</td><td>(b) (4) media (vehicle),
Bortezomib (positive control),
(b) (4) anti-CD19Δ CAR T cells (negative control)

Note: (b) (4) contains an anti-CD19 CAR lacking the T cell signaling domains</td></tr>
<tr><td colspan="2">Route of Administration</td><td>Intravenous (IV)</td></tr>
<tr><td colspan="2">Description of the Disease/Injury Model and Implant Procedure</td><td>Mice received 1×10^7 BCMA+ (b) (4) MM tumor cells/mouse via SC injections to establish SC xenografts.

Note: (b) (4) is a human MM cell line that has moderate to high levels of BCMA expression.

Two groups of mice received test and control articles 18 days post-tumor cell administration (Day 1). An additional group received repeat dosing of Bortezomib, which was began 18 days post-tumor cell administration on Days 1, 5, 8, 12, 15, 29, 22, and 25 at 1 mg/kg.

Note: The study included a deviation, in which mice were not administered Bortezomib on Day 12 due to significant weight loss observed in this group.</td></tr>
<tr><td colspan="2">Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test Article</th><th>Dose Level</th></tr>
<tr><td>1</td><td>Vehicle</td><td>N/A</td></tr>
<tr><td>2</td><td>Bortezomib</td><td>1 mg/kg</td></tr>
<tr><td>3</td><td>(b) (4)</td><td>5.85×10^6 cells/mouse
(2.92×10^8 cells/kg)*</td></tr>
<tr><td>4</td><td>bb2121</td><td>5.24×10^6 cells/mouse
(2.62×10^8 cells/kg)</td></tr>
</table>
*Dose per kg was extrapolated based on a 20 g mouse

Note: dose levels for (b) (4) and bb2121 were based on CAR-positive cells</td></tr>
<tr><td colspan="2">Dosing Regimen</td><td>Single administration</td></tr>
<tr><td colspan="2">Randomization</td><td>Yes</td></tr>
<tr><td colspan="2">Description of Masking</td><td>Not specified</td></tr>
<tr><td colspan="2">Scheduled Sacrifice Time Points</td><td>Day 85 post- test article administration</td></tr>
</table>

Key Evaluations and Assessments[6]:

Evaluations/ Assessments	Frequency and/or Details
Mortality (Survival)	Daily
Cageside / Clinical Observations (i.e., body condition, posture, eye appearance, and activity)	Daily
Body weights	Twice weekly
Tumor Volumes	Twice weekly

Key Results:

- The number of mice surviving until Day 85 was 0/10 (0%) for the vehicle control, 1/10 (10%) for Bortezomib, 0/10 (0%) for (b) (4), and 10/10 (100%) for bb2121. No control group mice survived until scheduled euthanasia due to reasons related to tumor growth (tumor volumes ≥ 3000 mm^3), except one mouse in the Bortezomib group. This mouse was euthanized for moribundity on Day 28 for reasons unrelated to tumor growth.

- Abnormal clinical signs reported in mice that received bb2121 included hunched posture (6/10) and slight unkempt fur (7/10) on or after Day 25-61. The vehicle group animals exhibited hunched posture (4/10), and light to mild necrosis of the tumor (10/10) on or after Day 22. The (b) (4) group exhibited abnormal clinical signs similar to vehicle control group with slight to mild necrosis of the tumor (10/10), slight hunched posture (6/10) and slight unkempt fur (5/10), generally on or after Day 12. These clinical observations in the vehicle and negative control groups are typical of animals exhibiting tumor progression. Mice that received Bortezomib exhibited hunched posture (10/10), unkempt fur (10/10), pallor (1/10), and weight loss (6/10) by Day 12. In the Bortezomib group, slight to mild tumor necrosis was reported (7/10) by Day 43. Differences in body weights between control animals and the bb2121 group were not significant.

- bb2121 exhibited anti-tumor activity, with tumors no longer detectable by Day 19. Control articles (vehicle and (b) (4)) did not exhibit any anti-tumor activity (Figure 2). Bortezomib exhibited transient anti-tumor activity due to the completion of the dosing regimen prior to the end of the study (last dose was received on Day 25).

