BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II Multicenter Trial of anti-B Cell Maturation Antigen Chimeric Antigen Receptor T Cell Therapy for Multiple Myeloma Patients with Sub-Optimal Response After Autologous Hematopoietic Cell Transplantation and Maintenance Lenalidomide

Version 2.0

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PROTOCOL SYNOPSIS - BMT CTN 1902

Phase II Multicenter Trial of anti-B Cell Maturation Antigen Chimeric Antigen Receptor T Cell Therapy for Multiple Myeloma Patients with Sub-Optimal Response After Autologous Hematopoietic Cell Transplantation and Maintenance Lenalidomide

Co-Principal Investigators: Alfred Garfall, MD Sergio Giralt, MD

Study Design: This study is designed as a Phase II, multicenter, single arm trial to assess anti-B Cell Maturation Antigen (BCMA) chimeric antigen receptor (CAR) T-cells (bb2121) to improve post autologous hematopoietic cell transplant (HCT) responses among patients with multiple myeloma (MM).

Primary Objectives: The primary objective is to evaluate the efficacy of BCMA CAR T cell therapy to improve the response in patients who received an upfront autologous HCT and lenalidomide maintenance.

Secondary Objectives: The secondary objectives include assessment of disease progression, response to treatment as determined by improved response and conversion to minimal residual disease (MRD) negativity, non-relapse mortality, progression free survival (PFS), incidence of cytokine release syndrome (CRS), incidence of prolonged cytopenias, and incidence of neurotoxicity

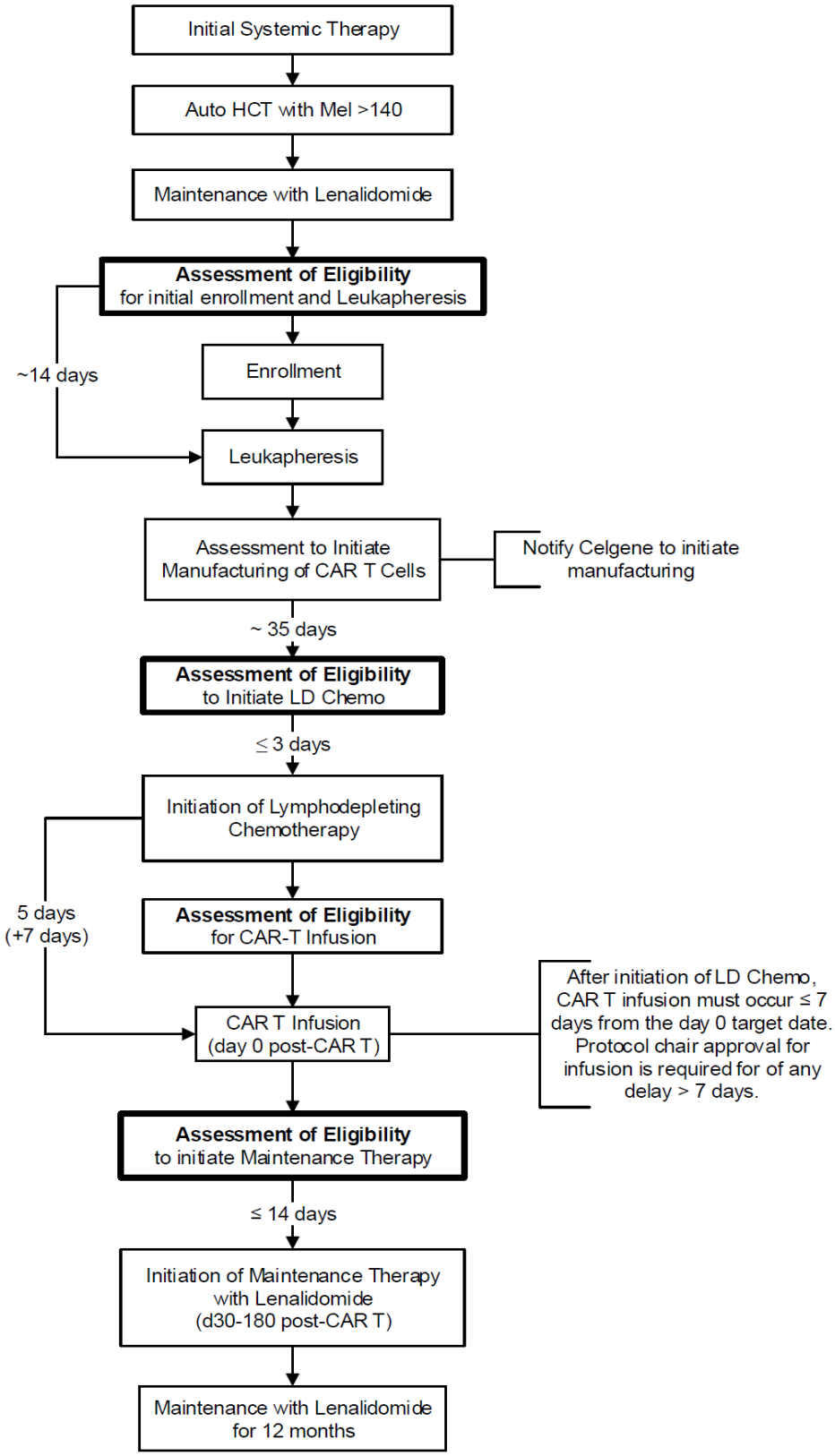
Exploratory Objectives: Exploratory objectives to be described include incidence of toxicities greater than or equal to grade 3 per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, incidence of infections per protocol-specific Manual of Procedures (MOP), maintenance feasibility, overall survival, disease response, CAR T-cell expansion, CAR T-cell persistence, BCMA expression, immune reconstitution

Eligibility Criteria: Eligible patients are greater than or equal to 18.00 and less than 71.00 years of age with MM with less than a very good partial response (VGPR) within 12 months after an autologous HCT with melphalan > 140mg/m^2, have initiated lenalidomide maintenance at least 6 months ago, and have not experienced disease progression since initiation of initial systemic anti-myeloma therapy.

Treatment Description: After meeting the eligibility criteria and enrolling on the trial, patients will undergo leukapheresis for collection of autologous lymphocytes, which will be sent to BMS/Celgene manufacturing facilities. Once cells have been manufactured, patients will then proceed to lymphodepleting chemotherapy with cyclophosphamide 300mg/m^2 and fludarabine 30mg/m^2 for 3 consecutive days followed by the infusion of BCMA CAR T-cells at a target dose of 450 x10^6 cells. Maintenance lenalidomide, starting at 10mg a day for 21 days of a 28-day cycle will be initiated at a minimum of at least 30 days, but no later than 180 days after the CAR T-cell infusion and will

	continue until the patient reaches 12 months post CAR T-cell infusion and continue free of progression.
Accrual Objective:	40 patients
Accrual Period:	22 months
Target Number of Sites:	15 sites
Study Duration:	Patients will be followed for 12 months after bb2121 infusion
Long Term Follow Up:	All patients will be followed for 15 years to meet regulatory requirements through a long term follow up protocol using the CIBMTR infrastructure.

BMT CTN 1902 STUDY SCHEMA



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CHAPTER 1

1 OVERVIEW

1.1 Background

Multiple myeloma (MM), is a plasma cell malignancy that affects approximately 31,000 new patients in the US yearly.[1] Treatment includes induction therapy with proteasome inhibitors (PIs), immune-modulatory drugs (IMIDs) and steroids. Eligible patients receive consolidation with high dose melphalan and autologous hematopoietic cell transplantation (HCT) followed by maintenance therapy. Treatment results in complete remission (CR) rates of 50% with median progression free survival (PFS) between 48 and 60 months. Disease recurrence is common and only a small percentage of patients are potentially cured.[2] Once patients relapse after first-line therapy, salvage therapies combining IMIDs, PIs, cytotoxic chemotherapy and monoclonal antibodies are effective in inducing remissions that last on average 12 to 24 months. Eventually MM becomes resistant to standard therapies and most patients will succumb from their disease.[3]

1.1.1 Autologous Stem Cell Transplantation in MM

Autologous HCT remains a cornerstone of MM therapy. Autologous HCT is safe with non-relapse mortality (NRM) rates of less than 2% in patients with a low comorbidity index score.[4] Several trials have shown a benefit in overall survival (OS) and PFS in MM patients.[5-10] The benefit of autologous HCT is maintained in patients treated with PI and IMIDs. In one study, patients were treated with lenalidomide and dexamethasone induction therapy and then randomized to receive either 6 cycles of oral melphalan based consolidation therapy or two 4-month cycles of high dose melphalan and autologous stem cell rescue (tandem transplants).[10] Patients were additionally randomized to receive maintenance therapy with lenalidomide or observation in a 2 by 2 overall design. Both PFS and 4-year OS were improved with autologous HCT compared to melphalan based consolidation therapy (43.0 months vs. 22.4 months and 81.6% vs. 65.3% respectively). Most recently, results from the French arm of the IFM/DFCI 2009 clinical trial became available.[6] The significance of this trial is that induction therapy included the best-known standard of care using both proteasome inhibitors as well as lenalidomide. A 3-year PFS of 61% was observed in the transplant arm compared to 48% in the non-transplant arm (stratified p value for log-rank test < 0.0002; HR= 1.5, 95% CI= 1.2-1.9). Even among patients achieving MRD-negative responses, PFS still trended in favor of transplantation.[11]

1.1.2 The Role of Maintenance Therapy after Autologous HCT

Therapy following autologous HCT remains controversial particularly in patients who achieve a complete response (CR). In the aforementioned trial where patients were randomized to receive autologous HCT followed by maintenance in a 2 by 2 design, median PFS was significantly increased with lenalidomide maintenance (41.9 months vs. 21.6 months) but 3-year OS was not significantly improved (88.0% vs. 79.2%).[12] The benefit of lenalidomide maintenance was further evaluated in a phase 3 trial of 614 patients with newly diagnosed MM to randomly receive lenalidomide if they had non-progressive disease after autologous HSCT.[12] Patients in the lenalidomide arm had a longer median PFS (41 versus 23 months), although OS was similar at four years (73 versus 75 percent). Lenalidomide treatment resulted in higher toxicity and incidence of second primary malignancies (3.1 versus 1.2 per 100 patient-years). In another phase 3 randomized study of patients with stable disease or better after autologous HCT, the study was unblinded after

interim analysis showed improved rates of disease progression in the lenalidomide treated group (20 % versus 44%).[13]] Mortality was higher in the placebo group with a trend toward significance (10% vs 5%, HR of 0.52, 95% CI 0.26 – 1.02). A higher benefit appeared to occur in patients who were not in CR after autologous HSCT. A recent meta-analysis of the published randomized trials showed a survival benefit for patients receiving lenalidomide maintenance.[14]

Regarding the target population for this study, it is estimated that 10-25% of patients will have < very good partial response (VGPR) after six months of maintenance therapy based on results from STAMINA[15], FORTE[16], and IFM-09[6].

1.1.3 Depth of Response Correlates to PFS and OS

Depth of response has been universally associated with treatment outcomes in MM.[17-22] Extensive evidence from trials incorporating autologous HCT show that CR, or maximal response after transplant, is associated with improved PFS and OS.[17, 18, 20-22] This benefit remains true when newer agents are incorporated into therapy as shown by the Arkansas group in the total therapy 2 and 3 trials incorporating thalidomide or thalidomide with bortezomib respectively.[17, 18, 21] Durability of CR is also important as patients who remained in CR for 3 years after the start of treatment had significantly superior survival when compared to patients who never achieved a CR or who relapsed within 3 years.[21] The use of multiparametric flow cytometry and polymerase chain reaction based gene sequencing led to more sensitive disease detection and the identification of minimal residual disease (MRD) even in patients who meet criteria for CR. MRD assessments have now been incorporated into the response criteria of the International Myeloma Working Group (IMWG).[23] MRD eradication was shown to have a prognostic significance on OS in patients with immunofixation based CR in patients treated on the GEM2000 protocol.[24] The impact of MRD negativity at a level of 10^{-5} and 10^{-6} either by multiparameter flow cytometry (MFC) or Next Generation Sequencing (NGS) as a surrogate for long-term disease control has been confirmed by other investigators.

1.1.4 Dynamics of Response While on Lenalidomide Maintenance Therapy

Data describing response kinetics to lenalidomide maintenance therapy is lacking outside of what is reported as PFS or OS in the lenalidomide maintenance trials. Thought leaders in the field of MM have noticed a plateau in the disease response that never quite reaches CR without frank progression. These patients linger in near CR, VGPR, or PR despite initial therapy, autologous HSCT and lenalidomide maintenance. In data describing the Memorial Sloan Kettering Cancer Center experience with lenalidomide maintenance in MM,[25] it was noted that patients continue to respond after starting lenalidomide maintenance with a median time to response of 132 days

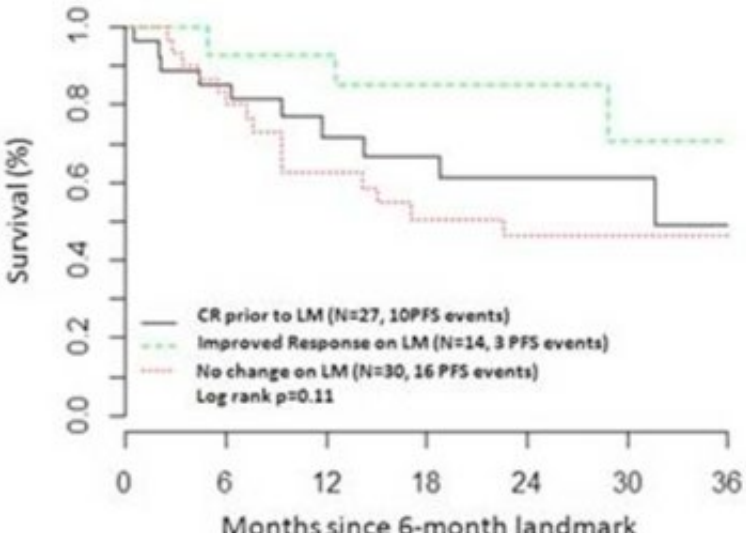


Figure 1.1.4: PFS by Response to Lenalidomide Maintenance from Shah, Gunjan L. et al.

and median duration of therapy of 21.5 months. Furthermore, lenalidomide maintenance increased the number of patients in CR from 38% to 60%. 40% of patients however remained in a VGPR or PR. Though not statistically significant (p=0.11), a clear trend or separation in the Kaplan-Meier curves measuring PFS was noted between patients who were in CR, patients not in CR but responded to lenalidomide maintenance, and non-responding patients (Figure 1.1.4). Twelve-month PFS was highest in patients who deepened their response on lenalidomide maintenance (93%) compared to patients already in CR (12-month PFS of 72%) or patients without a response to lenalidomide maintenance (12-month PFS of 63%). What these data suggest is that further deepening the response in MM patients, even during the maintenance stage of therapy, may impact survival. Adding a second agent in this particular setting, in patients without CR despite upfront therapy, is an attractive strategy to convert patients with residual disease into a CR and perhaps prolong their survival. The MSKCC data detailed above is the first to objectively describe this patient population, the group of patients who plateau their response to myeloma therapy, and this proposed study would be one of the first to recommend an intervention in this patient population.[25]

Table 1.1.4 demonstrates the kinetics of response during maintenance therapy for patients registered on BMT CTN 0702. Note that 19.9% (n=29) of patients on the single autologous HCT followed by lenalidomide maintenance arm had achieved a CR by 12 months. At 24 months the percentage of patients achieving a CR had risen to 29.5% (n=43) but only a few patients had further increases in their depth of response between 24 and 36 months.[15]

Table 1.1.4: Kinetics of Response During Maintenance Therapy on BMT CTN 0702

	Auto/Auto			Auto/RVD			Auto/Maint		
	N Events	N Evaluable Pts	%	N Events	N Evaluable Pts	%	N Events	N Evaluable Pts	%
Number not in CR at maintenance enrollment and evaluable for conversion to CR		125	100.0		112	100.0		146	100.0
Achieving CR by 3 mos post maintenance[1]	8	125	6.4	8	112	7.1	10	146	6.8
Achieving CR by 6 mos post maintenance[1]	15	125	12.0	16	112	14.3	21	146	14.4
Achieving CR by 12 mos post maintenance[1]	25	125	20.0	30	112	26.8	29	146	19.9
Achieving CR by 24 mos post maintenance[1]	35	125	28.0	37	112	33.0	43	146	29.5
Achieving CR by 36 mos post maintenance[1]	39	125	31.2	38	112	33.9	48	146	32.9

[1]Once a participant has achieved CR post maintenance by a given time period, the participant is included as an event at all future time periods. Conversion also had to occur within 38 months post randomization.

An ancillary study, PRIMeR, used MFC to conduct MRD assessments on the BMT CTN 0702 study. Patients were enrolled on a national 3-arm RCT[15] comparing 1) tandem autologous HCT, 2) single autologous HCT and 3) single autologous HCT, 4 cycles of lenalidomide, bortezomib, dexamethasone consolidation (auto+RVD); all 3 treatment arms included continuous lenalidomide maintenance until MM progression. A total of 437 of 758 patients enrolled in STAMiNA provided consent and had at least one analyzable sample for MRD by MFC. The MFC panel included 10 monoclonal antibodies (CD38, CD138, CD45, CD56, CD19, CD20, CD27, CD28, kappa, lambda) measured via 3 tubes of 6 colors each with a target of analyzing 2.5 × 10e5-1.5 × 10e6 events, depending on sample quality and quantity, yielding a sensitivity of 10e-5 to 10e-6. At a median follow-up of 38 months, there was no significant difference in PFS or OS by treatment arm in the subset of PRIMeR patients. Multivariate analysis of time to progression or death, adjusting for disease risk, demonstrated hazard ratios (HR) in MRD negative patients compared to MRD positive patients at baseline, premaintenance and at 1 year to be 0.66 (p=0.07), 0.48 (0<0.001) and 0.22 (p<0.001) respectively. Corresponding HRs for overall mortality were 0.81 (p=0.50), 0.77 (p=0.52)

and 0.10 (0<0.001). The proportion of MRD negative patients at 1 year was highest (odds ratio 1.2) among patients randomized to the tandem autologous HCT arm. Despite better outcomes, patients with MRD negative MM at 1 year still experienced disease progression (23% vs. 56% at 38 months after autologous HCT) despite continuous lenalidomide maintenance. Data from the PRIMeR study confirms that achievement of MRD negativity at 1 year is associated with improved outcomes.[26] We hypothesize that BCMA directed chimeric antigen receptor (CAR) T-cell therapy will be successful in converting a significant proportion of patients who have had a suboptimal response to autologous HCT and maintenance into a CR and that a large proportion of them will be MRD negative.

1.1.5 CAR T-Cell Therapy

In CAR T cell therapy for cancer, autologous T cells are genetically modified *ex vivo* to express a receptor that artificially redirects T cell specificity towards a cell-surface target specific for malignant cells.[27] Modified cells are reinfused, typically after a cycle of cytotoxic chemotherapy to deplete endogenous lymphocytes and promote *in vivo* proliferation of infused cells. The clinically active receptors developed over the last decade incorporate costimulatory signaling domains on the intracellular components, typically CD28 or 4-1BB. Multiple phase 1 studies of anti-CD19 CAR T cells demonstrated durable responses in highly refractory patients with B cell malignancies. These results led to pivotal multisite studies for two products that are now FDA-approved, tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel); Table 1.1.5 summarizes results of these key studies in pediatric/young-adult B cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Remarkably, a substantial portion of patients with initial CR remain disease-free with long-term follow-up and may be cured. Often patients have longstanding aplasia of normal B cells, suggesting durable anti-CD19 immune surveillance. Notable toxicities observed across CAR T cell products include cytokine release syndrome (CRS) and neurotoxicity.[28] These toxicities are typically manageable and short-lived but can be severe and life-threatening.