Figure 2: Tumor volume and survival of (b) (4) Xenograft Mice after the administration of bb2121

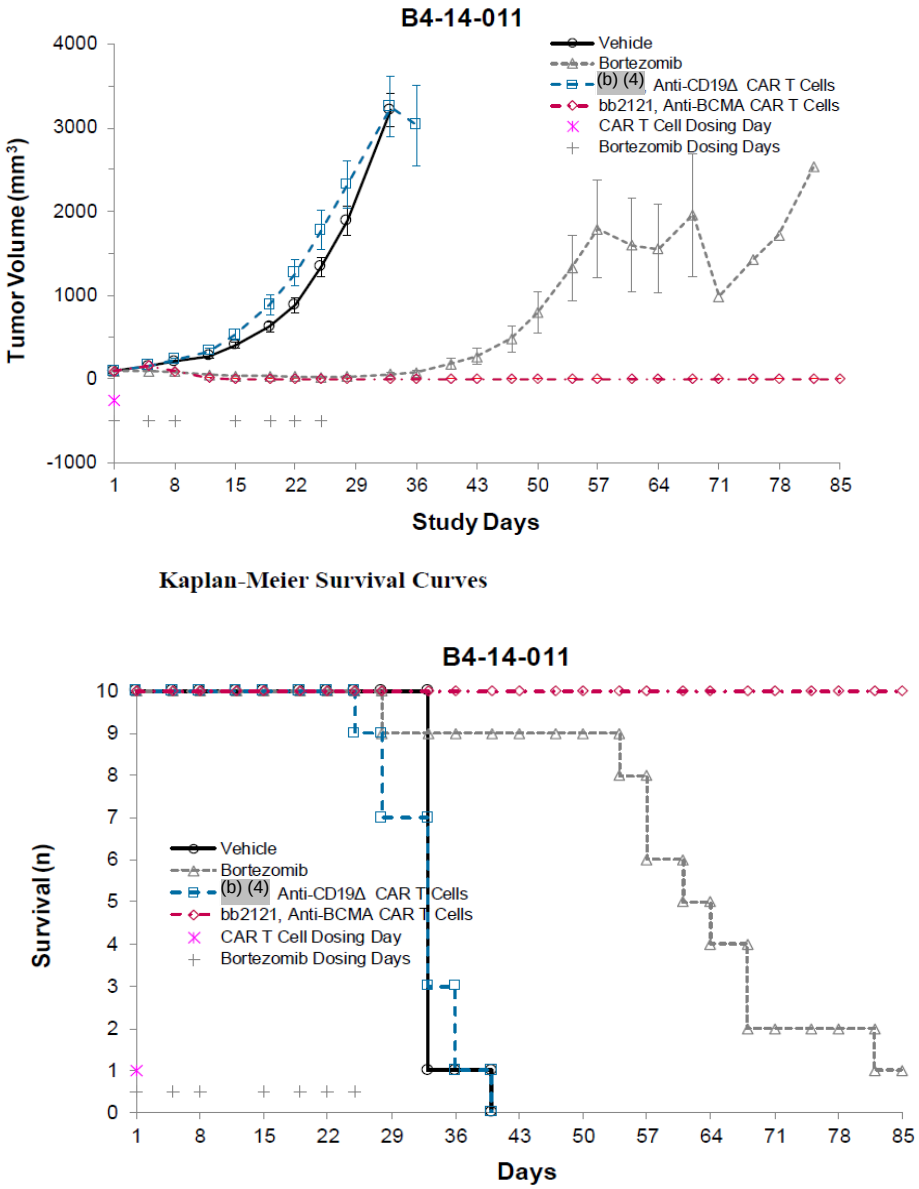

Figure 2: Tumor volumes (top) and survival (bottom) for (b) (4) mice with BCMA+ (b) (4) MM tumor cell xenografts administered bb2121 anti-BCMA CAR T cells, (b) (4) anti-CD19 CAR T cells, Bortezomib, or vehicle control.
Source: Module 2.6.2., Section 2.2.1, page 18

Reviewer comments:

- *The safety findings in the group receiving Bortezomib are likely due to the toxicities related to Bortezomib. Published studies have reported that Bortezomib is well tolerated in mice at doses up to 0.5 mg/kg. However, at a dose level of 1 mg/kg, adverse clinical findings were observed, similar to what was reported in this study (i.e., significant weight loss, lack of vitality, etc.).*[11]

- *This study demonstrated the anti-tumor activity of bb2121 which resulted in prolonged survival in this xenograft mouse model of MM.*

Study #6: Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with Large BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts (Study Report #B4-14-043)

Report Number		B4-14-043
Date Report Signed		26-AUG-2015
Title		Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with Large BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts
GLP Status		No
Testing Facility		(b) (4) Study Reference No.: B4-14-043
Objective(s)		To evaluate the activity of bb2121 in (b) (4) mice with large BCMA+ (b) (4) human MM subcutaneous (SC) xenografts.
Study Animals	**Strain/Breed**	(b) (4)
	Species	Mouse (*Mus musculus*)
	Age	6 weeks
	Body Weight	15-25 g
	#/sex/group	10/f/group
	Total #	65
Test Article(s)		bb2121
Control Article(s)		(b) (4) media (vehicle), Bortezomib, proteasome inhibitor (positive control), (b) (4), anti-CD19Δ CAR T cells (negative control)
Route of Administration		Intravenous (IV)

[11] LeBlanc, R., Catley, L.P., Hideshima, T., Lentzsch, S., Mitsiades, C.S., Mitsiades, N., Neuberg, D., Goloubeva, O., Pien, C.S., Adams, J., et al. (2002). Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. Cancer Res 62, 4996-5000.