Table 1.1.5: Results in Phase 1 studies of anti-CD19 CAR T-Cells in pediatric/young-adult B cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL)

Product	Study	Population	N	ORR	Durability	Ref
Tisa-cel	ELIANA	Rel/ref ALL, age 3-23	75	81%	59% of responders in rem @ M9-M12	[29] Maude et al. NEJM 2018
Tisa-cel	JULIET	rel/ref DLBCL	93	40% CR	79% of CRs in remission @12m	[30] Schuster NEJM 2019
Axi-cel	ZUMA-1	rel/ref DLBCL/PMBCL/tFL	101	40% CR	~70% of CRs in remission @ 12m	[31] Neelapu NEJM 2017

These promising results in heavily relapsed/refractory patients have led to trials incorporating CAR T cells into earlier lines of therapy in patients with poor prognosis and inadequate response to standard first-line therapy. The ZUMA-7 study is randomizing NHL patients who fail to achieve CR to standard first-line chemoimmunotherapy to axi-cel or standard salvage chemoimmunotherapy (NCT03391466). Similarly, in the upcoming BELINDA study, patients with aggressive B cell lymphoma who relapse after first-line therapy will be randomized to standard salvage therapy and auto-SCT or tisa-cel (NCT03570892) Gill et al. recently presented preliminary results of a Penn/Novartis study of anti-CD19 CARs in CLL patients responding to ibrutinib but who failed to achieve CR, which is a marker of poor prognosis.[32] CR was achieved in 94% of

patients, which compares favorably to ~25% ORR seen in several studies of anti-CD19 CARs in heavily relapsed/refractory patients.[33, 34] In addition to more favorable responses, toxicity was also less severe, likely due to the lower disease burden leading to less cytokine release syndrome. These results provide evidence in support of this protocol's design to evaluate CAR T cells in MM patients who fail to achieve CR to standard first-line therapy.

1.1.6 Anti-B Cell Maturation Antigen CAR T-Cell Therapy for MM

Initial studies of CAR T cell therapy for MM have targeted B cell maturation antigen (BCMA), a TNF receptor superfamily member that mediates plasma cell homeostasis through interaction with ligands in the bone marrow microenvironment. BCMA is expressed in most MM cases and on normal plasma cells but has little expression in other normal tissues.[35] Safety of targeting BCMA has been established in numerous CAR T cell studies, along with a recently published phase 1 study of an anti-BCMA antibody-drug conjugate and recently presented results with an anti-BCMA bispecific antibody.[36] No clinically significant on-target/off-myeloma toxicity has been identified in studies reported so far.

Initial studies of anti-BCMA CAR T cells focused on relapsed/refractory MM patients. Three phase-1 studies have presented or published mature follow-up data, which are summarized in Table 1.1.6. Additional clinical data on bb2121, which will be utilized in this study, are provided in a subsequent section. Collectively, data from these phase-1 studies demonstrate ability of anti-BCMA CAR T cells to induce cytoreductive responses, including some MRD-negative responses, in patients with advanced and heavily treated MM (median 7-8 prior lines of therapy). With longer follow-up, however, it appears even the patients with best initial responses remain likely to progress.

Table 1.1.6: Results of Phase I Studies of Anti-BCMA CAR T-Cells for Relapsed/Refractory MM Patients.

Trial	N	Median prior lines of therapy	ORR at optimal dose	VGPR/CR at optimal dose	Durability (at optimal doses)	Ref
NCI	26	7.5	81% (13/16)	63% (10/16)	Median PFS 7.1 months	[37, 38] Ali, S.A., et al.; Brudno, J.N., et al.
Penn/ Novartis	25	7	64% (7/11)	36% (4/11)	Median PFS 4.1 months	[39] Cohen, A.D., et al.
Bluebird/ BMS/Celgene	43	7.5	96% (21/22)	86% (19/22)	Median PFS 11.8 months	[40] Raje, N.S., et al.

1.1.7 Rationale for CAR T-Cells as a Component of First-Line MM Therapy

Emerging evidence suggests that the health of the T cells used in CAR T cell manufacturing is the main determinant of response. In an analysis of relapsed/refractory CLL patients treated with anti-CD19 CAR T cells, the phenotype of the T cells obtained at leukapheresis was the only pre-treatment patient- or disease-specific parameter associated with response. Specifically, higher frequency of a memory T cell subset defined by the CD8+ CD45RO- CD27+ phenotype was most strongly associated with favorable clinical response and more potent manufactured product.[41] Similarly, in MM patients treated on the Penn/Novartis anti-BCMA CAR study, both higher CD8+ CD45RO- CD27+ frequency and higher CD4/CD8 ratio were strongly associated with favorable

response, and no other clinical features were identified as predictive of response.[42] A subsequent analysis by the Penn group showed that CD8+ CD45RO- CD27+ frequency, CD4/CD8 ratio, and proliferative response to ex vivo stimulation were all significantly higher in leukapheresis products obtained after first-line therapy compared with those obtained from the heavily relapsed/refractory treated on their phase 1 anti-BCMA CAR T cell study.[43] The MSKCC group has shown that CD4/CD8 ratio inverts at early post-transplant time points but approaches normal in the 6-12 months after autologous stem cell transplant,[44] which is the window for intervention targeted by this study. Based on these data, CAR T cells manufactured from products obtained after completion of first line therapy may enable more durable responses than were observed in the heavily relapsed/refractory patients treated on the phase 1 studies. The association between disease burden and toxicity observed by several groups,[38, 45] along with experience of Gill et al. cited above with anti-CD19 CARs in CLL patients responding to ibrutinib, suggests that safety of CAR T cells may also be optimized if used as consolidation of early-line therapy rather than as salvage for refractory disease.

1.1.8 Idecabtagene Vicleucel (Ide-cel)

bb2121 is defined as an autologous T lymphocyte-enriched population that contains cells transduced with an anti-BCMA CAR lentiviral vector encoding a CAR targeting human BCMA. Anti-BCMA CAR lentiviral vector is used to transduce autologous T cells. This vector uses the murine leukemia virus-derived myeloproliferative sarcoma virus enhanced promoter to drive expression of the chimeric receptor, a multi-domain protein consisting of the extracellular antigen recognition domain (VL and VH), the CD8α hinge domain, a transmembrane domain (CD8 TM), and the intracellular CD137 co-stimulatory (4-1BB) and CD3zeta chain signaling domains.

Preclinical pharmacology of bb2121 showed desirable specificity against BCMA and potent activity of the CAR T cells leading to rapid and complete elimination of BCMA expressing tumors. In vitro, bb2121 was cytotoxic against a range of MM cell lines with varying levels of BCMA expression and this activity was not inhibited by soluble BCMA at physiologic concentrations in the cultures. There was no tonic signaling of bb2121 in the absence of BCMA target engagement and no in vitro cytotoxicity induced in cell lines lacking BCMA, underscoring the specificity of bb2121 for BCMA-expressing target cells. In vivo models showed a selective and higher antitumor activity of bb2121 in comparison to bortezomib in treatment of immune- deficient mice with large established BCMA-expressing tumors with complete remission and survival rates as high as 100% in mice after a single dose of bb2121.

In Phase 1 first-in-human clinical trial of bb2121 (CRB-401) in relapsed or refractory subjects, efficacy results have been observed with an acceptable safety profile. In this study, subjects with heavily pretreated relapsed or refractory (with high [>50%] BCMA expression) were treated with escalating doses (50, 150, 450, 800 x 106 CAR+ T cells) of bb2121 following lymphodepletion with fludarabine and cyclophosphamide. , Forty-three pts received bb2121 in the dose escalation and expansion phase of CRB-401. No dose-limiting toxicities were observed during dose escalation. Cytokine release syndrome (CRS) occurred in 27 of 43 (63%) treated subjects which was mild to moderate in the majority of subjects with only two cases of transient Grade 3 CRS. Neurotoxicity of any grade was observed in 14 of 43 (33%) using the System-Organ-Class (SOC) terms of dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. Most neurologic events were grade 1/2 and likely multifactorial in nature but did include one reversible grade 4 event (2.3%) with a finding of cerebral edema and no grade 3 events. There were

5 deaths on study, 3 due to disease progression at the 50 × 10^6 dose and 2 in patients treated at active doses (both were in CR from myeloma at the time of death; cardiac arrest and myelodysplasia following discontinuation). Overall response rate in 36 evaluable subjects in subjects treated at ≥ 150 × 10^6 CAR T-cells was 81% with a CR rate of 47% and a median duration of response of 10.9 months. Among 16 responding subjects evaluable for MRD status, all 16 subjects (100%) were MRD negative.[46] Based on these results, a target dose of 450 x 10^6 CAR T-cells with a minimum acceptable dose of 150 x 10^6 CAR T-cells is planned for this study based on the consistent efficacy and acceptable tolerability in this dose range.

Cytopenias have been observed after bb2121. As reported by Raje et al., in the recently completed phase 1 study, grade 3-4 neutropenia occurred in 32/33 subjects and grade 3-4 thrombocytopenia in 17/33 subjects[40]. Among those with grade 3-4 neutropenia, 31 recovered to ANC ≥ 1000/µl by week 4. Among those with grade 3-4 thrombocytopenia, 11 recovered to platelet counts ≥50,000/µl by week 4. Almost all patients had recovered to these thresholds by week 12 (Figure 1.1.8). Possible etiologies for the prolonged cytopenias include cyclophosphamide + fludarabine in the setting of weak marrow reserve from relapsed/refractory myeloma and extensive prior therapy and myelosuppressive effects of cytokine release syndrome.

Refer to the bb2121 Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

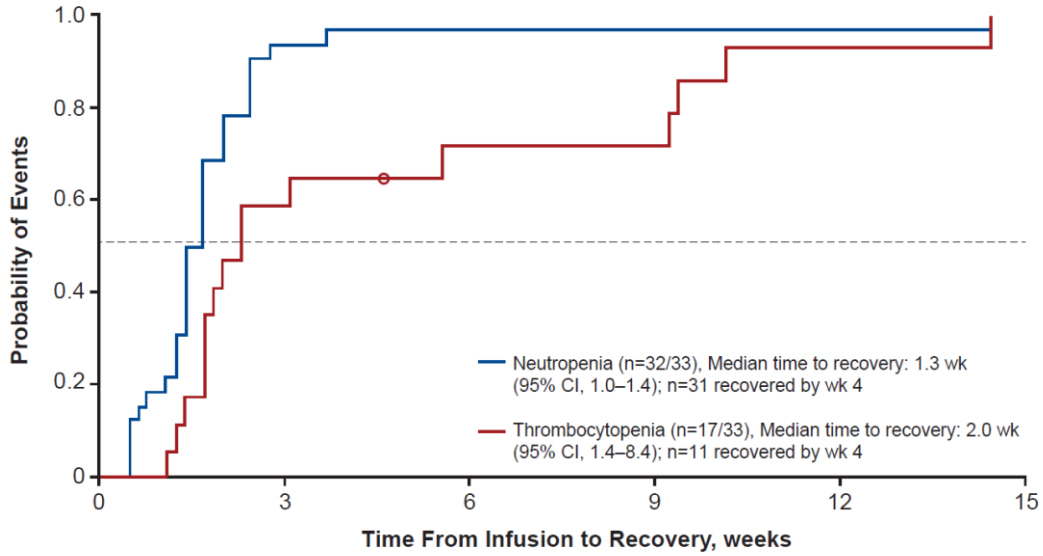


Figure 1.1.8: Rate of Recovery of Post-bb2121 Cytopenias as Reported by Raje et al. [40]

1.2 Study Specific Information

Based on the efficacy data of bb2121 in the setting of relapsed refractory MM, we hypothesize that this agent will be effective in improving the response of patients with myeloma that have not achieved a VGPR or better despite post-transplant maintenance. We propose to conduct a multicenter phase II study of bb2121 therapy in patients with myeloma who have failed to achieve a VGPR after high dose melphalan and autologous HCT followed by at least 6 months of lenalidomide maintenance. The primary objective is to assess the impact of bb2121 therapy on improving the depth of response in these patients. Secondary endpoints include determining the

effect of therapy on PFS, MRD, incidence of cytokine release syndrome (CRS), incidence of prolonged cytopenias, incidence of neurotoxicity, non-relapse mortality, overall survival. Additionally, this study includes several immunologic endpoints to understand the effect of bb2121 and the impact of expansion and persistence on outcomes.

1.3 Rationale for Study

Depth of response is an important surrogate marker for PFS and OS in patients with MM. With the currently available 4 drug induction therapy of daratumumab, bortezomib, lenalidomide and dexamethasone only60% of patients achieve a CR of which 70 to 80% are MRD negative. Considering that most patients in the United States continue to receive triple drug induction it is expected that if positive this study could be applicable to a large proportion of patients who fail to achieve a MRD negative CR to primary therapy. The BCMA targeted CAR genetically modified T cell bb2121 has shown dramatic responses in patients with relapsed refractory MM. Thus, it is logical to explore this agent as consolidation therapy for patients with myeloma that have failed to achieve a major response to primary therapy (i.e. less than VGPR). We postulate that treatment with bb2121 will result in further major responses in this patient population. The results of this study will allow us to plan a larger more definitive trial.

CHAPTER 2

2 STUDY DESIGN

2.1 Study Overview

This is a single-arm, phase II multi-center clinical trial to assess the ability of BCMA directed CAR-T therapy to improve response in MM patients who have failed to achieve at least VGPR after first-line therapy (induction followed by high-dose melphalan, autologous stem cell transplant and maintenance lenalidomide). Prior to enrollment, patients must have had an autologous HCT and initiated single agent lenalidomide maintenance with a response of less than a VGPR (in comparison to pre-induction status). Eligible patients will undergo leukapheresis, receive lymphodepleting (LD) chemotherapy followed by infusion of BCMA directed CAR-T cell therapy. Subjects will resume maintenance lenalidomide beginning at least 30 days after CAR-T cell infusion assuming they have recovered from the infusion and certain hematologic criteria have been met. Subjects will be followed on this protocol for one year.

2.2 Hypothesis and Study Objectives

2.2.1 Hypothesis

Infusion of bb2121 will result in a significant reduction in myeloma tumor burden as documented by the achievement of a complete remission in patients who failed to achieve a VGPR after high dose melphalan and maintenance therapy.

2.2.2 Primary Objective

The primary objective of this trial is to evaluate the efficacy of BCMA CAR T cell therapy to improve the response in patients who received an upfront autologous HCT and lenalidomide maintenance.

2.2.3 Clinical Secondary Objective

Clinical secondary objectives include: Assessment of disease progression, best disease response as described by conversion to MRD negativity and upgrade in clinical disease response, non-relapse mortality, progression free survival, incidence of CRS, incidence of prolonged cytopenias, and incidence of neurotoxicity.

2.2.4 Exploratory Objectives

Exploratory objectives to be described include: Incidence of toxicities greater than or equal to grade 3 per CTCAE version 5.0, incidence of infections per protocol-specific MOP, feasibility of reinitiating maintenance, overall survival, disease response, CAR T-cell Expansion, CAR T-cell persistence, BCMA expression, immune reconstitution

2.3 Patient Eligibility

Patients must meet specified eligibility criteria outlined in section 2.3.1 and 2.3.2 prior to initial enrollment. Additional criteria must also be met to continue to successive stages of the protocol.

2.3.1 Initial Inclusion Criteria

Patients must meet the following eligibility criteria prior to enrollment on the study and proceeding with leukapheresis:

1. Age greater than or equal to 18.00 years and less than 71.00 years.
2. Patients must meet the criteria for symptomatic MM requiring therapy (Appendix A) prior to initiating initial systemic anti-myeloma treatment[1].
3. Patients must have received initial systemic anti- myeloma therapy consisting of induction therapy and consolidation with high-dose melphalan (>140 mg/m^2) followed by an auto HCT (minimum cell dose of 2x10^6 CD34+ cells/kg (actual body weight) within 12 months from initiation of systemic anti-myeloma therapy.
4. Patient must have additional stored stem cells greater than or equal to 2x10^6 CD34+ cells per kg actual body weight.
5. Patients must be less than or equal to 12 months after autologous HCT at the time of enrollment
6. Patients must have initiated maintenance therapy with lenalidomide within 6 months after the auto HCT and have received at least 6 months of maintenance prior to enrollment.
7. Patients must have tolerated a minimum dose of lenalidomide 5 mg/day for 21 days of a 28-day cycle for greater than 2 cycles without having to stop due to toxicities.
8. Patients must have achieved less than a VGPR (Section 3.1) in reference to time of initiation of initial systemic anti-myeloma therapy[1] at study enrollment.
9. Patients must have Karnofsky performance greater than or equal to 70.
10. Patients must have recovered to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding Grade 2 neuropathy.
11. Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3 without filgrastim use in the prior 14 days.
12. Platelet count greater than 100,000/mm^3 (without platelet transfusion in the previous 7 days or thrombopoietin mimetics in the previous 28 days)
13. Hemoglobin greater than 9 g/dL (without red blood cell transfusion in the previous 7 days)
14. Creatinine Clearance (CrCl) greater than or equal to 60 mL/min, measured or estimated by Cockcroft-Gault equation.
15. Corrected serum calcium less than or equal to 13.5 mg/dL
16. Oxygen saturation greater than 92% on room air

[1] Anti-myeloma therapy is defined as systemic treatment intended to treat the underlying myeloma disease. Treatments intended to alleviate pain and other symptoms of disease are not considered anti-myeloma therapy.

17. Hepatic Function:
    a. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than or equal to 2.5 x upper limit of normal (ULN)
    b. Serum total bilirubin less than or equal to 2 x ULN. Patients who have been diagnosed with Gilbert's disease are permitted to exceed the defined bilirubin value of 2 x ULN.
18. International ratio (INR) or partial thromboplastin time (PTT) less than 1.5 x ULN.
19. Cardiac Function: left ventricular ejection fraction greater than 45% by echocardiogram or MUGA.
20. Patients must be willing and able to adhere to the study visit schedule and other protocol requirements including regulatory requirement of a 15 year follow up using the CIBMTR long term follow up mechanism.
21. Female patients of childbearing potential (FCBP[1]) must:
    a. Have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL prior to enrollment.
    b. Agree to use, and be able to comply with, TWO acceptable methods of birth control (Appendix C), one highly effective method and one additional effective (barrier) method AT THE SAME TIME, from screening through at least 1 year following bb2121 infusion or 4 weeks following discontinuation of lenalidomide, whichever is later.
    c. Agree to abstain from breastfeeding from screening through at least 1 year following bb2121 infusion or 4 weeks following discontinuation of lenalidomide, whichever is later.
22. Male patients must:
    a. Agree to use a condom during sexual contact with a pregnant female or a FCBP, even if he has undergone a successful vasectomy, from screening through at least 1 year following bb2121 infusion or 4 weeks following discontinuation of lenalidomide whichever is later.
    b. Must not donate sperm from screening through at least 1 year following bb2121 infusion or 4 weeks following discontinuation of lenalidomide whichever is later.

2.3.2 Initial Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Patients with a prior allogeneic hematopoietic cell transplant

[1] A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

2. Patients with disease progression (see Section 3.1.2 for disease progression definition) at any time prior to enrollment
3. Patients receiving any of the following less than 14 days prior to enrollment:
    a. Plasmapheresis
    b. Major surgery (as defined by the investigator)
    c. Radiation therapy other than local therapy for MM-associated bone lesions
    d. Use of any systemic anti-myeloma drug therapy[1]
    e. Any investigational agents
    f. Corticosteroids (Physiologic replacement, topical, intranasal and inhaled steroids are permitted)
4. Patients with known Central Nervous System (CNS) involvement with MM
5. Patients with a prior organ transplant requiring systemic immunosuppressive therapy
6. Patients who previously experienced toxicities related to lenalidomide resulting in permanent treatment discontinuation
7. Patients who experienced thromboembolic events while on full anticoagulation during prior therapy with an immunomodulatory agent (IMiD)
8. Patients unwilling to take DVT prophylaxis while on lenalidomide maintenance
9. Patients with history of greater than or equal to Grade 2 hemorrhage within 30 days of enrollment
10. Patient requiring ongoing treatment with chronic, therapeutic dosing of anticoagulants (e.g. Warfarin, low molecular weight heparin, Factor Xa inhibitors)
11. Patients with history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or other CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
12. Patients with active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or clinically significant amyloidosis
13. Patients with purely non-secretory MM [absence of a monoclonal protein (M protein) in serum as measured by electrophoresis and immunofixation and the absence of Bence Jones protein in the urine defined by use of conventional electrophoresis and immunofixation

[1] Anti-myeloma therapy is defined as systemic treatment intended to treat the underlying myeloma disease. Treatments intended to alleviate pain and other symptoms of disease are not considered anti-myeloma therapy.

techniques and the absence of involved serum free light chain greater than 100mg/L]. Patients with light chain MM detected in the serum by free light chain assay are eligible.

14. Patients with a history of Class III or IV congestive heart failure (CHF) or severe nonischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or hemodynamically significant ventricular arrhythmia within the previous 6 months prior to starting study treatment
15. Patients with ongoing treatment with chronic immunosuppressants (e.g. cyclosporine or systemic steroids at any dose). Physiologic replacement, intermittent topical, inhaled or intranasal corticosteroids are allowed
16. Patients with active clinically significant autoimmune disease, defined as a history of requiring systemic immunosuppressive therapy and at ongoing risk for potential disease exacerbation. Patients with a history of autoimmune thyroid disease, asthma, or limited skin manifestations are potentially eligible.
17. Patients seropositive for human immunodeficiency virus (HIV-1), chronic or active hepatitis B or C, or acute hepatitis A. If any history of exposure to hepatitis B or C then DNA PCR should be negative.
18. Patients with previous history of treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy
19. Patients with prior malignancies except resected basal cell carcinoma or treated carcinoma *in situ*. Cancer treated with curative intent less than 5 years prior to enrollment will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs. Cancer treated with curative intent greater than 5 years prior to enrollment is allowed.
20. Female patients who are pregnant (positive beta-HCG), or breastfeeding, or who intend to become pregnant during participation in the study
21. Patient with known allergy or hypersensitivity to any of the study medications, their analogues, or excipients in the various formulations of any agent.
22. Patient with serious medical of psychiatric illness likely to interfere with participation on this clinical study
23. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment.
24. Patients unwilling or unable to provide informed consent
25. Patients unable or unwilling to return to the transplant center for treatment and follow up.

2.3.3 Patient Eligibility Criteria for LD Chemotherapy

To be eligible to start LD chemotherapy, patients must meet the following criteria:

1. Females of childbearing potential (FCBP) must have a negative serum pregnancy test less than 7 days prior to LD chemotherapy

2. Platelet count greater than or equal to 100,000/mm^3 (without platelet transfusion within 7 days or thrombopoietin mimetics within 28 days)
3. Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3 (without filgrastim within 72 hours)
4. Hepatic function:
    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 2.5 × upper limit of normal (ULN)
    b. Serum total bilirubin less than or equal to 2 × ULN. Patients who have been diagnosed with Gilbert's disease are permitted to exceed the defined bilirubin value of 2 x ULN
5. Creatinine Clearance (CrCl) greater than or equal to 45 mL/min, measured or estimated by Cockcroft-Gault equation.
6. International ratio (INR) or partial thromboplastin time (PTT) less than 1.5 x ULN
7. No history of greater than or equal to Grade 2 hemorrhage within 30 days
8. Not receiving ongoing treatment with chronic, therapeutic dosing of anticoagulants (e.g. Warfarin, low molecular weight heparin, Factor Xa inhibitors)
    a. Patients not meeting this criterion may still be eligible to initiate LD chemotherapy with the approval of the Protocol Chairs and/or Officer
9. Patient must have no presence of active/uncontrolled infection requiring systemic therapy. Prophylactic antimicrobials are allowed.
10. No intercurrent illness or toxicity that would place the subject at undue risk of proceeding to LD chemotherapy
11. Patients must not be taking any of the prohibited medications as described in Section 2.7.2 including therapeutic doses of corticosteroids (defined as greater than 20 mg/day prednisone or equivalent) within 72 hours prior to LD chemotherapy. Physiologic replacement, topical, intranasal and inhaled steroids are permitted
12. No active urinary outflow obstruction
13. No evidence of disease progression since enrollment
14. Availability of manufactured cells

2.3.4 Patient Eligibility Criteria for CAR T-Cell (bb2121) Infusion

Administration will be delayed if a subject meets at least one of the following criteria on the day of scheduled CAR T-cell infusion[1]:

1. Suspected or active systemic infection

[1] If CAR T-Cell infusion is delayed greater than 7 days, refer to section 2.4.5.1.

2. Onset of fever greater than or equal to 38°C/100.4°F
3. Requirement for supplemental oxygen to keep saturation greater than 91%
4. Cardiac arrhythmia not controlled with medical management
5. Hypotension requiring vasopressor support
6. New onset or worsening of other non-hematologic organ dysfunction greater than or equal to Grade 3
7. Taking any of the prohibited medications as described in (Section 2.7.2)
8. Significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with CAR T-cell infusion.

2.3.5 Patient Eligibility Criteria for Maintenance Therapy After bb2121 Infusion between Day 30 and Prior to or on Day 90

Patients must have sufficiently recovered from CAR T-cell therapy at the time of initiation of maintenance therapy. Patients will be initiated on lenalidomide maintenance if they meet the following criteria:

1. Platelet count greater than or equal to 75,000/mm^3 (without platelet transfusion in prior 7 days or use of thrombopoietin mimetics within 28 days)
2. ANC greater than 1,000/mm^3 without growth factor support in the last 14 days.
3. Must have recovery from CAR T-cell toxicities (specifically cytokine release syndrome and neurotoxicity to Grade 1 or baseline of non-hematologic CAR-T related toxicities, with the exception of Grade 2 neuropathy)
4. No active, uncontrolled infections
5. No evidence of disease progression since initial enrollment on the study
6. Patient must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of the REMS® program.
7. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

2.3.6 Patient Eligibility Criteria for Maintenance Therapy After bb2121 Infusion after Day 90 and Prior to Day 180

1. Platelet count greater than or equal to 50,000/mm3 (without platelet transfusion within 7 days or thrombopoietin mimetics within 28 days).
2. ANC greater than 1000/mm3 (filgrastim allowed)

3. Must have recovery from CAR T-cell toxicities (specifically cytokine release syndrome and neurotoxicity to Grade 1 or baseline of non-hematologic CAR-T related toxicities, with the exception of Grade 2 neuropathy)
4. No active, uncontrolled infections
5. No evidence of disease progression since initial enrollment on the study
6. Patient must be registered into the mandatory Revlimid REMS® program and be willing and able to comply with the requirements of the REMS® program.
7. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

2.4 Treatment Plan

2.4.1 Treatment Prior to Enrollment

Patients must have received initial systemic anti- myeloma therapy consisting of induction therapy and consolidation with high-dose melphalan (>140 mg/m^2) followed by an auto HCT (minimum cell dose of 2x10^6 CD34+ cells/kg (actual body weight) within 12 months from initiation of systemic anti-myeloma therapy. Patients also must have initiated post-transplant maintenance therapy with lenalidomide for 6 months and have achieved less than VGPR to this prior sequence of therapies at the time of enrollment.

Patients must discontinue lenalidomide maintenance at least two weeks prior to enrollment on BMT CTN 1902. Lenalidomide maintenance will be held from enrollment until after CAR T-Cell infusion. Maintenance will be re-initiated per section 2.4.7 once the patient meets criteria in section 2.3.5 or 2.3.6.

2.4.2 Leukapheresis

Following the screening assessments and enrollment, if the subject is eligible to participate in the study, subjects will undergo a leukapheresis collection to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the bb2121 investigational product. Should a technical issue arise during the procedure or in the processing of the product, the subject may have a second collection procedure performed. More than one bb2121 product lot may be combined to meet the protocol target dose range. Subjects must continue to meet screening eligibility requirements for repeat leukapheresis .

Following the screening assessments and enrollment, patients will undergo a leukapheresis collection to obtain a sufficient quantity of peripheral blood mononuclear cells for the production of the bb2121 investigational product. Leukapheresis should occur approximately 14 days after initial enrollment. The BMT CTN should be notified if leukapheresis cannot occur within approximately 14 days of initial enrollment. The leukapheresis product must be shipped in a sterile container to BMS/Celgene's manufacturing facility. CAR-T manufacturing will be initiated upon receipt of patient apheresis material; no notification to proceed with manufacturing is required.

Treatment with the following therapies after enrollment and prior to leukapheresis is not permitted:

- Any prior systemic therapy[1], including experimental agents, for MM
- Corticosteroids. Physiologic replacement topical, intranasal and inhaled steroids are permitted.
- Localized radiation therapy to control pain is permitted.

2.4.3 CAR T-Cell (bb2121) Manufacturing

All bb2121 for this clinical trial will be manufactured by BMS/Celgene and are required to meet pre-defined release criteria. Any out of specification product must be communicated to the BMT CTN DCC to be escalated per the designated review pathway and addressed. In the event any lot release criteria is out of specification, the event must be reported to the BMT CTN via the Adverse Event Form per the instructions in section 4.5.5. The product will be reviewed by an independent non-conforming product monitor and escalated to the FDA by the BMT CTN in order to decide whether the product can be administered or whether a new manufacturing procedure will be performed. The product must not be infused until FDA approval is received and communicated by the BMT CTN to the site. CAR T-Cell (bb2121) manufacturing will be initiated at BMS/Celgene following leukapheresis. If there is any reason that the investigator feels that the patient will NOT be eligible for LD chemotherapy or bb2121 infusion within the allotted study window, he/she should notify the study team immediately.

2.4.4 LD Chemotherapy

LD chemotherapy will be initiated 5 days prior to planned bb2121 infusion (refer to Table 2.4.4 for LD treatment plan). Timing of LD chemotherapy will also be coordinated with BMS/Celgene in order to confirm that the bb2121 product is ready. The patient must meet criteria in section 2.3.3 in order to initiate LD Chemotherapy.

Chemotherapy will be administered per institutional guidelines. Patients will receive cyclophosphamide 300 mg/m^2 from Day -5 to Day -3 via intravenous infusion over 30 minutes (Table 2.4.4). Immediately following infusion of cyclophosphamide, patients will receive fludarabine 30 mg/m^2 from Day -5 to Day -3 via infusion over 30 minutes. On Day 0, patients will receive the bb2121 infusion.

2.4.4.1 Renal Insufficiency Dose Adjustment for Fludarabine

Fludarabine will be dose reduced based on renal function. Patients with creatinine clearance 50 to 70 mL/min should receive a 20% dose reduction (fludarabine 24 mg/m2) of each daily fludarabine dose. Patients with creatinine clearance (CrCl) of 45 to 49 mL/min should receive a 40% dose reduction (fludarabine 18 mg/m2) of each day of daily fludarabine dose. Fludarabine should not be administered to patients with severely impaired renal function (creatinine clearance less than 40 mL/min).

[1] Anti-myeloma therapy is defined as systemic treatment intended to treat the underlying myeloma disease. Treatments intended to alleviate pain and other symptoms of disease and/or administration of ≤160mg of dexamethasone or equivalent alternative steroid dose within a 30-day period are not considered anti-myeloma therapy.

Table 2.4.4: Lymphodepletion and CAR T Infusion Treatment Plan

Drug	Dose	Day -5	Day -4	Day -3	Day 0
Cyclophosphamide	300 mg/m^2 IV infusion over 30 min	X	X	X	
Fludarabine	30 mg/m^2 IV infusion over 30 minutes administered immediately after cyclophosphamide*	X	X	X	
bb2121 Infusion	Minimum dose of 150 × 10^6 CAR-T cells/infusion				X

*See section 2.4.4.1 for dose reduction guidelines in the event of renal insufficiency

2.4.5 CAR T-Cell (bb2121) Infusion:

All bb2121 cellular products must meet pre-defined release criteria. Upon completion of LD chemotherapy, subjects will be infused with bb2121 on Day 0 at a target dose of 450 × 10^6 CAR-T cells/infusion. Products that are safe to infuse but out of specification will be escalated for review as included in section 2.4.3. The product must not be infused until FDA approval is received and communicated by the BMT CTN to the site. However, considerations of a second leukapheresis for a second course of manufacturing will be made on a case by case basis. See Appendix H for additional details regarding bb2121 infusion process.

2.4.5.1 Delay in bb2121 Infusion

Subjects who do not meet eligibility to receive bb2121 (section 2.3.4) on the scheduled Day 0 will delay infusion until all criteria in section 2.3.4 are met. The patient should be re-assessed for eligibility to receive bb2121 daily until the criteria are met. Infusion may be delayed up to 14 days.

If subjects do not meet criteria to receive bb2121 within 7 days of the originally planned infusion day, the BMT CTN DCC must be notified in order to escalate per the designated review pathway. However, infusion may continue without approval.

For delays beyond 14 days, the BMT CTN 1902 protocol chairs and/or officer will decide whether bb2121 infusion is permitted and whether LD chemotherapy must be re-administered. Final decision on such delayed bb2121 infusion will rest with the BMT CTN 1902 protocol chairs and/or protocol officer.

2.4.5.2 Pre-Medication

Pre-medication will occur approximately 30 minutes prior to the infusion of bb2121 and will include acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Subjects should not receive corticosteroids as pre-medication.

2.4.5.3 Infusion Modifications for Infusion Reaction

Patients should not receive steroids after infusion. The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue bb2121 infusion at the same dose and rate

- Grade 2: administer symptomatic treatment; continue bb2121 with a reduced rate of administration
- Grade 3: stop administration of bb2121, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue bb2121 infusion.
- Grade 4: discontinue administration of bb2121 and administer symptomatic treatment as necessary; no further bb2121 should be administered.

2.4.6 Maintenance Treatment

All patients who meet the eligibility criteria to proceed with maintenance in sections 2.3.5 or 2.3.6 will re-start maintenance therapy with lenalidomide between 30 and 180 days after CAR T-cell infusion. Initiating maintenance therapy outside of this range may be permitted with prior approval from the Protocol Chairs and/or Officer. The BMT CTN DCC must be notified in advance in order to escalate per the designated review pathway. Eligibility criteria for initiation of maintenance therapy and corresponding starting dose requirements are summarized in Table 2.4.6A.

For patients that initiate maintenance between Day 30 and 90 post CAR T-cell infusion, Lenalidomide will be administered initially at a dose of 5 mg per day for 21 days every 28 days; dose will be increased to 10 mg daily with cycle 2 if patients previously tolerated this dose prior to enrollment and if no significant hematologic toxicity (as determined by investigator) developed on the 5 mg dose. Patients will continue lenalidomide until they reach 12 months from initiation of therapy or until one of the criteria in section 2.4.6.1 applies.

For patients that initiate maintenance between Day 91 and 180 post CAR T-cell infusion, Lenalidomide will be administered initially at a dose of 5 mg per day for 21 days every 28 days and continue at this dose for minimum of 3 cycles before dose increase to 10 mg will be considered.

Patients that require stem cell reinfusion may continue with maintenance therapy 30-60 days after the reinfusion, provided they meet eligibility criteria to proceed with maintenance therapy by Day 180 post CAR T-cell infusion.

DVT prophylaxis for patients will be given per institutional guidelines.

Patients who stop maintenance therapy for any reason prior to 12 months from initiation of maintenance will continue to be followed per protocol for 12 months post bb2121infusion. Upon completion of protocol specified maintenance therapy, patients will be treated at the investigator's discretion. However, it is recommended that patients continue receiving lenalidomide as per standard of care.

Table 2.4.6A: Eligibility and Dosing Requirements for Initiation of Maintenance Therapy Post CAR T Infusion

Eligibility and Dosing Requirements for Initiation of Maintenance Therapy Post CAR-T Infusion			
Days post CAR T Infusion	≥ 30 and ≤ 90	> 90 and ≤ 180[1]	> 180
Hematologic Eligibility Requirements[2] Platelet Count[3] ANC[4]	 > 75,000/mm^3 > 1000/mm^3	 > 50,000 /mm^3 > 1000/mm^3	 > 50,000/mm^3 > 1000/mm^3
Starting Lenalidomide Dose	10mg daily for 21 of 28-day cycles (first cycle at 5 mg)[5]	5mg daily for 21 of 28-day cycles[6]	Cannot initiate maintenance[7]

[1] Stem cell re-infusion may be performed per the cytopenia management guidelines in Appendix I prior to day 180 to meet the required hematologic eligibility requirements. The BMT CTN 1902 Protocol Chairs and/or Officer must be consulted prior to stem cell re-infusion.
[2] Refer to section 2.3.5 and 2.3.6 for full set of eligibility requirements for Initiation of Maintenance Therapy
[3] Platelet count requirements must be achieved without platelet transfusion within 7 days or thrombopoietin mimetics within 28 days
[4] Filgrastim allowed to achieve required ANC
[5]Maintenance dose after CAR T-cell in cycle two should be similar to the dose prior to enrollment. For example: if the patient was tolerating 10mg daily for 21 days out of 28-day cycle, the dose of 10mg should be the goal beyond cycle 2 post CAR T-cell. Patients should meet count requirements in table or dose must be reduced. 56-day delay is the maximum window in starting next cycle.
[6]If the 5mg dose is tolerated, the dose may be escalated per section 2.4.6.2 after completion of 3 cycles.
[7] Although the hematologic requirements need to meet the parameters above, maintenance therapy cannot be initiated beyond 180 days post CAR-T Cell Infusion without prior approval. See sections 2.3.6 and 2.4.6 for additional information.

2.4.6.1 Lenalidomide Maintenance Dose Modifications and Holds

Lenalidomide dose will be adjusted for toxicity. Table 2.4.6C describes the dose reduction steps to be utilized during maintenance therapy. In the presence of lenalidomide-related toxicities (Table 2.4.6B), the study drug will be held until the toxicity resolves then restarted at a reduced dose as described in Table 2.4.6D.

If lenalidomide is held for greater than 8 weeks for any reason, the BMT CTN DCC must be notified in order to escalate per the designated review pathway. Approval must be obtained prior to re-starting lenalidomide.

If lenalidomide is held for greater than or equal to 14 days for any reason, it will be considered a Protocol Deviation (PD) and will be reported following the BMT CTN DCC PD process.

Table 2.4.6B – Required Treatment Modification Guidelines for Lenalidomide Maintenance Therapy for Non-Hematologic Toxicities

Grade by NCI CTCAE v5.0 [1]	**Action**
Grade 3 neutropenia associated with fever (temperature ≥ 38. 5° C) or Grade 4 neutropenia	Hold lenalidomide. Follow CBC weekly. If the toxicity resolves to ≤grade 2 restart lenalidomide at next lower dose level. If neutropenia is the only toxicity for which a dose reduction is required, granulocyte growth factors could be considered at the discretion of the treating physician and the lenalidomide dose maintained.
Thrombocytopenia (platelet count < 30,000/mm³)	Hold lenalidomide. Follow CBC weekly. If the toxicity resolves to ≤ grade 2 restart lenalidomide at next lower dose level.
Non-blistering rash Grade 3	Hold lenalidomide: Follow weekly. Treatment with antihistamine may be initiated at the discretion of the investigator.