<table>
<tr><td>Description of the Disease/Injury Model and Implant Procedure</td><td>Immune-deficient mice received 1×10⁷ BCMA+ (b) (4) MM tumor cells/mouse via SC injections to establish SC xenografts.
Note: (b) (4) is a human MM cell line that has moderate to high levels of BCMA expression.

Mice received test and control articles 39 days post-tumor cell administration (Day 1). Bortezomib was administered on Days 1, 4, 8, and 11.</td></tr>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test Article</th><th>Dose Level*</th></tr>
<tr><td>D</td><td>Vehicle</td><td>N/A</td></tr>
<tr><td>C</td><td>Bortezomib</td><td>1 mg/kg</td></tr>
<tr><td>B</td><td>(b) (4)</td><td>3.28×10⁶ cells/mouse
(1.64×10⁸ cells/kg)</td></tr>
<tr><td>A</td><td>bb2121</td><td>6.16 ×10⁶ cells/mouse
(3.08×10⁸ cells/kg)</td></tr>
</table>
*Dose per kg was extrapolated based on a 20 g mouse

Note: dose levels for (b) (4) and bb2121 were based on CAR-positive cells</td></tr>
<tr><td>Dosing Regimen</td><td>Single administration</td></tr>
<tr><td>Randomization</td><td>Yes, based on tumor volumes.</td></tr>
<tr><td>Description of Masking</td><td>All in-life personnel were blinded to the identity of the test and control articles assigned to each group</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>Day 50 post-test article administration</td></tr>
</table>

Key Evaluations and Assessments[7]:

Evaluations/ Assessments	Frequency and/or Details
Mortality (Survival)	Daily
Cageside / Clinical Observations (i.e., body condition, posture, eye appearance, and activity)	Daily
Body weights	Twice weekly
Tumor Volumes	Twice weekly

Key Results:

- The number of mice surviving until Day 85 was 0/10 (0%) for the vehicle control, 3/10 (30%) for Bortezomib, 0/10 (0%) for (b) (4) and 10/10 (100%) for bb2121.
- The vehicle and negative control groups exhibited clinical signs consistent with tumor progression and were euthanized between Days 16-29. One animal in the Bortezomib

group was found dead and one animal was euthanized due to severe weight loss. Slight weight loss was observed in mice that received bb2121.

- bb2121 exhibited anti-tumor activity, with tumors no longer detectable by Day 19. Control articles (vehicle and (b) (4)) did not exhibit any anti-tumor activity. Bortezomib exhibited transient anti-tumor activity likely resulting from the completion of the dosing regimen prior to the end of the study.

Reviewer comment: *The study supports the anti-tumor activity of bb2121 and durability of effect following a single administration of bb2121.*

Study #7: Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) ***Mice with BCMA+*** (b) (4) ***Human Multiple Myeloma Subcutaneous Xenografts (Study Report #B4-14-047)***

Report Number		B4-14-047
Date Report Signed		26-AUG-2015
Title		Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts
GLP Status		No
Testing Facility		(b) (4) Study Reference No.: B4-14-043
Objective(s)		To evaluate the pharmacologic dose response of bb2121 in (b) (4) mice with BCMA+ (b) (4) human MM subcutaneous (SC) xenografts.
Study Animals	**Strain/Breed**	(b) (4)
	Species	Mouse (*Mus musculus*)
	Age	8 weeks
	Body Weight	15-25 g
	#/sex/group	9/f/group
	Total #	102
Test Article(s)		bb2121
Control Article(s)		(b) (4) media (vehicle), Bortezomib, proteasome inhibitor (positive control)
Route of Administration		Intravenous (IV)
Description of the Disease/Injury Model and Implant Procedure		Immune-deficient mice received 1×10^7 BCMA+ (b) (4) MM tumor cells/mouse via SC injections to establish SC xenografts. **Note**: (b) (4) is a human MM cell line that has moderate to high levels of BCMA expression. Mice received test and control articles 20 days post-tumor cell administration (Day 1). Vehicle and bb2121 was administered on Day 1. Bortezomib was administered on Days 1, 5, 10, 14, and 21.