Grade by NCI CTCAE v5.0 [1]	Action
(Generalized rash ≥ 25% BSA)	If the toxicity resolves to ≤ grade 1 restart lenalidomide at next lower dose level.
Non-blistering rash Grade 4	Discontinue lenalidomide permanently. Continue to follow the patient per-protocol
Desquamating (blistering) rash any Grade	Discontinue lenalidomide permanently. Continue to follow the patient per-protocol
Venous thrombosis/embolism ≥ Grade 3 (DVT or cardiac thrombosis; intervention indicated)	Hold lenalidomide and start anticoagulation per institutional guidelines. Restart therapy and maintain dose level.
Other non-hematologic toxicity assessed as Lenalidomide-related ≥ Grade 3	Hold lenalidomide. If the toxicity resolves to ≤ grade 2 restart lenalidomide at next lower dose level.
Hyperthyroidism or Hypothyroidism	Hold lenalidomide. Evaluate etiology and initiate appropriate therapy. Restart lenalidomide at next lower dose level.
Pregnancy[2]	Discontinue lenalidomide study drug.

[1]Please consult NCI CTCAE version 5.0 for **Grade** descriptions. The **"≥ Grade 3" descriptions** listed above are minimums
[2]If a subject, or the partner of a male study subject, misses her period or if her pregnancy test or her menstrual bleeding is abnormal, pregnancy testing and counseling must be performed (Section 4.5.2.3).

Table 2.4.6C- Lenalidomide Dose Reduction Steps During Lenalidomide Maintenance Therapy

Lenalidomide Dose Reduction Steps for Non-Hematologic Toxicity	
Dose at Time of Toxicity	**Dose reduction**
10 mg daily for 21 days every 28 days	5 mg daily for 21 days every 28 days
5 mg daily for 21 days every 28 days	2.5 mg daily for 21 days every 28 days
2.5 mg daily for 21 days every 28 days	Discontinue Lenalidomide

2.4.6.2 Lenalidomide Maintenance Dose Re-Escalation

Patients that initiate lenalidomide at a dose of 5mg daily for 21 days every 28 days may be re-escalated as shown in Table 2.4.6D to a maximum of 10 mg daily for 21 days every 28 days.

If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75,000/μL, the study drug dose may be re-escalated as shown in Table 2.4.8D, one step per cycle to a maximum of 10 mg daily for 21 days every 28 days.

Table 2.4.6D – Lenalidomide Dose Re-Escalation Steps During Lenalidomide Maintenance Therapy

Current Patient Dose	Dose Re-Escalation
2.5 mg daily for 21 days every 28 days	5 mg daily for 21 days every 28 days
5 mg daily for 21 days every 28 days	10 mg daily for 21 days every 28 days
10 mg daily for 21 days every 28 days	No more dose escalations permitted

2.5 Risks and Toxicities

All organ toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. CRS and neurotoxicities will be graded according to the ASTCT consensus grading criteria (Appendix I).

2.5.1 Leukapheresis Risks

Risks of this collection are related to placement of an intravenous leukapheresis catheter that can be associated with bleeding and pain. The leukapheresis procedure has a risk of hypocalcemia, thrombocytopenia, anemia, leukopenia and bleeding diathesis.

2.5.2 LD Chemotherapy Risks

Common side effects of fludarabine and cyclophosphamide include bone marrow cytopenias and immune suppression which increase the risk of bleeding and infection and may be exacerbated by bb2121 treatment.

2.5.2.1 Cyclophosphamide Risks

Cyclophosphamide side effects include:

- Cardiac and vascular: heart failure (which can result in edema, effusion, dyspnea
- Cutaneous: alopecia, rash, hyperpigmentation of skin and nails
- Gastrointestinal: nausea, vomiting, diarrhea, anorexia, abdominal pain, mucositis, stomatitis
- General: lethargy
- Hematologic: leukopenia, thrombocytopenia, anemia
- Pulmonary: pulmonary fibrosis
- Endocrine: amenorrhea, gonadal function impairment, sterility, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) - with associated cerebral edema
- Genitourinary: hemorrhagic cystitis
- Miscellaneous: infection, allergic reaction including anaphylaxis, secondary malignancy

2.5.2.2 Fludarabine Risks

Fludarabine side effects include:

- Gastrointestinal: vomiting, anorexia, nausea, mucositis
- General: fatigue, fever, chills
- Hematologic: anemia, thrombocytopenia, neutropenia
- Hepatic: increased liver function tests
- Neurologic: paresthesia, confusion, seizure, agitation, visual disturbances, pain
- Pulmonary: cough, shortness of breath
- Renal: renal impairment, hematuria

- Miscellaneous: infection, general organ damage

2.5.3 CAR T Therapy (bb2121) Toxicities

Administration of bb2121 may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

2.5.3.1 Cytokine Release Syndrome (CRS)

Administration of CAR T cells is associated with CRS and it has been reported frequently following treatment with bb2121. CRS is a potentially serious disorder associated with uncontrolled activation and proliferation of CAR T cells and associated cytokine secretion. CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (e.g., altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity). Laboratory abnormalities may include cytopenias, coagulopathy, electrolyte, renal and liver function abnormalities as well as C-reactive protein (CRP), ferritin and cytokine elevations. Organ dysfunction, in particular, cardiac, pulmonary and neurologic dysfunction, can be observed as part of CRS. Refer to Appendix I for CRS grading and management guidelines.

2.5.3.2 Neurologic Toxicities

CAR T-cell therapy is associated with potentially serious neurologic toxicities and life-threatening neurotoxicity has been reported with bb2121. The etiology and optimal management of neurologic toxicities remains unclear. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity, and can accompany CRS (precede or follow other CRS symptoms) or can occur in isolation. Refer to Appendix I for neurotoxicity management guidelines.

2.5.3.3 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a potentially serious disorder associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. MAS is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating natural killer (NK) cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis.[47] While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

2.5.3.4 Tumor Lysis Syndrome

Both LD chemotherapy and bb2121 may cause tumor lysis syndrome (TLS) in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS.

2.5.3.5 Plasma Cell Aplasia and Hypogammaglobulinemia

Plasma cell aplasia is an expected off-tumor, on-target toxicity of bb2121. The expected duration of plasma cell aplasia is unknown but may persist as long as bb2121 CAR T cells remain in the body. Prolonged plasma cell aplasia is expected to result in hypogammaglobulinemia which can also be observed as a manifestation of myeloma itself. Hypogammaglobulinemia may increase the risk of bacterial and other infections including opportunistic infections and viral reactivation. Serum immunoglobulin levels will be obtained from all subjects prior to and at regular time points following bb2121 treatment.

2.5.3.6 Replication Competent Lentivirus, Clonality and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of replication competent lentivirus (RCL) during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due, at least in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of bb2121.[48]

Concern for possible neoplastic transformation due to the location of the vector integration into the host genome has arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice[49, 50] and monkeys[51] and a single clinical study reporting development of leukemia in subjects with X-linked severe combined immunodeficiency (SCID) who received retroviral-modified CD34+ hematopoietic stem cells,[52] including one subject who died.[53] Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or subjects treated in trials of gene-modified T cells have been reported to date.

Data has recently been published on the integration sites of retroviral and lentiviral vectors used for T cell modification in clinical trials.[54-56] No clonality of integration sites was observed with exception of a single case recently reported by Fraietta et al. in which the vast majority (94%) of CAR T cells at peak expansion were derived from a single transduced cell [57]. Further study on this case revealed disruption of the TET2 gene and a hypomorphic mutation in the patient's second TET2 allele. Importantly, this clonal T cell expansion seemed to be antigen-driven as the population contracted with elimination of the patients CLL and thus did not represent an oncologic transformation. Further studies identified epigenetic reprogramming instigated by TET2 disruption as the likely mechanism for the proliferative advantage exhibited by this clone[57]. Though this event did not result in malignant transformation, it supports the rationale for long-term follow-up of patients treated with genetically modified cellular therapies.

2.5.3.7 Infections

Administration of CAR T cells following LD chemotherapy is associated with risk of bacterial and opportunistic infections, and infections have been reported following treatment with bb2121. Risk factors for infection include immune dysfunction from myeloma, LD chemotherapy (i.e., fludarabine and cyclophosphamide) and associated lymphopenia and myelosuppression, and bb2121 treatment-associated toxicities. CRS may exacerbate and delay recovery from cytopenias, and treatment of CRS and neurotoxicity with corticosteroids may also increase infection risk.

Finally, plasma cell aplasia following bb2121 treatment is an expected on-target toxicity of BCMA targeted CAR T cell therapies and may result in chronic hypogammaglobulinemia.

Infections may include bacterial, fungal, pneumocystis, viral reactivation and symptomatic viral infections (e.g., cytomegalovirus (CMV), hepatitis B virus, respiratory viruses and other viruses). Infections may be life threatening or fatal. Death from CMV pneumonia (with low level concurrent pneumocystis infection) following treatment with bb2121 has occurred. bb2121 treated subjects will undergo frequent monitoring for recovery from cytopenias and lymphopenia for at least 6 months following bb2121 infusion.

2.5.3.8 Prolonged Cytopenias

Prolonged cytopenias have been observed in MM patients after CAR T cell therapy in prior studies of bb2121 and other CAR T cell products. The etiology is likely multifactorial, with the following contributing factors: (1) myelosuppressive effects of LD chemotherapy, (2) low bone marrow reserve from prior myeloma therapy, (3) high MM disease burden in the relapsed/refractory population studied in these prior trials, and (4) CAR T cell activation and cytokine release syndrome, including macrophage activation (i.e., hemophagocytosis). In this trial, the recent myeloablative chemotherapy and AHCT may increase the risk of prolonged cytopenias compared to prior bb2121 studies, which generally did not administer bb2121 in the early post-transplant period. However, compared to the patient population on prior bb2121 studies, patients on this study will have received less prior MM therapy and are expected to have a lower overall disease burden; these factors may decrease risk of prolonged cytopenias. Guidelines for evaluation and management of prolonged cytopenias after bb2121 are described in Appendix J.

2.5.4 Lenalidomide Related Toxicities

Common toxicities described for lenalidomide include:

- Cardiac: hypotension
- Constitutional: Weakness, insomnia, rigors, chills, sweating, weight loss and fever
- Dermatologic: rash, dry skin, itching
- Endocrine: hypothyroidism
- Gastrointestinal: Constipation, dehydration, dry mouth, diarrhea, dyspepsia, nausea, vomiting and stomatitis
- Hematologic: anemia, neutropenia, leucopenia, lymphopenia and thrombocytopenia; thromboembolic events (deep vein thrombosis and pulmonary embolism)
- Infection
- Metabolic: hypokalemia, liver damage
- Musculoskeletal: arthralgia, back/neck pain, joint pain, muscle cramp and weakness
- Neurologic: Somnolence, dizziness, headache, tremor, asthenia, paresthesia, and numbness
- Pulmonary: cough, dyspnea, pneumonitis
- Renal: increased creatinine, renal failure
- Reproductive: teratogenicity and miscarriage
- Subsequent neoplasms

Pregnancy reporting:

See Section 4.5, Adverse Event Reporting.

Other instructions related to lenalidomide:
During maintenance, only one cycle (maximum 28-day supply) of therapy may be dispensed to the patient each month. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients taking more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. See Section 4.5 and Appendix C (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and D (Revlimid REMS program).

2.5.5 Subsequent Neoplasms and Long Term Follow up

Autologous HCT and lenalidomide are standard of care interventions that have been known to increase the risk for subsequent neoplasms. The investigational intervention included in this trial may further increase risk of subsequent neoplasms. According to regulatory requirement related to genetically modified cellular products, recipients are required to be followed for 15 years to primarily monitor the development of subsequent neoplasm (Section 4.1.2) . Patients will co-enroll in the long term follow up protocol using the Center for International Blood and Marrow Transplant Research (CIBMTR) Cellular Therapy Registry (Chapter 4) similar to the mechanism proposed for commercial Ide-cel.

2.6 Supportive Care and Toxicity Management

2.6.1 LD Chemotherapy Supportive Care and Toxicity Management

The following medications/supportive therapies are recommended during LD chemotherapy, as applicable:

- Pre-hydration will be administered per institutional guidelines prior to initiating LD chemotherapy. Hydration post LD chemotherapy may be administered if required per institutional guidelines.
- The antiemetic regiment will be based on institutional guidelines. Dexamethasone or other systemic steroids are not permitted.
- The use of ondansetron, oral or IV, or similar serotonin inhibitor, on days –5, -4, and -3 prior to chemotherapy is suggested.
- Chemotherapy-induced cytopenias should be managed with myeloid growth factor, blood product transfusion support, and prophylactic anti-microbials according to local institutional guidelines. Myeloid growth factor may be administered per institutional guidelines. It is recommended that myeloid growth factor be administered per physician discretion no earlier than 7 days post bb2121 infusion.

2.6.2 CAR T-cell (bb2121) Infusion Supportive Care and Toxicity Management

2.6.2.1 Infusion Reaction Management

Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused bb2121. Rigors may be treated with meperidine (Demerol®).

2.6.2.2 Prolonged or Recurrent Cytopenia Management

A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, CD4 lymphopenia (CD4 less than 200/µl) and/or recent use of corticosteroids. Viral reactivation and other serious opportunistic infections should be considered in these settings and prophylactic, preemptive or symptomatic treatment with anti-microbial, anti-fungal, anti-pneumocystic and/or antiviral therapies should be considered, per local institutional guidelines. Refer to Appendix J for Cytopenia Management Guidelines.

2.6.2.3 Cytokine Release Syndrome Management

Supportive management for CRS includes anti-pyretic for fever control, intravenous fluids to vasopressor agents for hypotension and supplemental oxygen to positive pressure ventilatory support for hypoxia.

In some cases, tocilizumab, an anti-IL-6R antibody, will be required for treatment of moderate to severe CRS. Tocilizumab must be available at the site prior to infusion of the subject. Tocilizumab is administered at a dose of 8 mg/kg (maximum dose 800 mg). Other anti-IL-6 agents could be considered in the event of severe CRS not responding to tocilizumab and discussion with the protocol chairs is recommended. Dosing of any other anti-IL-6 agent should be per prescribing information. Refer to Appendix I for detailed CRS management guidelines.

2.6.2.4 Neurologic Symptom Management

Neurologic symptoms may begin 3 to 23 days (median 10 days) after CAR T cell infusion and in severe cases may require admission to the ICU for frequent monitoring, respiratory support, or intubation for airway protection. Any signs or symptoms of neurotoxicity (other than headache) should prompt hospitalization. Patients with neurotoxicity can be treated with corticosteroids, anti-convulsive agents and in rare cases cyclophosphamide. Refer to Appendix I for neurotoxicity management guidelines.

2.6.2.5 Tumor Lysis Syndrome Management

Subjects at high risk for Tumor Lysis Syndrome (TLS) should receive prophylactic treatment per standard clinical practice. Treatment of TLS should be administered per institutional standards. In severe cases hemodialysis may be required.

2.6.2.6 Intravenous Immunoglobulin (IVIG) Therapy

Intravenous immunoglobulin (IVIG) therapy may be used per institutional guidelines.

2.6.2.7 Antiviral Therapy

Antiviral therapy with appropriate antiviral agent for HBV is recommended for subjects with known history of hepatitis B exposure (i.e., HBcAb-positive) to prevent HBV reactivation. Prophylactic anti-viral therapy may be stopped 12 months after CAR T-cell infusion.

After stopping prophylaxis, it is recommended that HBV DNA should be tested every three months indefinitely due to uncertain risk of HBV reactivation after CAR T-cell therapy targeting plasma cells. Subjects with known history of hepatitis B exposure who cannot tolerate or have contraindications to antiviral therapy should be monitored every three months with HBV DNA testing. Appropriate first-line agents for prophylaxis include entecavir, tenofovir, and lamivudine (note that lamivudine has higher resistance rates). Any subject who develops a positive HBV DNA test or positive HBsAg test on-study should be evaluated by a gastroenterologist or infectious disease specialist.

2.6.2.8 Pneumocytis Jiroveci Prophylaxis

It is recommended that Pneumocystis jiroveci prophylaxis continue for 6 months following administration of fludarabine.

2.6.2.9 Vaccination

Avoid administration of vaccines during and for 6 months following bb2121 infusion. Administration of vaccines should begin 6 months post bb2121 infusion per institutional guidelines. Live vaccines should be avoided for 2 years following bb2121 infusion.

2.6.3 Lenalidomide Supportive Care

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Prophylaxis for DVT/PE will be done according to institutional guidelines.

2.7 Concomitant Medications

Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

2.7.1 Permitted Concomitant Medication and Procedures

Subjects with myeloma-associated bone disease may receive bisphosphonate therapy prior to study entry, unless such therapy is contraindicated. The use of bisphosphonates is permitted throughout the study.

Platelet/red blood cell transfusions and hematopoietic growth factors are also permitted during the study unless specifically noted. Leukocyte filters are encouraged for all platelet and packed RBC transfusions. Concurrent use of hormones for non-cancer related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

2.7.2 Prohibited Concomitant Medications and Procedures

The following medications are prohibited during the study. A protocol deviation must be reported via the BMT CTN DCC PD process if a subject receives any of the following during the study:

- Systemic steroids: dexamethasone, prednisone or other corticosteroids are not allowed unless used for the treatment of CRS or neurotoxicity, or as described below. If steroids are to be administered, it should be discussed with the protocol team unless in the setting of acute clinical requirements (e.g., Grade 3 or 4 CRS). Generally, the only setting for administration of systemic corticosteroids will be CRS management or severe neurotoxicity, following the guidelines in Section 2.6.2.2 and Appendix I.
- Therapeutic doses of steroids may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable bb2121 cells. Pretreatment containing steroids may be given for necessary medications (e.g., IVIG or in the setting of radiologic contrast allergy) after discussion with the sponsor. Premedication with steroids for bb2121 infusion is not allowed. Physiologic replacement, dosing of steroids (less than or equal to 12 mg/m2/day hydrocortisone or equivalent [less than or equal to 3 mg/m2/day prednisone or less than or equal to 0.45 mg/m2/day dexamethasone]) is allowed. Use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted unless otherwise specified.
- Any systemic anti-myeloma therapy within 14 days prior to leukapheresis.
- Bridging myeloma therapies between leukapheresis and LD chemotherapy
- Any systemic anti-myeloma therapy within 14 days of LD chemotherapy until the patient completes follow up
- Any concurrent chemotherapy, immunotherapy, biologic, experimental or hormonal therapy until the patient completes follow up. Palliative radiotherapy for treatment of symptomatic bone or soft tissue lesions is allowed.
- Avoid administration of vaccines during and for 6 months following bb2121 infusion. Administration of vaccines should begin 6 months post bb2121 infusion per institutional guidelines. Live vaccines should be avoided for 2 years following bb2121 infusion.

The following medications should be used with caution during the study. The protocol team must be notified if a subject receives any of these during the study.

- Any concurrent chemotherapy, radiation therapy, immunotherapy, biologic or hormonal therapy for cancer treatment (including treatment of myeloma after documented progression).
- Herbal and natural remedies are to be avoided.

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers unless used for the management of severe CRS or neurotoxicity.

2.8 Study Drug Supply

2.8.1 Lenalidomide

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of the maintenance phase of this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with BMS/Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS®program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies.

Lenalidomide will be provided by BMS/Celgene and distributed by Biologics, Incorporated. Patients must be registered in the Revlimid REMS program in order to receive lenalidomide through the program (please see Appendix D).

Lenalidomide (NSC 703813)

NOTE:

Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) study patients must be counseled through the Revlimid REMS program. A maximum 28-day supply may be dispensed to a patient at one time. For more information please refer to www.revlimidrems.com. Only use the study specific drug request form per patient for ordering through Biologics.

Chemical Name: 3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione

Other Names: CC-5013, Revlimid™, CDC-501

Classification: Immunomodulatory Agent

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$ **M.W.:** 259.25

Mechanism of Action:

Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition

of angiogenesis, inhibition of hematopoietic tumor cell proliferation, modulation of stem cell differentiation and up regulating responses of T cells and NK cells.