<table>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test Article</th><th>Dose Level*</th></tr>
<tr><td>F</td><td>Vehicle</td><td>N/A</td></tr>
<tr><td>D</td><td>Bortezomib*</td><td>1 mg/kg</td></tr>
<tr><td>E</td><td>bb2121</td><td>6.16 ×10^1 cells/mouse
(3.08×10^3 cells/kg)</td></tr>
<tr><td>C</td><td>bb2121</td><td>6.16 ×10^2 cells/mouse
(3.08×10^4 cells/kg)</td></tr>
<tr><td>B</td><td>bb2121</td><td>6.16 ×10^3 cells/mouse
(3.08×10^5 cells/kg)</td></tr>
<tr><td>G</td><td>bb2121</td><td>6.16 ×10^4 cells/mouse
(3.08×10^6 cells/kg)</td></tr>
<tr><td>A</td><td>bb2121</td><td>6.16 ×10^5 cells/mouse
(3.08×10^7 cells/kg)</td></tr>
<tr><td>H</td><td>bb2121</td><td>6.16 ×10^6 cells/mouse
(3.08×10^8 cells/kg)</td></tr>
</table>
**Dose per kg was extrapolated based on a 20 g mouse*
</td></tr>
<tr><td>Dosing Regimen</td><td>Single administration</td></tr>
<tr><td>Randomization</td><td>Yes, based on tumor volumes.</td></tr>
<tr><td>Description of Masking</td><td>All in-life personnel were blinded to the identity of the test and control articles assigned to each group</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>Day 23 post-test article administration</td></tr>
</table>

Key Evaluations and Assessments[8]:

Evaluations/ Assessments	Frequency and/or Details
Mortality (Survival)	Daily
Cageside / Clinical Observations (i.e., body condition, posture, eye appearance, and activity)	Daily
Body weights	Twice weekly
Tumor Volumes	Twice weekly

Key Results:

- All animals survived the duration of the study.
- Animals that received bb2121 exhibited dose-dependent clearance of BCMA+ tumors (Figure 3). Specifically, animals that received bb2121 at dose levels of 6.16 ×10^1 to 6.16 ×10^4 CAR+ T cells/mouse showed no reduction in tumor volume. Dose levels of 6.16

$\times 10^5$ and 6.16 $\times 10^6$ CAR+ T cells resulted in complete elimination of tumors by Day 20 and Day 12, respectively.

- Animals that received Bortezomib exhibited reduced tumor volumes, but not tumor clearance. Animals in the vehicle control group did not exhibit any decrease in tumor volumes.
- Administration of bb2121 did not induce significant weight loss in the animals, in contrast to Bortezomib.

Figure 3: Tumor volume of (b) (4) Xenograft Mice after the administration of bb2121 at varying dose levels

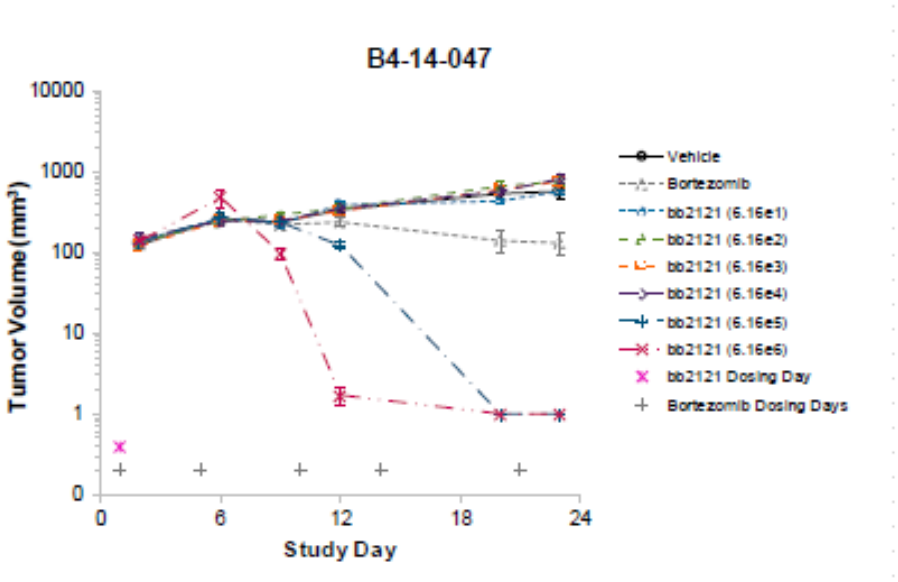

Figure 3: Tumor volumes for (b) (4) mice with BCMA+ (b) (4) MM tumor cell xenografts administered varying dose levels of bb2121 anti-BCMA CAR T cells between 6.16×10^1 – 6.16×10^6 cells/mouse, Bortezomib, or vehicle.
Source: Module 4.2.1.1. B4-14-047, page 8

Reviewer comment: *This study demonstrated that bb2121 anti-tumor activity is dose-dependent.*

Study #8: Evaluation of the Pharmacologic Activity of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+/CD19+ (b) (4) Human Burkitt's Lymphoma Systemic Xenografts (Study Report #B4-14-050)