Drug Supply and Storage:

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with BMS/Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS®program.

Further information about the Revlimid REMS® program is available at www.celgenerisk management.com.

Administration:

Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

Dispensing:

Only enough lenalidomide for one cycle may be dispensed at one time.

Patient Care Implications and Counseling:

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Potential Drug Interactions:

Periodic monitoring of digoxin levels is recommended during co-administration with lenalidomide. Monitor patients receiving concomitant warfarin per standard practice guidelines. Lenalidomide is not a substrate of human CYP enzymes, nor is it an inhibitor or inducer.

Drug Ordering and Accountability:

The REMs program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling will be provided by Biologics, Inc. prior to drug distribution. Please refer to Appendix D (Lenalidomide REMs program). The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program. All physicians must be registered prescribers of Revlimid® in the REMs program. Physician registration allows access to the REMs software to enroll patients in the REMs program. The prescriber should submit the Registration Form via fax number 919-256-0794 or REMsOnline ***(RAO)***for Revlimid®) to BMS/Celgene Customer Care. Please reference Appendix D (REMs program) and follow the directions for submitting the registration. Biologics, the distributor of the lenalidomide, will not

dispense or ship Revlimid® prior to BMS/Celgene's receipt of registration. Prescription information MUST BE entered using the REMs study specific electronic prescription form referenced in Appendix D (REMs program). An authorization **number** must be on the prescription form at the time of faxing. Prescriptions for Revlimid® must be sent to Biologics Clinical Trial Division at the following FAX number: 919-256-0794. A maximum of a 28-day supply of Revlimid® may be dispensed per cycle sent to the actual address noted on the REMs electronic prescription form. Biologics will verify the authorization number and complete the patient counseling. Patients will be provided with instructions from Biologics with each new dispense on the procedures for return of any un-used Revlimid® capsules. Refer to Appendix D (REMs program).

2.9 Patient Withdrawal from Study and Off Study Criteria

Patients on the BMT CTN 1902 study have voluntarily agreed to the study and may withdraw at any time. Additionally, the treating physician may discontinue therapy with reasonable justification. The following criteria would result in discontinuation of study therapy:

- Disease progression
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

After enrollment, patients who withdraw from the study for any reason prior to 12 months from infusion will continue to be followed per protocol for 12 months post infusion unless the patient withdraws consent for study follow up. In the event of patient withdrawal, written documentation of the withdrawal must be provided to the BMT CTN.

2.10 Study Conduct

This study will be conducted in accordance with the protocol, protocol-specific Manual of Procedures (located on the BMT CTN SharePoint Website), and the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
b. Applicable ICH Good Clinical Practice (GCP) Guidelines
c. Applicable laws and regulations

The National Marrow Donor Program (NMDP) single Institutional Review Board (IRB) of Record will oversee this study and conduct the study-specific reviews as required by federal regulations and per the NMDP IRB Standard Operating Procedures (SOPs).

Site personnel will enter data in the electronic case report form (eCRF) in Advantage eClinical as described in the BMT CTN 1902 Forms Guide. Source documentation should be made available for monitoring visits, audits and regulatory inspections as described in the protocol-specific MOP.

Participating Principal Investigators (PIs) bear ultimate responsibility for training of site staff as well as the scientific, technical, and administrative aspects of conduct of the protocol, even when

certain tasks have been delegated to coinvestigators, sub-investigators, or staff. The PIs have a responsibility to protect the rights and welfare of patients and comply with all requirements regarding the clinical obligations and all other pertinent requirements in 21 CFR part 312. In addition to following applicable federal, state, and local regulations, investigators are expected to follow ethical principles and standards and receive training in GCP every three years and human subjects training within the past 3 years and thereafter as per institutional requirements.

CHAPTER 3

3 STUDY ENDPOINTS AND DEFINITIONS

3.1 Definition of Disease Status

Until disease progression, all disease classifications are relative to the patient's disease status prior to initial systemic anti-myeloma therapy. The response categories described below are in congruence with the International Myeloma Working Group consensus criteria for myeloma response [23].

3.1.1 Response Categories

Stringent Complete Response (sCR):

sCR requires, in addition to CR (defined below), all of the following:

- Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells.

Complete Response (CR):

CR requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation. The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)[1].
- Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Very Good Partial Remission (VGPR)

VGPR requires, in addition to PR (defined below), all of the following:

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis.

  OR

[1] If not clinically indicated, radiographs are not required to document CR.

- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein less than 100 mg/24hrs.
- For free light chain only disease, VGPR requires a 90% reduction of involved light chain

Partial Response (PR)

PR requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and reduction in 24-hour urinary monoclonal paraprotein either by greater than or equal to 90% or to less than 200 mg/24 hours.
- If the serum and urine M-protein are unmeasurable, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio,
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%,
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas if present at baseline (by radiography or clinical examination)[1].

Minimal Response (MR)

- Greater than or equal to 25% and less than 50% reduction in the level of serum monoclonal paraprotein and reduction in 24-hour urinary monoclonal protein by 50-89%.
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas if present at baseline (by radiography or clinical examination).

Stable Disease (SD)

- Patients who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease (section 3.1.1) are considered to have stable disease (SD).

3.1.2 Disease Progression Definitions

Progressive Disease (PD) from CR or sCR

Progression from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.
- Abnormal FLC levels of greater than 10 mg/dl, only in patients without measurable paraprotein in the serum and urine.

[1] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD

- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca greater than 11.5 mg/dL or greater than 2.8 mmol/L) not attributable to any other cause.

Progressive Disease (PD) for Patients not in CR or sCR

For patients not in CR or sCR, progressive disease requires one or more of the following:

- Greater than 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- Greater than 25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg paraprotein /24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be greater than 10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- Greater than 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca greater than 11.5 mg/dL or greater than 2.8 mmol/L) not attributable to any other cause.

3.2 Primary Endpoint

The primary endpoint is achieving a complete response or better (CR or sCR) as assessed by the 6-month time point after BCMA CAR T-cell therapy in MM patients with suboptimal disease responses after an autologous HCT and lenalidomide maintenance.

3.3 Clinical Secondary Endpoints

3.3.1 Disease Progression

Disease progression defined according to Section 3.1.2 or initiation of off protocol anti-myeloma therapy is the event for this endpoint. Death without documentation of disease progression is the competing event. Patients alive without disease progression at last contact are considered censored for this event.

3.3.2 Disease Response

Disease response will be assessed according to Section 3.1.1. The following will be reported in all patients as defined below:

- Proportion of patients achieving upgrade in response following enrollment (SD to MR or greater, MR to PR or greater, or PR to VGPR or greater)
- Conversion to MRD negativity. MRD will be assessed by multi-color flow at 10^{-5} level.

3.3.3 Non-Relapse Mortality

Non-Relapse Mortality (NRM) is defined as death occurring in a patient from causes other than disease relapse or progression. Disease progression is the competing event for NRM. Patients alive without disease progression at last contact are considered censored for this event.

3.3.4 Incidence of Cytokine Release Syndrome (CRS)

Overall incidence of CRS of any grade and grade 3 or 4 CRS post CAR T-cell infusion will be reported on all patients.

3.3.5 Incidence of Prolonged Cytopenias

Overall incidence of prolonged cytopenias will be reported. Prolonged cytopenia is defined as failure to achieve ANC greater than 500/mm^3 or platelet count greater than 20,000/mm^3 (with or without support) by 30 days post CAR T-cell infusion.

3.3.6 Incidence of Neurotoxicity

Overall incidence of CAR T-cell related neurotoxicity per the ASBMT immune effector cell associated neurotoxicity syndrome (ICANS) Consensus Grading (Appendix I).

3.3.7 Progression Free Survival

Progression free survival (PFS) is defined as progression of disease or death from any cause. Surviving patients without disease progression will be censored at the date of last contact.

3.3.8 Feasibility of Re-Initiation of Lenalidomide Maintenance

Time to re-initiation of lenalidomide maintenance therapy following CAR T cell infusion will be summarized using the cumulative incidence estimator, treating death as a competing risk. Cumulative incidence at 180 days post infusion will be summarized along with a 90% confidence interval.

3.4 Exploratory Endpoints

3.4.1 Incidence of Toxicities Grade ≥ 3 per CTCAE Version 5.0

All Grade 3 or higher toxicities will be tabulated. The proportion of patients experiencing cytokine release syndrome CRS will be reported including overall and grades 3-4 based on the ASTCT grading outlined in Appendix I.

3.4.2 Incidence of Infections per Protocol-Specific MOP

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each patient.

3.4.3 Maintenance Feasibility

The feasibility of resuming maintenance following enrollment by 180 days after CAR T-cell infusion will be described. The proportion of patients initiating maintenance at 180 days following bb2121 infusion will be reported.

3.4.4 Overall Survival

The event is death from any cause. The time to this event is the time from initial enrollment to death, loss to follow-up, or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored.

3.4.5 CAR T-Cell Expansion

Quantitation of CAR T-cells in peripheral blood will be determined at specified timepoints by quantitative PCR assay, measured in copies/mcg genomic DNA. Peak CAR T-cell expansion will be compared between subjects who are and are not in CR at 12 months, and between subjects who are and are not progression-free at 12 months.

3.4.6 CAR T-Cell Persistence

Quantitation of CAR T-cells in peripheral blood will be determined at specified timepoints by quantitative PCR assay, measured in copies/mcg genomic DNA. Persistence will be measured in 2 ways: 1) as an area under the curve (AUC) over first 6 months post CAR T-cell infusion; and 2) as still having detectable CAR T-cells at 6 months post CAR T-cell infusion. AUC_{6mos} and 6-month persistence will be compared between subjects who are and are not in CR at 12 months, and between subjects who are and are not progression-free at 12 months.

3.4.7 BCMA Expression

BCMA expression at specified timepoints will be determined by immunohistochemical staining of bone marrow biopsy specimens and/or flow cytometric analysis of bone marrow aspirate material, in order to assess for baseline expression and potential loss of expression post-treatment. Both percent of MM cells that stain positive as well as staining intensity will be reported.

3.4.8 Immune Reconstitution

The cellular composition of marrow (T-Cells, B-Cells, Natural Killer Cells, dendritic cells, and myeloid derived suppressor cells) will be quantified at the specified timepoints by flow cytometry.

CHAPTER 4

4 PATIENT REGISTRATION, ENROLLMENT AND EVALUATION

4.1 Enrollment Procedures

Patients will be enrolled in a two-step process for eligibility assessment and to schedule apheresis as the first step of CAR T-cell manufacturing. Patients will be enrolled after receiving their first autologous transplant and at least 6 months of maintenance therapy with lenalidomide, and prior to leukapheresis. Once a potentially eligible patient is identified, the BMT CTN study team will review and confirm a manufacturing spot with BMS/Celgene for that patient. The clinical center will then proceed to register the patient with BMS/Celgene to schedule leukapheresis and to initiate the chain of custody process. Once the clinical center completes the patient registration with BMS/Celgene they can enroll the patient into the first segment in Advantage eClinical, the electronic data capture system, and complete enrollment procedures. At the time of enrollment, an authorized user at the clinical center completes the demographics and primary eligibility, which includes questions confirming that the patient signed consent, meets the eligibility criteria for study entry and tentative date for leukapheresis will be recorded.

Advantage eClinical will utilize a multi-segment approach to assess eligibility criteria and allow for enrollment into the various stages of the trial. A set of eCRF Guidelines will provide clinical site users the necessary details to properly navigate and interpret data capture across these segments.

4.1.1 Product Manufacturing, Release and Infusion

Product manufacturing timeline initiates with the scheduling of leukapheresis, which will be managed through the standard BMS manufacturing process. Pheresis procedures will follow standard procedures and the product will be shipped to BMS/Celgene for manufacturing. BMS will maintain the chain of custody of the product and communicate with the clinical center on the status of product manufacturing. Upon completion of manufacturing, BMS will determine whether the product falls within specification to be released according to standard criteria applied to all bb-2121 products. If a manufactured product is determined to be out of specification, this will be escalated as included in sections 2.4.3 and 4.5.5. This will be reviewed by the non-conforming product medical monitor and escalated to the FDA. The product must not be infused until FDA approval is received. This decision will be made on a case-by-case basis and the patient and center will be informed by the BMT CTN

For products that fall within specification, the shipment and additional coordination will be done between BMS chain of custody personnel and the center. Initiation of LD chemotherapy, product thawing and infusion will proceed considering patient eligibility and following standard operating procedures.

4.1.2 Long Term Follow-up

All patients will be followed for 15 years using the CIBMTR Cellular Therapy Registry. For patients who were not previously reported to the CIBMTR, they must be consented to the CIBMTR Research Database Protocol, which covers data sharing of transplants and cellular therapies. Participating centers will then generate a CIBMTR Research Identification Number (CRID) and report using the cellular therapy essential data (CTED) forms. For patients who previously consented to share data with the CIBMTR prior to the autologous HCT and have a CRID number, no additional consent is required. If the patient received the autologous transplant at a different institution, patients should be reconsented to the CIBMTR Research Database protocol which includes transplant and cellular therapies.

Patients will also sign consent for collection of biospecimen if indicated to work up for clinical manifestations of recombinant competent lentivirus (RCL), including but not limited to subsequent neoplasm. The CIBMTR long term follow up for patients enrolled in the BMT CTN 1902 clinical trial will collect annual clinic visits starting in year 2 to year 15 to monitor the need to collect samples for RCL testing.

4.2 Study Monitoring

4.2.1 Follow-Up Schedule

The follow up schedule for study visits after enrollment in Advantage eClinical and subsequently after CAR T-cell infusion are outlined below in tables 4.2.1A and 4.2.1B, respectively. The follow up schedule is the intended schedule; however, the date of the follow up evaluations may vary due to delays in treatment or treatment interruption related to Adverse Events and toxicities. The visit window for the scheduled evaluations is included in each table. Patients will be followed for 12 months post bb2121 infusion.

4.2.1A: FOLLOW-UP SCHEDULE AFTER ENROLLMENT

Study Visit	Target Day
Pre-Enrollment Screening	≤ 30 days prior to enrollment unless otherwise specified
Leukapheresis	approximately 14 days post-enrollment
Screening to Initiate LD Chemo	≤ 7 days prior to Initiating LD Chemo
Initiation of LD Chemo	5 days prior to planned bb2121 infusion
Screening for bb2121 Infusion	Day of bb2121 infusion
bb2121 Infusion	≤ 7 days after the planned date of bb2121 infusion
Pre-Maintenance Screening	≤ 14 days prior to maintenance initiation
Maintenance Start	Day 30-180 post bb2121 infusion

[1] bb2121Infusion must occur ≤ 7 days after the planned date of infusion. If bb2121 infusion is delayed beyond Day 7, the Protocol Chairs must be notified. Protocol Chair approval for infusion is required for any delay > 14 days.

4.2.1B: FOLLOW UP SCHEDULE POST-CAR T-CELL INFUSION

Study Visit	Target Day Post Infusion
Day 4, 7,10, 14, 21	+/- 2 days
Day 30, 60, 90, 180, 270, 365	+/- 7 days

4.3 Patient Evaluations

4.3.1 Pre-Enrollment Evaluations and Requirements

The following screening evaluations must be performed less than or equal to 30 days prior to initial enrollment after informed consent has been obtained, as specified in **Table 4.3A:**

1. History, physical examination, height, and weight
2. Karnofsky Performance Score
3. Cardiac Assessment (performed less than or equal to 12 weeks from enrollment): Left ventricular ejection fraction by echocardiogram (ECHO) or MUGA.
4. Infectious Disease Markers: Hepatitis panel (Hepatitis B and C) and HIV Antibody
5. Laboratory Disease Evaluation (multiple myeloma restaging should be done after completion of at least 6 months of lenalidomide maintenance)
    a. Quantitative serum immunoglobulins
    b. Serum protein electrophoresis (SPEP)
    c. 24 hours urine to determine protein excretion, urine electrophoresis (UPEP)
    d. Immunofixation of urine and serum regardless of SPEP and UPEP results
    e. Serum free light chains ratios (FLC)

The following screening evaluations will be performed less than or equal to 14 days prior to enrollment after informed consent has been obtained, as specified in **Table 4.3A:**

1. CBC with differential
2. Liver functions and blood chemistries: Serum creatinine, corrected serum calcium, total bilirubin, AST, ALT.
3. Calculated or measured creatinine clearance
4. Pregnancy test, serum beta-HCG (sensitivity of at least 50 mIU/mL) for FCBP
5. Oxygen saturation by pulse oximetry
6. Coagulation Panel including partial thromboplastin time (PTT), international normalized ration (INR), fibrinogen

4.3.2 Evaluations Required Following Initial Study Enrollment:

1. CBC with differential (performed within 24 hours prior to leukapheresis)
2. Leukapheresis Product for bb2121 manufacturing

4.3.3 Evaluations Required Prior to Initiating LD Chemotherapy

The following baseline evaluations to determine eligibility for LD chemotherapy must be performed less than or equal to 7 days prior to initiating LD chemotherapy unless otherwise noted, as specified in Table 4.3A

1. History, physical examination, height, and weight
2. CBC with differential
3. Liver functions and blood chemistries: Serum creatinine, total bilirubin, AST, ALT.
4. Calculated or measured creatinine clearance
5. Pregnancy test, serum beta-HCG (sensitivity of at least 50 mIU/mL) for FCBP
6. Assessment for toxicities and adverse events
7. Laboratory Disease Evaluation (may be performed ≤ 14 days prior to initiating LD chemotherapy)
    a. Quantitative serum immunoglobulins
    b. Serum protein electrophoresis (SPEP)
    c. 24 hours urine to determine protein excretion, urine electrophoresis (UPEP)
    d. Immunofixation of urine and serum regardless of SPEP and UPEP results
    e. Serum free light chains (FLC) ratio
8. Bone Marrow Evaluation: local assessment of unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients (may be performed less than 14 days prior to initiating LD chemotherapy).
9. Coagulation Panel including partial thromboplastin time (PTT), international normalized ration (INR), and fibrinogen
10. Baseline evaluation for Neurotoxicity including Immune-effector Cell Encephalopathy (ICE) and Immune Effector Cell Associated Neurotoxicity (ICAN) (see Appendix I)
11. Protocol-required Samples for Correlative Studies and Future Research[1] (Table 4.3B)
    a. Bone marrow aspiration (16 mL)
    b. Peripheral blood (71 mL)

4.3.4 Evaluations and Requirements Prior to CAR T-Cell Infusion

The following evaluations will be performed locally on the day of and prior to bb2121 infusion (all results are required prior to infusion except CRS panel):

1. History, physical examination, height, and weight
2. CBC with differential

[1] See appendix B for details

3. Liver functions and blood chemistries: Serum creatinine, total bilirubin, AST, ALT.
4. CRS panel: ferritin C-reactive protein

4.3.5 Evaluations and Requirements Following CAR T-Cell Infusion

Assessments will be performed on Days 4, 7, 10, 14, and 21 post bb2121infusion (unless otherwise indicated). More frequent evaluations may occur as clinically indicated. Refer to Table 4.3A for details on assessments to be performed:

1. History, physical examination including height, and weight
2. CBC with differential
3. Evaluation for Neurotoxicity including Immune-effector Cell Encephalopathy (ICE) and Immune Effector Cell Associated Neurotoxicity (ICAN) (see Appendix I)
4. Evaluation for CRS (see Appendix I)
5. CRS panel: ferritin and C-reactive protein
6. Assessment for toxicities and adverse events
7. Protocol-required Samples for Correlative Studies and Optional Future Research (Table 4.3B):
    a. Peripheral blood (16 mL) on Day 4, 7, 14, and 21 post-bb2121 infusion

The following assessments are required monthly for the first 3 months following bb2121 infusion then every 3 months thereafter until 12 months following bb2121 infusion (unless otherwise indicated). Refer to Table 4.3A for details on assessments to be performed:

1. History, physical examination height, and weight
2. CBC with differential
3. Liver functions and blood chemistries: Serum creatinine, total bilirubin, AST, ALT
4. Pregnancy test, serum beta HCG (sensitivity of at least 50 mIU/mL) for FCBP monthly until at least 1 year following lymphodepleting chemotherapy or 4 weeks following discontinuation of lenalidomide whichever is later. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with bb2121. Any decision regarding contraception after bb2121 infusion should be discussed with the treating physician.
    c. For FCBP that initiate lenalidomide:
        i. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix C).

ii. The subject must follow the requirements of the Revlimid REMS® program of the BMS/Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. The patient will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate in order to take the telephone surveys regarding compliance with the program.