The objective of this study was to evaluate bb2121 delivered both early and delayed with respect to tumor progression in (b) (4) mice bearing (b) (4) human Burkitt's lymphoma (BL) systemic xenografts, which express low levels of BCMA. In this study, female (b) (4) mice were IV engrafted with 2×10^6 (b) (4) BL tumor cells/mouse. (b) (4) media (vehicle), (b) (4) (positive control anti-CD19 CAR T cells), (b) (4) (negative control anti-CD19Δ CAR T cells lacking a critical CAR signaling domain), and bb2121 derived from a healthy human donor were injected IV into tumor-bearing (b) (4) mice at 8 or 18 days post-tumor cell administration. The total T cells administered was 10×10^6 cells/mouse (3.28×10^6, 2.71×10^6 and 6.16×10^6 CAR+ T cells for (b) (4) and bb2121, respectively). Mice were monitored for 51 days post-tumor cell injection. Clinical observations were conducted daily, and body weights were recorded twice weekly. Tumor volume was examined twice weekly by bioluminescence.

The vehicle and (b) (4) controls had no effect on the growth of the tumors, which resulted in weight loss and tumor-related mortality in their respective groups. (b) (4) administered 8 days post-tumor cell administration exhibited tumor growth inhibition (i.e., mice showed no tumor growth) for the duration of the study. When administered 18 days post-tumor cell administration, (b) (4) exhibited transient anti-tumor activity, in which tumor reduction was reported for ~ 5 days followed by tumor regrowth. When bb2121 was administered 8 days post-tumor cell administration, bb2121 exhibited tumor growth inhibition for the duration of the study. When administered 18 days post-tumor cell administration, bb2121 exhibited tumor reduction approaching complete tumor clearance by the end of the study. All animals that received (b) (4) and bb2121 survived the duration of the study.

Reviewer comments:

- *This study is of limited relevance for the proposed indication. However, it indicates that bb2121 can exert anti-tumor activity against xenografts that express low levels of BCMA when delivered early or delayed with respect to tumor progression.*

- *The differences observed in the anti-tumor activity of (b) (4) and bb120 may be due to the 2-fold greater CAR+ T cell dose administered for bb2121 compared to (b) (4) (due to differences in transduction rates), differences in the CD19 and BCMA expression profile for the (b) (4) cells, and potential functional/potency differences in the two products.*

Study #9: Evaluation of the Pharmacologic Dose Response of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with BCMA+/CD19+ (b) (4) Human Burkitt's Lymphoma Systemic Xenografts (Study Report #B4-14-065)

The objective of this study was to evaluate bb2121 dose-response in (b) (4) mice bearing (b) (4) human Burkitt's lymphoma (BL) systemic xenografts, which express low levels of BCMA. In this study, female (b) (4) mice were IV engrafted with 2×10^6 BCMA+ (b) (4) BL tumor

cells/mouse to establish systemic leukemia/lymphoma xenografts. (b) (4) media (vehicle) and bb2121 derived from a healthy human donor were injected IV into ten groups of tumor-bearing (b) (4) mice at the dose levels indicated in the table below 9 days post-tumor cell administration. The dose levels are based on total CAR+ T cells.

Group	Test Article	Dose Level
I	Vehicle	N/A
H	bb2121	7.0×10^2 CAR+ cells/mouse
C	bb2121	3.5×10^3 CAR+ cells/mouse
D	bb2121	7.0×10^3 CAR+ cells/mouse
B	bb2121	3.5×10^4 CAR+ cells/mouse
F	bb2121	7.0×10^4 CAR+ cells/mouse
G	bb2121	3.5×10^5 CAR+ cells/mouse
E	bb2121	7.0×10^5 CAR+ cells/mouse
J	bb2121	3.5×10^6 CAR+ cells/mouse
A	bb2121	7.0×10^6 CAR+ cells/mouse

Mice were monitored for 44 days post-tumor cell injection. Clinical observations were conducted daily and body weights were recorded twice weekly. Tumor growth was examined twice weekly by bioluminescence.

Mice that received bb2121 exhibited dose-dependent clearance of (b) (4) tumor cells. Specifically, At the highest dose levels of 3.5×10^6 and 7.0×10^6 CAR+ T cells/mouse, bb2121 inhibited tumor growth and resulted in tumor clearance. At the dose levels 3.5×10^5 and 7.0×10^5 CAR+ T cells/mouse, bb2121 inhibited tumor growth transiently, as the tumor started to regrow ~Day 25. Mice that received vehicle or $\leq 7.0\times10^4$ CAR+ T cells/mouse exhibited unchecked tumor growth, resulting in significant weight loss and tumor-related mortality.

Reviewer comments:

- *This study is of limited relevance for the proposed indication. However, this study demonstrates dose-dependent anti-tumor activity of bb2121 against tumor cell xenografts that express relatively low levels of BCMA.*

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies were conducted.

PHARMACOKINETIC STUDIES

Biodistribution of bb2121 was assessed in Study #10.

Summary List of Pharmacokinetics Studies[9]

Study Number	Study Title / Publication Citation	Report Number
10	An Investigative Study to Evaluate the Pharmacologic Activity, Pharmacokinetics, Pharmacodynamics, Biodistribution and General Safety of bb2121 Anti-BCMA CAR T cells in (b) (4) Mice with and Without BCMA+(b) (4) Human Multiple Myeloma Subcutaneous Xenografts	B4-15-090

Study #10: An Investigative Study to Evaluate the Pharmacologic Activity, Pharmacokinetics, Pharmacodynamics, Biodistribution, and General Safety of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with and without BCMA+ (b) (4) Human Multiple Myeloma Subcutaneous Xenografts (B4-15-090)

Report Number		B4-14-065
Date Report Signed		26-AUG-2015
Title		An Investigative Study to Evaluate the Pharmacologic Activity, Pharmacokinetics, Pharmacodynamics, Biodistribution, and General Safety of bb2121 Anti-BCMA CAR T Cells in (b) (4) Mice with and without BCMA+ (b) (4) Human Multiple Myeloma Subcutaneous Xenografts
GLP Status		No
Testing Facility		(b) (4) Study Reference No.: B4-14-043
Objective(s)		To evaluate the activity, PK, PD, BD, and general safety of bb2121 anti-BCMA CAR T cells in (b) (4) mice with and without BCMA+ (b) (4) human MM tumor cell line SC xenografts.
Study Animals	**Strain/Breed**	(b) (4)
	Species	Mouse (*Mus musculus*)
	Age	11 weeks
	Body Weight	15-25 g
	#/sex/group	9, 13, or 14/f/group
	Total #	85
Test Article(s)		bb2121
Control Article(s)		(b) (4) media (vehicle), (b) (4), anti-CD19Δ CAR T cells (negative control)
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		Groups A, B. C did not receive tumor xenografts. Groups D, E, F received 1×10^7 (b) (4) tumor cells/mouse via SC injection to establish systemic leukemia/lymphoma xenografts. Mice received test and control articles 9-days post-tumor cell administration.

<table>
<tr><td>Study Groups and Dose Levels</td><td>
<table>
<tr><th>Group</th><th>Test Article</th><th>Dose Level*</th></tr>
<tr><td>A</td><td>Vehicle</td><td>N/A</td></tr>
<tr><td>B</td><td>(b) (4)</td><td>3×10^6 cells/mouse
1.5×10^8 cells/kg</td></tr>
<tr><td>C</td><td>bb2121</td><td>3×10^6 cells/mouse
1.5×10^8 cells/kg</td></tr>
<tr><td>D</td><td>Vehicle</td><td>NA</td></tr>
<tr><td>E</td><td>(b) (4)</td><td>3×10^6 cells/mouse
1.5×10^8 cells/kg</td></tr>
<tr><td>F</td><td>bb2121</td><td>3×10^6 cells/mouse
1.5×10^8 cells/kg</td></tr>
</table>
**Dose per kg was extrapolated based on a 20 g mouse*

Note: dose levels for (b) (4) and bb2121 were based on CAR-positive cells</td></tr>
<tr><td>Dosing Regimen</td><td>Single administration</td></tr>
<tr><td>Randomization</td><td>Yes, based on tumor volumes.</td></tr>
<tr><td>Description of Masking</td><td>All in-life personnel were blinded to the identity of the test and control articles assigned to each group</td></tr>
<tr><td>Scheduled Sacrifice Time Points</td><td>Days 1 (before administration of cell product), 2, 4, 8, 11, 15, 18, 22, 25 and 29</td></tr>
</table>

Reviewer comment: *Justification for the timepoints selected was not provided. However, the timepoints selected appear to capture the peak expansion and decline of bb2121 levels(although not the complete elimination/clearance of these cells).*

Key Evaluations and Assessments[10]:

Evaluations/ Assessments	Frequency and/or Details
Mortality (Survival)	Daily
Cageside / Clinical Observations (i.e., body condition, posture, eye appearance, and activity)	Daily
Body weights	Twice weekly
Tumor Volume (Bioluminescence Imaging)	Twice weekly
PK: Quantification of CAR+ T cells in peripheral blood ((b) (4)) and xenograft tissues ((b) (4) or (b) (4))	Days 1 (pre-dose, 5 minutes, 4 hours post-dose), 2, 4, 8, 11, 15, 18, 22, 25 and 29
PD: Quantification of sBCMA in serum ((b) (4)) in relation to amount of BCMA+ tumor cells in xenograft tissues ((b) (4))	Days 1 (pre-dose, 5 minutes, 4 hours post-dose), 2, 4, 8, 11, 15, 18, 22, 25 and 29