5. Assessment for toxicities and adverse events
6. Evaluation for Neurotoxicity including Immune-effector Cell Encephalopathy (ICE) and Immune Effector Cell Associated Neurotoxicity (ICAN)
7. Laboratory Disease Evaluation
    a. Quantitative serum immunoglobulins
    b. Serum protein electrophoresis (SPEP)
    c. 24 hours urine to determine protein excretion, urine electrophoresis (UPEP)
    d. Immunofixation of urine and serum regardless of SPEP and UPEP results
    e. Serum free light chains ratios (FLC)
8 Bone Marrow Evaluation: local assessment of unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients
9. Protocol-required Samples for Correlative Studies and Optional Future Research[1] (Table 4.3B):
    a. Peripheral blood (16 mL) on Day 60, 180, and 270 post-bb2121 infusion
    b. Peripheral blood (71mL) on Day 30, 90, 365 post-bb2121 infusion
    c. Bone Marrow Aspirate on Day 30 (14mL), 90 (16mL), 180 (8mL), 365 (16mL) post-bb2121 infusion

4.3.6 Pre-Maintenance Evaluations and Requirements

The following evaluations to determine eligibility for maintenance initiation must be performed less than or equal to 14 days prior to the initiation of lenalidomide maintenance therapy unless otherwise noted below.

1. History, physical examination including routine neurologic examination, height, and weight
2. Assessment for toxicities and adverse events
3. CBC with differential
4. Liver functions and blood chemistries: Serum creatinine, total bilirubin, AST, ALT.

[1] See appendix B for details

5. Pregnancy test, serum beta-HCG (sensitivity of at least 50 mIU/mL) for FCBP Women are required to have 2 pregnancy tests prior to the initiation of lenalidomide as follows (Appendix C)
    a. The first is required within 10 to 14 days prior to prescribing lenalidomide,
    b. The second is required within 24 hours of prescribing lenalidomide.

4.3.7 Evaluations at the Time of Disease Progression

1. Protocol-required Samples for Correlative Studies and Optional Future Research[1] (Table 4.3B):
    a. Peripheral blood (71mL)
    b. Bone Marrow Aspirate (16mL)

[1] See appendix B for details

TABLE 4.3A: PATIENT CLINICAL ASSESSMENTS

Study Assessments	**Pre-Enrollment Screening** (≤ 30 days prior to enrollment)	**Leukapheresis** (≤ approximately 14 days post-initial enrollment)	**Pre-LD Chemo Screening** (≤ 7 days prior to initiating LD Chemo)	**Pre-bb2121 Infusion Screening / bb2121 Infusion** (≤ 7 days after planned date of bb2121 infusion)	**Pre-Maintenance Screening** (≤ 14 days prior to maintenance initiation)	**Days Post bb2121 Infusion**							**Disease Progression[7]**
						4, 7, 10, 14, 21 (+/- 2 days)	**30** (+/- 7 days)	**60** (+/- 7 days)	**90** (+/- 7 days)	**180** (+/- 7 days)	**270** (+/- 7 days)	**365** (+/- 7 days)	
Demographics and Informed Consent	**X**												
Eligibility Assessment[8]	**X**		**X**	**X**	**X**								
History, physical exam, weight and height	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Karnofsky performance score	**X**												
Cardiac Assessment: ECHO or MUGA	**X**												
Infectious Disease Markers: Hepatitis and HIV	**X**												
CRS Panel: ferritin C-reactive protein				**X**		**X**							
CBC, differential, platelet count, liver functions, and blood chemistries[1]	**X[12]**	**X[11]**	**X[6]**	**X**	**X**	**X[13]**	**X[6]**	**X**	**X[6]**	**X**	**X**	**X[6]**	**X[6]**
Evaluation of Creatinine Clearance	**X[12]**		**X**										
Pregnancy test[2]	**X[12]**		**X**		**X[9]**		**X**	**X**	**X**	**X**	**X**	**X**	
Oxygen saturation by pulse oximetry	**X[12]**												
Quantitative serum immunoglobulins	**X**		**X[10]**				**X**	**X**	**X**	**X**	**X**	**X**	
SPEP and immunofixation	**X**		**X[10]**				**X**	**X**	**X**	**X**	**X**	**X**	
24 Hour Urine for UPEP, protein excretion and immunofixation	**X**		**X[10]**				**X**	**X**	**X**	**X**	**X**	**X**	
Serum free light chain ratio	**X**		**X[10]**				**X**	**X**	**X**	**X**	**X**	**X**	

Study Assessments	**Pre-Enrollment Screening** (≤ 30 days prior to enrollment)	**Leukapheresis** (≤ approximately 14 days post-initial enrollment)	**Pre-LD Chemo Screening** (≤ 7 days prior to initiating LD Chemo)	**Pre-bb2121 Infusion Screening / bb2121 Infusion** (≤ 7 days after planned date of bb2121 infusion)	**Pre-Maintenance Screening** (≤ 14 days prior to maintenance initiation)	**Days Post bb2121 Infusion**							**Disease Progression[7]**
						4, 7, 10, 14, 21 (+/- 2 days)	**30** (+/- 7 days)	**60** (+/- 7 days)	**90** (+/- 7 days)	**180** (+/- 7 days)	**270** (+/- 7 days)	**365** (+/- 7 days)	
Local assessment of unilateral bone marrow aspirate and biopsy			**X[10]**				**X**		**X**	**X**	**X[3]**	**X**	
Coagulation Panel including PTT, INR, and fibrinogen	**X[12]**		**X**										
Evaluation for CRS						**X**							
Toxicity assessment[4]			**X[5]**		**X**	**X[5]**	**X[5]**	**X[5]**	**X[5]**	**X[5]**	**X[5]**	**X[5]**	

[1]Blood chemistries include: serum creatinine, corrected serum calcium (if applicable), AST and ALT as required per protocol.
[2] For female of childbearing potential: A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
[3]Bone Marrow aspirate and biopsy required only to confirm CR in patients if suspected due to other assessments, e.g. serology.
[4]The toxicity assessment will include a review of **all** toxicities including ICANS (immune-effector cell associated neurotoxicity syndrome), myelotoxicity and appropriate lab evaluations experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity or Myelotoxicity form in EDC using CTCAE version 5.
[5] Toxicity Assessment will include Neurotoxicity Assessments (ICE and ICAN) and Myelotoxicity Assessments (see Appendix I)
[6] CBC needs to be collected and results reported in CRF at the same time as optional research samples are collected.
[7] Only needed for patients that progress while in study follow up and optional research samples are being collected.
[8]Eligibility to proceed to next stage of trial will be assessed at each timepoint as indicated.
[9]Two pregnancy tests required prior to the initiation of lenalidomide: The first required within 10 to 14 days prior to prescribing lenalidomide and the second required within 24 hours of prescribing lenalidomide (see Appendix C).
[10]To be performed ≤ 14 days prior to initiating LD chemotherapy.
[11]CBC with differential required within 24 hours prior to leukapheresis to determine ALC.
[12]To be performed ≤ 14 days prior to enrollment and after ICF has been obtained.
[13]Only CBC with differential required.

TABLE 4.3B: SAMPLE COLLECTION TIME POINTS

Sample Collection	Leuka-pheresis	Pre-LD Chemo	Days Post CAR-T Cell Infusion										Disease Progression[1]
			4	7	14	21	30	60	90	180	270	365	
Bone Marrow Aspirate													
MRD, BCMA expression and Immune Profiling Assessment (6mL)		X					X[2]		X	X		X	X
MRD Assessment by NGS (2 mL)		X							X	X		X	X
CAR-T Cell expansion and persistence (2 mL)		X					X		X			X	X
Optional Repository Sample for Future Research (6 mL)		X					X		X			X	X
Total Maximum Marrow Volume (mL)		**16**					**14**		**16**	**8**		**16**	**16**
Peripheral Blood													
CAR-T Cell expansion and persistence (8mL)		X	X	X	X	X	X	X	X	X	X	X	X
Immune Reconstitution (10mL)		X					X		X			X	X
Optional Repository Sample for Future Research - PBMC (45mL)		X					X		X			X	X
Optional Repository Sample for Future Research – Serum (8mL)		X	X	X	X	X	X	X	X	X	X	X	X
Total Maximum Blood Volume (mL)		**71**	**16**	**16**	**16**	**16**	**71**	**16**	**71**	**16**	**16**	**71**	**71**
Leukapheresis													
Leukapheresis product for bb2121 manufacturing	X												

[1] Only required for patients that progress while in study follow up
[2] Only Immune Profiling Assessment done from Day 30 sample

4.4 Data Reporting

4.4.1 Criteria for Forms Submission

Forms that are not entered into the EDC system, Advantage eClinical® within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the EDC and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File.

Internal Data Monitoring

It is the responsibility of the site PI to ensure the validity of all patient data as well as the safety of all patients.

Data Monitoring and Auditing

The Data Safety and Monitoring Board (DSMB) for the BMT CTN will convene as per standard procedure to review serious toxicities and adverse events for the purpose of determining whether the trial should be modified or stopped. Triggers for referral to the DSMB are described in the Interim Analysis and Stopping Guidelines of **Section 5.3.** If the monitoring of the safety endpoints described in **Section 5.3** results in a trigger for consultation with the DSMB, the DSMB may make recommendations about whether to continue accrual.

Records

Any publication or presentation will refer to patients by a unique patient number and not by name to assure patient confidentiality.

4.4.2 Reporting Patient Deaths

Recipient death information must be entered into the EDC within 24 hours of knowledge of the patient's death via a Death Form. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in EDC. In addition, any death occurring from the infusion of bb2121 through 60 days following the infusion (or longer to include 21 days of lenalidomide maintenance) must also be reported via the Adverse Event Reporting process described in section 4.5 below.

4.4.3 Center for International Blood and Marrow Transplant Research (CIBMTR) Data Reporting

Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). Enrollment in BMT CTN 1902 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post- transplant Comprehensive Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted

directly to the CIBMTR at the times specified on the Form Submission Schedule. Patients will be followed by the CIBMTR from time of autologous transplant through 15 years post-transplant.

4.5 Adverse Event Reporting

AE reporting requirements are summarized below and in table 4.5. Any unanticipated serious adverse events (SAEs) from time of enrollment through the study defined follow up are required to be reported. All SAEs must be reported from the infusion of bb2121CAR-T therapy through 60 days after the infusion completes or through 21 days of lenalidomide maintenance, whichever is longer. All grades of non-serious AEs must also be reported from the infusion of bb2121 CAR-T therapy through the longer of either 60 days after the infusion completes or through 21 days of lenalidomide maintenance either by 1) reporting of all grades of toxicities anticipated for the participant population captured on the Toxicity or Myelotoxicity Form or 2) completion of the Adverse Event Form (single page only) for any event not captured on the Toxicity or Myelotoxicity Form. In addition, any SAEs occurring after that 60-day period/21 days of lenalidomide maintenance up to disease progression assessed as related to the investigational product bb2121 must be reported. Any occurrence of grade 4 myelotoxicity after initiating lenalidomide that persists for more than 4 weeks despite interruption/discontinuation of lenalidomide is also required to be reported as an SAE, as outlined in section 4.5.4.1. From the 61st day following the completion of the bb2121 infusion or the 22nd day of lenalidomide maintenance, only non-serious AEs captured through the Toxicity and Myelotoxicity Form are required to be reported. All reported SAEs are to be followed up until resolved, judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

SAEs related to lenalidomide after 21 days of maintenance should be reported to BMS/Celgene under the voluntary reporting mechanism.

Infections and deaths are collected separately in EDC as this is a study endpoint; however, should an infection or death meet the SAE criteria and be assessed by the investigator as related to bb2121, the infection or death must also be reported following the SAE reporting guidelines.

Underlying disease relapse events are collected in the EDC separately because they are part of the endpoint analysis. Events of underlying disease relapse are not to be reported as AEs/SAEs for this study.

Table 4.5 AE Reporting Phases

	Enrollment – 60 days post completion of bb2121 infusion or 21 days of lenalidomide maintenance, whichever is longer	61 days post completion of infusion or 22nd day of lenalidomide maintenance, whichever is longer – completion of AE reporting*
Unanticipated SAEs or grade 4 anticipated event not collected elsewhere in the study database (following protocol-specific MOP Guidelines)		X
All SAEs	X	
SAEs related to bb2121	X	X
Infections that are SAEs and related to bb2121	X	X
Grade 4 myelotoxicity after initiating lenalidomide persisting for more than 4 weeks despite interruption/discontinuation of lenalidomide	X	X
Deaths related to b2121	X	X
All anticipated AEs for the patient population captured via the Toxicity Form	X	X
All anticipated hematologic AEs for the patient population captured via the Myelotoxicity Form+	X	X
All AEs not captured through the Toxicity Form)	X	

*Completion (whichever is longer) of reporting will occur at 1) completion of study defined follow-up, death or a withdrawal criterion outlined in section 2.9; 2) progression of disease; OR 3) following diagnosis of a subsequent neoplasm meeting a criterion in section 4.5.
^Any SAE assessed by the investigator as related to bb2121 after the patient meets a criterion to stop reporting SAEs will still require reporting.
+ The Myelotoxicity Form will capture data on grade 4 myelotoxicities including whether the study lenalidomide is interrupted/disrupted and the duration of the interruption/disruption, along with a brief summary of the clinical details for grade 4 myelotoxicities that cause lenalidomide to be held for > 4 weeks.

4.5.1 Definitions

Adverse Event: An AE is any untoward medical occurrence in a patient administered an investigational product or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a medical (investigational) product, whether or not related to the investigational product.

Serious Adverse Event: An SAE, as defined per 21 CFR 312.32, is any adverse event that results in one of the following outcomes, regardless of causality and expectedness:

- **Results in death**

- **Is life-threatening**. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect**; or
- **Is an important medical event when**, based upon appropriate medical judgment, it may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered an SAE). Any event is considered a SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

- **An adverse event can be Anticipated or Unanticipated in regard to the patient population for this study. Anticipated adverse events** are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered anticipated when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- **Unanticipated adverse events** are those that vary in nature, intensity or frequency from information in the current adverse event list, the Investigator's Brochure, the package insert, or when it is not included in the informed consent document as a potential risk.

4.5.2 Classification of Adverse Events by Severity

The severity refers to the intensity of the reported event. The Investigator must categorize the severity of each reportable SAE according to the NCI CTCAE version 5.0. CTCAE guidelines can be referenced at the following website: http://ctep.cancer.gov/reporting/ctc.html. For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of one through five using the following CTCAE guidelines:

1. **Grade 1**: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2. **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3. **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4. **Grade 4**: Life-threatening consequences; urgent intervention indicated
5. **Grade 5**: Death related to AE

4.5.3 Classification of Adverse Events by Relationship to Investigational Product

The relationship of each reported event to the study treatment will be assessed by the Investigator; after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the SAE, temporal relationship to any study treatment interventions and de-challenge or re-challenge according to the following guidelines:

1. **Possibly, Probably, or Definitely Related:** there is a reasonable possibility that the study treatment caused the event. A relationship of possibly, probably or definitely related to the investigational product is considered related for the purposes of regulatory authority reporting.
2. **Unlikely, or Not Related:** There is no reasonable possibility that the investigational product caused the event. An unlikely or not related relationship to the investigational product is not considered related for the purposes of regulatory authority reporting.

4.5.4 Required Adverse Event Reporting

Adverse event reporting will be consistent with BMT CTN procedures (protocol-specific Manual of Procedures), unless otherwise specified in section 4.5 above. The protocol-specific MOP defines reporting based on the terms Unexpected and Expected; however, for this study, the reporting will be based on the terms Unanticipated and Anticipated in addition to the MOP definition of Unexpected and Expected.

SAEs that require reporting as specified in section 4.5 will be reported through an expedited AE reporting system via an EDC**. Life-threatening and fatal SAEs must be reported within 24 hours of knowledge of the event. All other SAEs must be reported within one business day of knowledge of the event.** Events entered in EDC will be reported using NCI's CTCAE Version 5.0.

Non-serious AEs will be reported using NCI's CTCAE Version 5.0 as specified in section 4.5. For anticipated AEs, this may include reporting at regular intervals as defined on the Form Submission Schedule, including calendar-driven eCRFs (e.g., Toxicity) or event-driven eCRFs (e.g., Relapse/Progression, Infection, Secondary Graft Failure and Death).

The Data and Safety Monitoring Board (DSMB) will receive reports of all unanticipated/unexpected SAEs upon review by the BMT CTN Medical Monitor. A summary of all reported SAEs will be reviewed by the DSMB annually.

Since this study is under an FDA Investigational New Drug, all suspected and unexpected fatal or life-threatening adverse events are reported to the FDA within seven calendar days after receipt of the information from the site, following FDA guidelines. All suspected and unexpected other serious adverse events are reported to the FDA within fifteen days of receipt of the information (21 CFR 312.32). Unexpected for regulatory reporting will be assessed by the BMT CTN Medical Monitor and will include events that are not included in the bb2121 Investigator's Brochure. If the Medical Monitor assesses the event to be unrelated to the study, then the event will not require expedited reporting but will be included in a summary report issued annually. In addition, any event of grade 4 myelotoxicity after initiating lenalidomide and persisting for more than 4 weeks despite interruption/discontinuation of lenalidomide will be reported in an expedited fashion to the FDA. Safety reporting to the FDA will be done by the BMT CTN based upon date of initial entry on the Adverse Event Forms and requires no additional action from the participating site.

4.5.4.1 Adverse Event Reporting of Myelotoxicity

Patients who develop neutropenia and thrombocytopenia (myelotoxicity) after initiation of lenalidomide that persists for more than 4 weeks despite interruption/discontinuation of lenalidomide are required to be reported in an expedited fashion via the Adverse Event Form, along with completion of the calendar-driven Myelotoxicity Form. These events will be assessed by the BMT CTN Medical Monitor and will be reported to the FDA as an expedited safety report.

4.5.4.2 Adverse Event Reporting Following Progression

If a patient meets the protocol defined definition of progression (Section 3.1.2), SAEs and non-serious AEs are no longer required to be reported on the Adverse Event Form once the patient is more than 60 days from the completion of bb2121 or 21 days of lenalidomide maintenance, whichever is longer. Any bb2121-related SAEs would require reporting following the SAE reporting guidelines.

4.5.4.3 Adverse Event Reporting Following a Subsequent Neoplasm

Participants on this study are at risk of developing subsequent neoplasms. While subsequent neoplasms do not require expedited reporting, unless meeting one of the other criteria for AE/SAE reporting, the diagnosis of a subsequent neoplasm may alter reporting required for other AEs/SAEs. Adverse Event reporting following a subsequent neoplasm is dependent on the treatment received.

- If a patient experiences a subsequent neoplasm resulting in initiation of non-protocol systemic therapy, SAEs are no longer required to be reported once the patient is more than 60 days from completion of bb2121 or 21 days of lenalidomide maintenance, whichever is longer.