Biodistribution	Days 1 (pre-dose), 2, 4, 8, 11, 15, 18, 22, 25 and 29 Tissues evaluated included the bone marrow, kidney, liver, lung, and spleen

Note: *A deviation from protocol, body weights were not recorded for groups without xenografts.*

Key Results:

No Xenografts

- Mice that received vehicle, (b) (4), or bb2121 exhibited little to no clinical signs.
- Mice that received (b) (4) and bb2121 exhibited mean peripheral blood CD3+, CD3+/CD4+ and CD3+/CD8+ T cell counts that peaked at Day 2 and then declined for the remainder of the study.
- Liver, kidney, and bone marrow (b) (4) minimally (very rare) or not at all for CD3+ T cells. CD3+ T cells detection was more prevalent on Days 8 and 15 in the lungs and spleen.

MM Xenografts

- Mice that received bb2121 experienced tumor reduction and tumor clearance by Day 18. Mice that received (b) (4) exhibited increasing tumor volumes until Day 15. At this point, three mice in the (b) (4) group continued to experience tumor growth, while 4 mice showed a decline in tumor volume over the remainder of the study. The sponsor hypothesizes that the phenomenon seen with this negative control is due to a (b) (4) between the (b) (4) phenotype of the (b) (4) human MM tumor cell line and the human donor T cells causing a non-specific (CD19Δ CAR-independent) T cell graft versus xenograft response.
- In the bb2121 group, peripheral blood CD3+, CD3+/CD4+, and CD3+/CD8+ T cell counts reached an initial peak at Day 2, declined to a plateau by Day 8; peaked again at Day 11 (~20-fold higher than the initial peak on Day 2), and declined until the end of the study (Day 29). CAR+ T cells represented ~25% of the observed peripheral blood T cells. In the (b) (4) group, peripheral blood CD3+, CD3+/CD4+, and CD3+/CD8+ T cell counts peaked at Day 2, then declined in some mice and increased in others by Day 15 before gradually declining for the remainder of the study.
- In the xenograft tissue of mice administered bb2121, CD3+ T cells increased from 0% at Day 1 to 80% of tumor tissue area by Day 11. After Day 11, tumors were no longer present in this group. In mice administered (b) (4), CD3+ T cells represented $\leq$ 1% of the tumor tissue on Day 11 and 22. However, CD3+ T cells representation increased to 50% on Day 25 and 70% on Day 29.

- In the mice that received bb2121, CD3+ T cells were detected in all tissues tested (i.e., liver, lungs, kidneys, spleen, and bone marrow), peaking on Days 8 or 15, before declining to low or undetectable levels by Day 29. In the mice that received (b) (4), CD3+ T cells were detected in the liver, spleen, lung, kidney and bone marrow on Days 8 and 15 before declining to an undetectable level by Day 29 in most animals.

- Mean serum sBCMA concentrations increased as tumors grew in the vehicle and (b) (4) groups and declined in animals in the (b) (4) groups that had reduced tumor volumes.

Reviewer's comments:

- *The bb2121 CAR T cell distribution profile was assessed via* (b) (4) *of human CD3+ T cells which includes both CAR+ and CAR- T cells. It was confirmed that CAR+ T cells represented ~25% of CD3+ T cells during peak expansion (Day 11) based on analysis of peripheral blood cells by* (b) (4)

- *The reported cell distribution profile is consistent with other CD19 CAR T cell products in which the cells have been observed to widely distribute in the organs well-perfused with blood, including the lungs, blood, bone marrow, liver and spleen when evaluated in* (b) (4) *mice.*[12,13]

TOXICOLOGY STUDIES

Developmental and Reproductive Toxicology (DART) Studies:

No DART studies were conducted.

Genotoxicity Studies:

Traditional genotoxicity studies were not conducted using bb2121; however, given the use of a lentiviral vector to stably integrate the anti-BCMA CAR into the T cell genome, a risk associated with insertional mutagenesis exists. The applicant provided integration analyses conducted using bb2121.

Study Number	Study Title / Publication Citation	Report Number
11	Integration Site Analysis	RPT-018619

Study #11: Vector Insertion Site Analysis of Clinical ide-cel [bb2121] Drug Product Lots Report (Study Report #RPT-018619)

[12] Wen H, Qu Z, Yan Y, Pu C, Wang C, Jiang H, Hou T, Huo Y. Preclinical safety evaluation of chimeric antigen receptor-modified T cells against CD19 in NSG mice. Ann Transl Med. 2019 Dec;7(23):735. doi: 10.21037/atm.2019.12.03. PMID: 32042751; PMCID: PMC6990014.