- If a patient experiences a subsequent neoplasm that does *not* result in initiation of non-protocol systemic therapy, Adverse Events will continue to be reported per section 4.5 of the protocol.
- Any bb2121-related SAEs would be reported until end of study.
- Requests to discontinue Adverse Event Reporting for events that do not meet the criteria above will be considered on a case-by-case basis.

4.5.4.4 Pregnancy Reporting

Pregnancies, suspected exposure of a pregnant woman (including female partner of a male patient and exposure to lenalidomide while dispensing) and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring at any time after the subject received bb2121 infusion therapy or lenalidomide; or within 28 days of the last dose of lenalidomide, 1 year after the last dose of LD chemo, are considered immediately reportable events. Therapy with lenalidomide is to be discontinued immediately and any unused drug should be returned. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported through the expedited AE reporting system in EDC. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The Investigator should ensure that the pregnant participant or pregnant partner of a male participant has consulted a general practitioner or gynecologist as soon as possible and that the contact details of the healthcare provider who is following the pregnancy are provided to the investigator.

The Investigator will follow the female subject until completion of the pregnancy and must notify BMT CTN immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the expedited AE reporting system in EDC.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE using the expedited AE reporting system in EDC, within 24 hours of the investigator's knowledge of the event.

All neonatal deaths that occur in connection with *in utero* exposure to lenalidomide should be reported within 28 days of birth, without regard to causality through the expedited AE reporting system in EDC. In addition, any infant should be followed for 1 year after birth and report any SAE through the expedited AE reporting system within 24 hours of the Investigator's knowledge of the event. After 1 year any suspected SAE event should be reported to BMS/Celgene.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject receiving bb2121 therapy or lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. Attempts should be made to obtain consent from the female partner so that the information in section 4.5.4.3 can be provided for female partners of male participants and pregnancy outcomes.

4.5.5 Reporting of Special Situations

There are other special situations that require reporting through the AE expedited reporting system in EDC. If any of the following events occur, they are required to be reported within one business days of the site's knowledge of the event, if the event occurs from the start of LD chemo through 21 days of lenalidomide or 60 days following bb2121, whichever is later:

- Mishandling or misuse of bb2121 upon receipt of the product at the treatment center
- Overdose, abuse and misuse that meets one of the criteria of a serious adverse event
    - Overdose, as defined for this protocol, refers to lenalidomide and bb2121 dosing only.
    - On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide or bb2121 assigned to a given patient, regardless of any associated adverse events or sequelae.
        - PO any amount over the protocol-specified dose
        - IV 10% over the protocol-specified dose
    - On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.
    - On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.
    - Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.
- Medication errors that meet one of the criteria of a serious adverse event
- Occupational exposure of any kind
- Public health emergency
- Any lot release criteria that is out of specification
- BMS/Celgene product technical complaint whether or not it leads to an adverse event
    - Technical complaints can include but not limited to delivery of bb2121 in a defective bag or other issues with the product itself.

Each of the above listed other special situations are to be considered medically important, even if no other serious criteria apply. These are immediately reportable via the expedited AE reporting system in EDC and must be reported within one business day of the Investigator's first knowledge of the event.

Any product that is out of specification for any lot release criteria, the event will be reported to the FDA as part of the escalation pathway.

CHAPTER 5

5 STATISTICAL CONSIDERATIONS

5.1 Study Design

This study is designed as a single-arm Phase II multi-center trial to investigate the use of anti-BCMA CAR T-cells to upgrade post autologous HCT responses among patients with MM. The primary endpoint is complete response (CR) by 6 months following initiation of LD chemotherapy. We plan to enroll n=40 patients on this trial in order to get at least n=33 evaluable patients receiving the final selected dose of bb2121 infusion. There will be a safety run-in with staggered enrollment (see below, section 5.1.3) to assess for excess early toxicity of CAR T cells in this new clinical setting or prolonged cytopenias that limit resumption of maintenance lenalidomide; this run-in will start with the standard CAR T cell dose of 450 x10^6 cells and may include up to 6 patients at this dose, if still there are toxicity concerns the dose will be reduced to 300 x 10^6 cells which will then be the selected dose for this study. Only patients who are assigned to receive the selected dose in the run in will be evaluable for the primary endpoint. Once the final dose is selected for further enrollment, we will enroll up to 40 total patients at that dose, including those in the run-in. Assuming the potential for dose de-escalation after the first 6 patients were enrolled in the run in phase and at least 1 patient dropping out from enrollment before initiation of LD chemotherapy, this will result in at least n=33 evaluable patients at the final selected dose. It is estimated that 13 months of accrual will be necessary to enroll the targeted sample size after completion of the safety run in. Accrual will be reported by race, ethnicity, gender, and age.

5.1.1 Study Duration

Participants will be followed on trial for 12 months after initiation of CAR T cell infusion for primary, secondary, and exploratory endpoints.

5.1.2 Randomization and Blinding

This is a single arm trial with no randomization and no blinding.

5.1.3 Safety Run-In and Staggered Enrollment

5.1.3.1 Toxicities that will Govern Safety Run-In and Stagger.

The following toxicities will trigger expansion of the safety run-in to six subjects or study pause depending on their frequency:

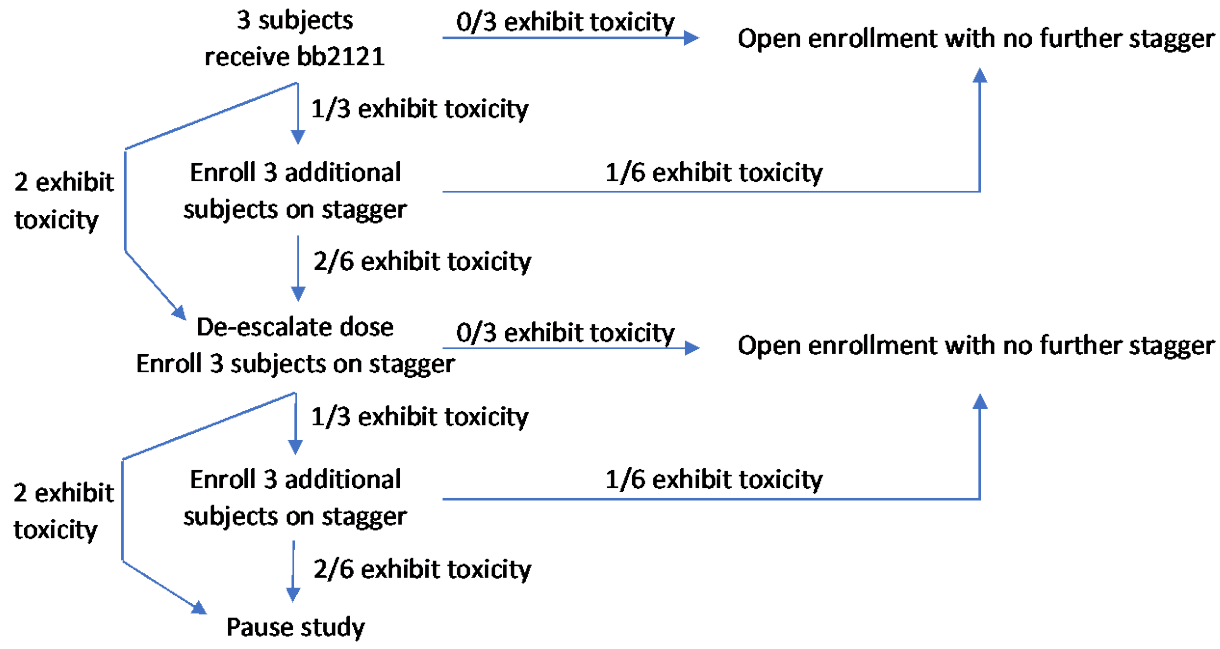
a) Failure to start maintenance lenalidomide within 60 days of bb2121 infusion and continue with dose ≥5 mg/day for 21 days continuously without development of sustained grade 4 (failure to resolve to grade ≤3 within 7 days with supportive care, which may include filgrastim) neutropenia or thrombocytopenia.

b) Occurrence of grade 4 or higher cytokine release syndrome.

5.1.3.2 Progress through Safety Run-In

During the safety run-in, subjects will be enrolled in groups of 3. The second subject in each group will not proceed with lymphodepleting chemotherapy or bb2121 infusion until the preceding subjects starts lenalidomide by 60 days after bb2121 infusion. The third subject in each group will not proceed with lymphodepleting chemotherapy or bb2121 infusion until the first patient completes at least 21 days of lenalidomide maintenance and the second subject is able to start lenalidomide maintenance by 60 days after bb2121 infusion. Of note, according to section 2.3.5, subjects must be ≥30d post-infusion and have achieved ANC >1000/mm^3 and platelet count ≥75,000/mm^3 before initiating maintenance therapy. At discretion of the sponsor, enrollment and bb2121 manufacturing for subsequent subjects may proceed during post-infusion waiting period of preceding subjects. The first 3 subjects will be followed until they have completed 21 days of maintenance therapy without interruption due to hematologic toxicity before additional subjects are enrolled.

If none of the first 3 subjects experience toxicities in section 5.1.3.1, enrollment will proceed without further inter-patient stagger. If 1 of the first 3 subjects experience a toxicity in section 5.1.3.1, an additional 3 subjects will be enrolled with intra-patient stagger as detailed in the preceding paragraph. If 2 of the toxicities in section 5.1.3.1 above occur during the safety run-in, the safety run-in will restart with the bb2121 dose reduced to 300 x 10^6 cells. If 2 of the toxicities in section 5.1.3.1 occur during the safety run-in after dose de-escalation, further bb2121 infusions and enrollment will be paused for further review.



5.1.4 Primary Endpoint

The primary endpoint is achieving a complete response or better (CR or sCR) as assessed by the 6-month time point after BCMA CAR T-cell therapy in MM patients with suboptimal disease responses after an autologous HCT and lenalidomide maintenance. The primary objective of this clinical trial is to estimate the proportions of patients achieving CR by 6 months, along with 90%

confidence intervals, and to determine whether the use of bb2121 to upgrade post autologous HCT responses is sufficiently promising to warrant further study. Data from BMT CTN 0702 suggests that less than 10% of patients not in CR after autologous HCT and 6 months of maintenance therapy will get into CR within a subsequent 6 months of maintenance therapy (see Table 1.1.4). We will use a hypothesis testing framework to assess the potential efficacy of the addition of bb2121 cells to upgrade post autologous transplant responses. Specifically, we will test the null hypothesis that the 6-month probability of CR is less than or equal to 10% against the alternative that it is greater than 10%, using a one-sided 5% significance level.

5.2 Sample Size Considerations

Assuming a 5% one-sided significance level, a sample size of n=33 or more evaluable patients receiving BCMA CAR T-cell therapy at the final selected dose will have at least 90% power to conclude the 6-month CR rate is greater than 10% when the true 6-month CR rate is 30% (a 20% absolute improvement over the unpromising rate), using an exact binomial test. Furthermore, the expected margin of error of the 90% confidence interval when the observed 6-month CR rate is 30% is approximately +/-13%, assuming an evaluable sample size of n=33.

5.3 Interim Analysis and Stopping Guidelines

There will be no interim analyses for efficacy or futility for this trial.

Safety monitoring rule will include three safety endpoints, CRS, ICANS and non-relapse mortality. For CRS the occurrence of at least two cases of grade 4 CRS (ASTCT Grading) will trigger a DSMB review. For ICANS, the occurrence of at least one event of grade 4 ICANS will trigger a DSMB review. For non-relapse mortality within 28 days of bb2121 cell infusion, based on the expected infrequency (less than 1% based on rate in BMT CTN 0702 within 28 days following second autologous HCT) of the event, the occurrence of two or more non-relapse deaths within 28 days of infusion will trigger a DSMB review.

In addition, the safety monitoring rule will also include bone marrow dysfunction/failure and prolonged cytopenias. For bone marrow dysfunction or failure, there are two rules that will trigger DSMB review: 1) the occurrence of one bone marrow failure requiring CT rescue; and 2) if 15% of patients are unable to start lenalidomide maintenance by Day 60 after CAR-T infusion. A DSMB review will also be triggered if 15% of patients who are able to start lenalidomide maintenance are unable to sustain therapy due to cytopenia-driven interruption. Interruption of maintenance is defined as stopping maintenance cycles due to cytopenias and inability to resume for more than 60 days. Thresholds for discontinuation of maintenance are based on table 2.4.6, and details of 15% stopping rule for being unable to start or sustain lenalidomide maintenance are given below in Table 5.3.

Table 5.3: Stopping rule for patients unable to start or sustain lenalidomide maintenance or unable to sustain therapy due to cytopenia-driven interruption

# of patients	# of events
1-6	1
7-13	2
14-20	3
21-26	4
27-33	5

At a point that any of these monitoring rules are triggered, the NHLBI will be notified in order that the DSMB can be advised to review the data. Policies and composition of the DSMB are described in the protocol's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review.

5.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all participants. Characteristics to be examined may include: age, gender, race/ethnicity, Karnofsky performance status, cytogenetics,/ LDH,/ Beta 2 microglobulin, lines/types of initial systemic anti-myeloma therapy, interval from diagnosis of symptomatic MM to enrollment, interval from initial systemic therapy to enrollment, Light chain disease, Chemo vs. non-chemo mobilization, timing from transplant to enrollment and to CAR T-Cell infusion, duration of lenalidomide therapy, initial response at enrollment, myeloma risk status

5.5 Analysis Populations and General Analysis Guidelines

5.5.1 Primary Analysis Population

All patients starting LD chemotherapy prior to receiving a bb2121 infusion on study will be included in the primary analysis population. Time to event analyses will be started at the time of LD chemotherapy. Analyses for the primary and secondary endpoints will use the primary analysis population, except as otherwise specified. The primary analysis will occur once all patients have been followed for 6 months, ERC adjudication completed, and data is locked. The primary analysis population will also be used for all analyses of safety data. Note that if there is a dose de-escalation in the run-in phase before selecting the final dose, then outcomes of patients at the initial higher dose will be described separately.

5.5.2 General Analysis Guidelines

Primary analyses for the primary, secondary, and exploratory endpoints will use the primary analysis population. Analyses of each endpoint in each population will follow the analysis plans as described below in sections 5.6 - 5.8. We expect minimal missing data (less than 5%) for the primary endpoint and secondary endpoints based on past experience with transplant and cellular therapy trials. If more than 10% of a key primary or secondary outcome is missing, we will apply an appropriate imputation method and conduct corresponding sensitivity analyses. If there is a dose de-escalation in the run-in stage, analyses as described below will apply to the final selected

dose, while patients at the higher dose will be summarized separately in a descriptive manner due to the small numbers of patients at that dose.

5.5.3 As Treated Analysis

The analysis plan will include as treated analysis among patients who received CAR T cell infusion including patients who received OOS product. All outcomes will be analyzed in this cohort.

5.6 Analysis of Primary Endpoint

If there is no censoring prior to 6 months and prior achieving a CR, then the probability of CR by 6 months will be estimated using proportions. 90% confidence intervals will be provided based on exact binomial distributions. A one-sided exact binomial test comparing the estimated proportion of patients in CR by 6 months against a null hypothesis or uninteresting value of 10% will be conducted using a 5% one-sided significance level. If there is censoring present prior to 6 months and prior to achieving a CR, then the probability of CR by 6 months will be estimated using the cumulative incidence technique, with death as a competing risk and patients alive without CR at last contact considered censored. 90% confidence intervals for the cumulative incidence will be computed using the complementary log-log transformation.

5.7 Analysis of Secondary Endpoints

Analysis of secondary endpoints will be primarily descriptive, using estimates along with 90% confidence intervals, as detailed below.

5.7.1 Response to Treatment

The proportion of patients achieving an upgrade in their response at any timepoint, and the proportion of patients who achieve MRD negativity at any timepoint will be described. Duration of response upgrade will be summarized using the Kaplan-Meier estimate, where death or loss of response upgrade are considered events, and the time to event is measured as the time from documentation of response upgrade to death, loss of response upgrade, or last contact.

5.7.2 Progression-Free Survival (PFS)

PFS survival will be estimated using the Kaplan-Meier estimator. Progression of disease or death from any cause will be considered events and surviving patients without disease progression will be censored at the date of last contact. A point estimate and 90% confidence interval will be provided for the probability of PFS at 12 months.

5.7.3 Non-Relapse Mortality (NRM)

NRM will be estimated using the cumulative incidence function, treating progression as a competing event. A point estimate and 90% confidence interval will be provided for the cumulative incidence at 100 days, 6 months and 12 months post-transplant.

5.7.4 Progression of Disease

Progression will be estimated using the cumulative incidence function, treating death prior to progression as a competing event. A point estimate and 90% confidence interval will be provided for the probability of progression at 12 months post-transplant.

5.7.5 Incidence of Cytokine Release Syndrome (CRS)

Proportions of patients who experience CRS will be tabulated by grade (according to ASTCT criteria) and time period after infusion of CAR T-cells.

5.7.6 Incidence of Prolonged Cytopenias

Proportions of patients who experience prolonged cytopenias will be tabulated.

5.7.7 Incidence of Neurotoxicity (ICANS)

Proportions of patients who experience neurotoxicity (according to ASTCT criteria) will be tabulated by grade.

5.7.8 Feasibility of Reinitiation of Lenalidomide Maintenance

Time to reinitiation of lenalidomide maintenance therapy following CAR T cell infusion will be summarized using the cumulative incidence estimator, treating death as a competing risk. Cumulative incidence at 180 days post infusion will be summarized along with a 90% confidence interval.

5.8 Analysis of Exploratory Endpoints

5.8.1 CAR T-Cell Expansion

Quantitative summaries of CAR T-cell expansion measurements (median, range, IQR) will be provided at specified timepoints. Peak CAR T-cell expansion will be compared between subjects who are and are not in CR at 1 year, and between subjects who are and are not progression-free at 1 year, using Mann-Whitney Wilcoxon tests.

5.8.2 CAR T-Cell Persistence

Persistence will be summarized on each patient using AUC over the first 6 months or using presence of detectable CAR T-cells at 6 months post bb2121infusion. AUC will be compared between subjects who are and are not in CR at 1 year, and between subjects who are and are not progression-free at 1 year, using Mann-Whitney Wilcoxon tests. Presence of detectable CAR T cells at 6 months post infusion will be compared between subjects who are and are not in CR at 1 year, and between subjects who are and are not progression-free at 1 year, using chi-square test or Fisher's exact test as appropriate.

5.8.3 BCMA Expression

BCMA expression will be compared between baseline and post-CAR-T infusion using Wilcoxon signed rank tests.

5.8.4 Immune Reconstitution

Quantitative summary measures (median, range, IQR) will be provided for lymphocyte subsets at baseline and various time points after CAR T cell infusion.

5.8.5 Overall Survival

Overall survival will be estimated using the Kaplan-Meier estimator. Death from any cause will be the event and surviving patients will be censored at the date of last contact. A point estimate and 90% confidence interval will be provided for the probability of OS at 12 months.

5.8.6 Overall Toxicity

All greater than or equal to grade 3 toxicities according to CTCAE version 5.0 will be categorized by SOC and preferred term (PT) using the MedDRA dictionary, and the number of AEs will be summarized by SOC, PT, peak grade. The number and percentage of participants with at least 1 grade 3 or higher AE will be summarized by SOC and PT. Detailed listings of unexpected SAEs, including severity and relationship to treatment, will be presented.

5.8.7 Infections

The number of grade 2 or higher infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after infusion of BCMA CAR T-cells.