[13] Singh AP, Zheng X, Lin-Schmidt X, Chen W, Carpenter TJ, Zong A, Wang W, Heald DL. Development of a quantitative relationship between CAR-affinity, antigen abundance, tumor cell depletion and CAR-T cell expansion using a multiscale systems PK-PD model. MAbs. 2020 Jan-Dec;12(1):1688616.

Lentiviral vector integration was characterized to evaluate the risk of insertional mutagenesis associated with the transduction of T cells with the anti-BCMA02 CAR construct. Standard (b) (4) was performed to identify vector integration sites (IS) across 20 clinical bb2121 drug product lots. Per the applicant, the lots were selected based on their respective surface CAR expression (% CAR+) and vector copy number (VCN).

Key Results:

- The insertion profile demonstrates: 1) a significant correlation between VCN and IS, 2) an integration preference for the coding regions of genes rather than promoter regions, and 3) high polyclonality.

- Across the samples tested, the lentiviral vector predominantly integrated into T cell genomes as a single copy into a locus. Less than (b) (4) of characterized insertions contained at least two vector sequences within a read window. These data suggest that the lentiviral vector does not form concatemers or hotspots when inserted into T cell genomes.

- A total of (b) (4) out of (b) (4) individual high confidence insertion sites (HC-IS) were identified within the (b) (4) window of the transcription start sites (TSS) of selected cancer-associated genes. The highest frequency of any one insertion event was found to be (b) (4).

- Consistent with what is observed with wild type HIV, the density of genes, CpG dinucleotides, DNaseI hypersensitivity sites, and average GC base content increased significantly with the lentiviral vector HC-IS density.

Reviewer comment: *The study report concludes that there were no concerning findings related to the integration profile and that the integration pattern observed for BCMA02 lentiviral is consistent with wild type HIV and other lentiviral described in the literature. This reviewer concurs with the conclusions.*

Carcinogenicity/Tumorigenicity Studies:

No carcinogenicity or tumorigenicity studies were conducted for bb2121. However, the applicant evaluated IL-2 independent growth in Study #10.

Study Number	Study Title / Publication Citation	Report Number
12	NVR-001448: IL-2 Independent Growth as a Gain of Function Assessment in Clinical and Normal Healthy Donor bb2121 Drug Product Report	RPT-018530

Study #12: NVR-001448: IL-2 Independent Growth as a Gain of Function Assessment in Clinical and Normal Healthy Donor bb2121 Drug Product Report (Study Report #RPT-018530)

To assess the potential for malignant transformation, bb2121 generated from five donors with MM, two healthy donors, and control untransduced T cells were co-cultured in the presence or absence of IL-2. Cells were collected for assessment of cell growth at (b) (4)-day timepoints, then harvested and evaluated for phenotypic composition (by (b) (4)) and T cell receptor (TCR) clonal diversity.

There was no proliferation detected within cultures without IL-2 for all T cell product lots assessed, and all cells died by Day (b) (4). There was a variable increase in CAR expression frequency and CAR T cell proliferation observed in the patient-derived and healthy donor-derived drug products co-cultured with IL-2. There was an overall decrease in clonal diversity observed in all the groups tested (i.e., bb2121 did not appear to influence clonality in this study). All groups cultured with IL-2 continued to expand until these samples were sub-cultured in decreasing amounts of IL-2. Sub-culturing lead to a rate of cell contraction that was similar between groups.

Reviewer comments:

- *Based on the clinical lots assessed, bb2121 did not exhibit any growth/expansion in the absence of exogenous 1L-2 support. In the presence of IL-2, the T cell populations of the expanded cultures were skewed toward positive expression of CAR expression. This indicates that there may be some proliferation bias mediated by CAR expression. The applicant attributes these results to tonic signaling that has been heavily reported in literature.[14] This reviewer concurs with this rationale.*

- *Based on the results from Studies11 and 12 and the nature of the cell product (i.e., terminally differentiated T cells), this reviewer agrees that the risk of uncontrolled growth of bb2121 is low.*

APPLICANT'S PROPOSED LABEL

No changes were made for Section 8 of the applicant's proposed label. Section 13 was revised for clarity and to remove unnecessary text.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

[14] Gomes-Silva, D., Mukherjee, M., Srinivasan, M., Krenciute, G., Dakhova, O., Zheng, Y., Cabral, J., Rooney, C. M., Orange, J. S., Brenner, M. K., & Mamonkin, M. (2017). Tonic 4-1BB Costimulation in Chimeric Antigen Receptors Impedes T Cell Survival and Is Vector-Dependent. Cell reports, 21(1), 17–26.

KEY WORDS/TERMS

ABECMA®, Idecabtagene vicleuce, ide-cel, bb2121, multiple myeloma, B cell maturation antigen, BCMA CAR T cells, Chimeric Antigen Receptor, pharmacology, toxicology, lentivirus, tumor-bearing mice, (b) (4) mice

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