APPENDIX A

CRITERIA FOR SYMPTOMATIC MULTIPLE MYELOMA

All three required:

1. Monoclonal plasma cells in the bone marrow greater than or equal to 10% and/or presence of a biopsy-proven plasmacytoma
2. Monoclonal protein present in the serum and/or urine[a]
3. Myeloma defining events (1 or more)
    a. Myeloma- related organ dysfunction[b]:
        i. Calcium elevation in the blood (serum calcium greater than 10.5 mg/l or upper limit of normal)
        ii. Renal insufficiency (serum creatinine greater than 2mg/dl)
        iii. Anemia (hemoglobin less than 10 g/dL)
        iv. Lytic bone lesions or osteoporosis[c]
    b. Any one or more of the following biomarkers of malignancy:
        i. Clonal bone marrow plasma cell percentage greater than or equal to 60%
        ii. Involved: uninvolved serum free light chain ratio greater than or equal to 100
        iii. Greater than1 focal lesion of MRI

*Note: These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

[a] If no monoclonal protein is detected (nonsecretory disease), then ≥30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

[b] A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

[c] If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then greater than or equal to 30% plasma cells are required in the bone marrow.

*Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. The Hematology Journal (2003) 4, 379–398

APPENDIX B

LABORATORY PROCEDURES

Collection of MANDATORY Samples bb2121 Production, Immunologic Endpoints, and Additional Future Correlative Laboratory Studies

Bone marrow aspirate and peripheral blood will be collected for patients who consent to the BMT CTN 1902 study. Sample collection will be performed periodically throughout the study and will provide clinical samples required for correlative laboratory testing associated with critical immunologic study endpoints.

- **Leukapheresis Sample for bb2121 manufacturing and cell content evaluation:** A required sample of a sufficient quantity of peripheral blood mononuclear cells (PBMCs) collected via leukapheresis is required for the production of the bb2121 investigational product. Leukapheresis sample should be collected per the BMT CTN 1902 SOPs. Once the sample is collected at the specified time point, it will be shipped on the day of collection directly to the BMS/Celgene manufacturing facility. Additionally, the study team will request from the BMS/Celgene manufacturing facility, three 1.8 mL cryopreserved aliquots of both the leukapheresis and the final CAR T-cell product to be sent to the BMT CTN Biorepository for a future study team correlative to perform an extensive cell composition analysis for each product.

- **Research Samples for Laboratory Correlatives Associated with Immunologic Endpoints:** Required research samples for study-specific immunologic correlatives include the collection of blood and marrow aspirate samples as summarized in the table below (and in table 4.3B). The correlative studies include (1) MRD assessment & BCMA expression by flow cytometry, (2) MRD assessment by NGS, (3) Peripheral blood immune reconstitution and marrow immune profiling by flow cytometry, and (4) the evaluation of CAR T-Cell expansion and persistence. Once the samples are collected at specified time points, they will be shipped on the day of collection directly to either a specified ancillary study laboratory for processing and testing or BMT CTN Biorepository for processing and long-term research aliquot storage. These samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures and shipping instructions will be found in the BMT CTN 1902 Research Sample Information Guide.

Collection of OPTIONAL BMT CTN Biorepository Samples Supporting Additional Planned Correlative Studies and Future Research:

Bone marrow aspirate, peripheral blood PBMC, and serum, will be collected and stored to support some planned correlative studies and future research. Once the samples are collected at the transplant center at specified time points, they will be shipped on the day of collection to the BMT CTN Central Processing Laboratory for final processing and storage at the BMT CTN Research Repository. The collection, processing, and shipping of these biospecimens are summarized in the table below (and in table 4.3B). These samples will be tracked through GlobalTrace. Detailed procedures regarding specimen collection schedules, procedures and shipping instructions will be found in the BMT CTN 1902 Research Sample Information Guide.

Mandatory Research Samples Associated with bb2121 Manufacturing and Immunologic Study Endpoints					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping Location**
Leukapheresis Sample for bb2121 manufacturing	Peripheral Blood	Per BMS/Celgene bb2121 manufacturing guidance	At the time of leukapheresis, ≤ approximately 14 days following enrollment	Per BMS/Celgene bb2121 manufacturing guidance	BMS/ Celgene Manufacturing Facility
MRD & BCMA Expression Assessment And Immune Profiling	6 mL Bone Marrow Aspirate	Collect bone marrow aspirate sample and place 6 mL into a green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	Prior to initiation of LD chemotherapy; at days 30, 90, 180 and 365 post-bb2121 infusion; and at the time of disease progression (if applicable). **Note**: Only Immune Profiling Assessment done from Day 30 sample	Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection to RPCI by priority overnight FED EX delivery.	RPCI Laboratory
MRD Assessment by NGS	2 mL Bone Marrow Aspirate	Collect bone marrow aspirate sample and place 2 mL into a lavender top plastic BD Vacutainer® tubes containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with the EDTA anticoagulant.	Prior to initiation of LD chemotherapy; at days 90, 180 and 365 post-bb2121 infusion; and at the time of disease progression (if applicable).	Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection to the BMT CTN Research Repository by priority overnight FED EX delivery.	BMT CTN Research Repository
Immune Reconstitution	10 mL Peripheral Blood	Collect blood sample and place 10 mL into a green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	Prior to initiation of LD chemotherapy; at days 30, 90, and 365 post-bb2121 infusion; and at the time of disease progression (if applicable).	Blood sample tube will be shipped at ambient temperature on the day of collection to the PRCI laboratory by priority overnight FED EX delivery.	RPCI Laboratory

Mandatory Research Samples Associated with bb2121 Manufacturing and Immunologic Study Endpoints					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping Location**
CAR T Cell Expansion and Persistence	2 mL Bone Marrow Aspirate	Collect bone marrow aspirate sample and place 2 mL into a lavender top plastic BD Vacutainer® tube, containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with EDTA anticoagulant	Prior to initiation of LD chemotherapy; at days 30, 90 and 365 post bb2121 infusion; and at the time of disease progression (if applicable).	Bone marrow aspirate sample tube will be shipped at ambient temperature on the day of collection to the BMT CTN Research Repository by priority overnight FED EX delivery.	BMT CTN Research Repository
	8 mL Peripheral Blood	Collect blood sample and place 8mL into a lavender top plastic BD Vacutainer® tube, containing EDTA anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with EDTA anticoagulant.	Prior to initiation of LD chemotherapy; at days 4, 7, 14, 21, 30, 60, 90, 180, 270, and 365 post bb2121 infusion; and at the time of disease progression (if applicable).	Blood sample tube will be shipped at ambient temperature on the day of collection to the BMT CTN Research Repository by priority overnight FED EX delivery.	BMT TCN Research Repository

Mandatory Biorepository Samples Supporting Additional Planned Research Sample Collections Studies					
Purpose	**Sample Type**	**Sample Collection Summary**	**Dates Samples Obtained**	**Shipping Specifications**	**Shipping /Storage Location**
Future Research	6 mL Bone Marrow Aspirate	Collect bone marrow aspirated sample and place 6 mL into a green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	Prior to initiation of lymphodepleting LD chemotherapy; at days 30, 90, and 365 post-bb2121CAR T Cell infusion; and at the time of disease progression (if applicable).	Bone marrow aspirate tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of marrow aliquots.	BMT CTN Research Repository
Future Research	45 mL Peripheral Blood	Collect blood sample in green top plastic BD Vacutainer® tubes, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.	Prior to initiation of LD chemotherapy; at days 30, 90, and 365 post-bb2121 infusion; and at the time of disease progression (if applicable).	Peripheral blood tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of PBMC aliquots.	BMT CTN Research Repository
Future Research	8mL Peripheral Blood (serum)	Collect blood sample in a Red/Gray Top BD SST™ Tube with Silica Clot Activator & Polymer Gel. Let sample sit upright in rack for 30-60 minutes. Centrifuge for 10 minutes. Gel barrier will form separating the serum specimen from clot.	Prior to initiation of LD chemotherapy; at days 4, 7, 14, 21, 30, 60, 90, 180, 270, and 365 post-bb2121 infusion; and at the time of disease progression (if applicable).	Serum blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots.	BMT CTN Research Repository

APPENDIX C

RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and, 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Criteria for females of childbearing potential (FCBP)
This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling
All counseling will be conducted through the Revlimid REMS™ program.

Contraception
Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and, 4) for at least 28 days after study treatment discontinuation.

[†] A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or, 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

Highly effective methods:

Intrauterine device (IUD)

Hormonal (birth control pills, injections, implants)

Tubal ligation

Partner's vasectomy

Additional effective methods:

Male condom

Diaphragm

Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

The following pregnancy testing guidelines will be used throughout the study. Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 50 mIU/mL) prior to prescribing study drug. The first pregnancy test must be performed within 10-14 days prior to prescribing study drug and the second pregnancy test must be performed within 24 hours prior to prescribing study drug (prescriptions must be filled within 7 days as required by Revlimid REMS™). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.
- FCBP must commit either to abstain continuously from heterosexual intercourse or to use TWO methods of reliable birth control AT THE SAME TIME—one highly effective form of contraception and one additional effective contraceptive method as defined below. Contraception must begin 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for at least 1 year following bb2121

infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests, or 4 weeks following discontinuation of lenalidomide, whichever comes later.

Male Subjects:

- Agree to use a condom during sexual contact with a pregnant female or a FCBP, even if he has undergone a successful vasectomy, from screening through at least 1 year following bb2121 infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests; or 4 weeks following discontinuation of lenalidomide whichever is later.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

APPENDIX D

REVLIMID OVERVIEW

Revlimid REMS® for Study Participants

Revlimid REMS® description:
A program that allows patients enrolled in authorized clinical trials access to free Revlimid® through the Revlimid REMS® program.

Access to the Revlimid REMS® **Program:**

1. **All physicians must be registered prescribers of Revlimid® in the Revlimid REMS® Program All clinical sites must have access to the Revlimid REMS® software to enroll patients in the Revlimid REMS® program**
   1) Prescriber submits Registration Form via fax or RevAssist® Online ***(RAO*** for Revlimid) to BMS/Celgene Customer Care.
   2) Prescriber is registered within 15 minutes.
   3) Registration confirmation fax is sent to prescriber's office via fax. (For RAO, the confirmation notification is displayed on the screen immediately)
   4) Starter Kit is sent to prescriber's office (overnight). The starter kit will contain the following:
      - Instructions For Prescribers
      - Patient Resource Packs
      - Guide to English and Non-English Materials
      - Computer software used to generate Patient-Physician Agreement Forms (PPAF)

2. **All studies must have an FDA letter of IND exemption or an active IND, active IRB approval and BMS/Celgene required regulatory documents.**

3. **Patients must sign the research specific IRB-approved informed consent and be enrolled in a BMS/Celgene-approved Medical Affairs clinical trial using Revlimid®**

4. **BMS/Celgene Customer Care Center must be contacted to confirm if a patient needs to be registered by calling 1-888-423-5436**

5. **Patients must also sign the appropriate PPAF form and follow all the procedures of the Revlimid REMS® Program**
   1) Patient and Prescriber complete the PPAF together.
   2) The form is faxed to BMS/Celgene Customer Care or submitted electronically through ***RAO***.
   3) Patient is registered within 15 minutes.
   4) Confirmation fax is sent to prescribing office notifying them that the patient is now registered. For RAO, the confirmation notification is displayed on the screen immediately.

6. **Patients and prescribers must take the phone surveys as required by the Revlimid REMS® Program (The PPAF generated for the patient determines which phone survey questions will be asked.) An authorization number is provided at the completion of the phone survey, the authorization number should be noted on the prescription form.**

   Patient Survey requirements:
   - For men: Do not need to call BMS/Celgene the first month but must call monthly starting the second month.
   - For females of non - childbearing potential: Must call for the first month and then call every 6 months after.
   - For females of childbearing potential: Must call for the first month and then every month after.

Prescribing Revlimid® in the Revlimid REMS® program

- BMS/Celgene Medical Affairs Operations will activate the study with Biologics upon receipt of all required regulatory documents.
- Biologics will not dispense or ship Revlimid® prior to BMS/Celgene's notification of activation.
- Prescription information MUST BE entered using **the BMT CTN 1902 Revlimid REMS® study specific electronic prescription form.** This form can be found on the BMT CTN SharePoint website (https://bmtctnsp.net)
- **An authorization number** must be on the prescription form at the time of faxing.
- Prescriptions for Revlimid® must be sent to Biologics Clinical Trial Division at the following FAX number: 919-256-0794
- Only a 28-day supply of Revlimid® may be provided per cycle sent to the actual address noted on the **Revlimid REMS® electronic study specific prescription form.**
- **Biologics will verify the authorization number** and complete the patient counseling.

Protocol compliance and drug return

- Patients will be required to return unused drug to the study site for destruction per institutional guidelines.
- Sites may request that patients maintain a diary and/or to bring their bottles in for a pill count at each visit in order to review "**patient compliance."**

IMPORTANT INFORMATION ABOUT Revlimid REMS®

- To avoid fetal exposure REVLIMID®(lenalidomide) is only available under a special restricted distribution program called Revlimid REMS®
- Only prescribers registered with Revlimid REMS® can prescribe REVLIMID®(lenalidomide)
- Only Revlimid REMS® contract pharmacies can dispense REVLIMID®(lenalidomide)
- In order to receive REVLIMID® (lenalidomide), patients must enroll in Revlimid REMS® and agree to comply with the requirements of the Revlimid REMS® program
- Information about REVLIMID®(lenalidomide) and the Revlimid REMS® program can be obtained by calling the BMS/Celgene Customer Care Center toll-free at 1-888-423-5436, or at www. REVLIMID.com

How to Fill a REVLIMID® (lenalidomide) Prescription

1. Healthcare provider (HCP) instructs patient to complete patient survey
2. HCP completes survey
3. HCP completes patient prescription form
4. HCP obtains Revlimid REMS® authorization number
5. HCP provides authorization number on patient prescription form
6. HCP faxes form, including prescription
7. HCP advises patient that a representative from a Revlimid REMS® contract pharmacy will contact them
8. Revlimid REMS® contract pharmacy conducts patient education
9. Revlimid REMS®contract pharmacy calls for confirmation number
10. Revlimid REMS®contract pharmacy ships REVLIMID® with the FDA-approved MEDICATION GUIDE

APPENDIX E

HUMAN SUBJECTS

1. Subject Consent

A conference will be held with the patient, and family to discuss this study and alternative treatments available for the treatment of multiple myeloma. The conference will be conducted by the Principal Investigator or other designated physician. Potential risks associated with the study interventions should be discussed as objectively as possible. Consent will be obtained using an IRB-approved consent.

The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of MM in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX F

KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

APPENDIX G
NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX H

BB2121 INFUSION PROCESS

bb2121 Preparation and Cell Thawing

bb2121 must be delivered to the pre-defined department responsible for receiving cell products, thawed at the infusion site in a ~37°C water bath or approved thawing instrument and infused immediately within 1 hour; alternately, bb2121 may be thawed in the appropriate cell manipulation facility and administered as soon as possible within a maximum of 1 hour after thawing. If multiple drug product bags are to be administered to meet the protocol assigned dose, each bag will be thawed and administered 1 bag at a time within a maximum of 1 hour for each bag until the appropriate volume and corresponding CAR T-cell dose has been administered. In the event of a delay in completing the planned bb2121 infusion within 1 hour of thaw, bb2121 should still be administered; the reason for the delay should be recorded in the eCRF and the Sponsor will be notified.

All procedures involving bb2121 must be performed using aseptic techniques by trained personnel. See bb2121 Product Receipt, Preparation, and Administration Manual for more detail.

bb2121 Premedication

Premedication should occur approximately 30 minutes prior to the infusion and should include acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25 to 50 mg orally (or equivalent). Subjects should not receive corticosteroids as pre-medication.

bb2121 Infusion

bb2121 will be given on Day 0 (+ 14-day window), after lymphodepletion on Days -5, -4 and -3 at a target dose of 150 to 450 × 10^6 CAR T-cells/infusion with a minimum dose of 150 × 10^6 CAR+ T cells/infusion.

On Day 0, bb2121 will be administered IV through non-filtered tubing (**IMPORTANT—AN IN-LINE LEUKOCYTE FILTER MUST NOT BE USED**). A central venous access device, such as a Hickman line or peripherally inserted central catheter (PICC) line, may be utilized and is encouraged in subjects with poor peripheral access.

Vital signs are to be monitored prior to bb2121 infusion, midway through the infusion, upon completion of the infusion, and then every 15 minutes thereafter for the first hour, and hourly for the next 4 hours. Infusion reactions, including anaphylaxis, will be managed according to the medical judgment of the physician overseeing the infusion.

Dose for Subjects for Whom the Targeted Dose Cannot be Manufactured

bb2121 is manufactured on a per-subject basis and there is expected to be heterogeneity in the number of CAR T-cells that are manufactured for each subject. Subjects who have product manufactured with a dose of less than 150 x 10^6 CAR T-cells may proceed to a 2nd leukapheresis procedure for a second attempt at bb2121 manufacturing. The administered bb2121 dose may be composed of more than one manufactured product from the same subject.

APPENDIX I

MANAGEMENT GUIDELINES FOR CYTOKINE RELEASE SYNDROME (CRS) AND NEUROLOGIC TOXICITIES

(1) Cytokine release syndrome (CRS)

Administration of cellular products such as chimeric antigen receptor (CAR)-expressing T cells can be associated with cytokine-associated toxicity due to systemic production and release of various cytokines into the circulation. Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is a toxicity that occurs as a result of immune activation.[58, 59]

(1.1) Pathophysiology of CRS

The hallmark of CRS is immune activation resulting in elevated inflammatory cytokines. CRS clinically manifests when large numbers of lymphocytes (B cells, T cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated with therapeutic monoclonal antibody (mAb) infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), and anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. CRS is also frequently observed following administration of bi-specific T cell engaging antibodies for leukemia, and adoptive cellular immunotherapies for cancer, most notably CAR T cells. Incidence, time to onset and severity of CRS due to CAR T cells is at least partially dependent on the infused cell dose and tumor burden/antigen density, presumably due to more rapid and higher levels of CAR T cell activation. Onset of CRS symptoms typically occurs days to occasionally weeks after the CAR T cell infusion, usually preceding maximal *in vivo* T cell expansion. CRS is associated with elevated interferon gamma (IFNγ), interleukin (IL)-6, and tumor necrosis alpha (TNFα) levels, and increases in IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fractalkine although the patter of elevated cytokines varies among subjects.[60, 61] IL-6 has been identified as a central mediate of toxicity in CRS. IL-6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. High levels of IL-6, present in the context of CRS, likely initiates a proinflammatory IL-6-mediated signaling cascade.

(1.2) Clinical presentation of CRS

CRS is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (**Table I1**),[58] and management can be complicated by concurrent conditions. CRS usually occurs within two weeks after infusion.[62, 63]

- Fever, especially high fever (≥ 38.5 °C or ≥ 101.3 °F), is a commonly observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms, and appropriate cultures must be obtained, and empiric antibiotic therapy initiated per institutional standard of care.

- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS.
- With other CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap.

Table I1: Clinical Signs and Symptoms Associated with CRS

Organ System	**Symptoms**
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, headache
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Acute kidney injury, azotemia
Gastrointestinal	Nausea, vomiting, diarrhea
Skin	Rash
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic*	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

*Adapted from Lee 2014,[58] Neurologic symptoms are typically reversible and can occur independent of CRS. Neurologic symptoms should be graded and treated independently even if overlapping with CRS.

(1.3) Clinical management of CRS

Across various CAR T cell products, early manifestations of CRS can predict more severe toxicity for both CRS and neurotoxicity.

Subjects with B-cell acute lymphoblastic leukemia (ALL) and high burden of disease are at high risk of developing CRS.[64] Subjects with non-Hodgkin lymphoma (NHL) who have high baseline tumor burden (measured by the sum of product of the perpendicular diameters [SPD] or high serum lactate dehydrogenase [LDH ≥ 500 U/L] prior to the start of lymphodepletion) also have a higher risk of developing CRS and/or neurotoxicity.[65]

High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

It should be noted that, although useful for identifying subjects at higher risk for developing CRS, CPR, ferritin, and serum cytokine levels should not be used for CRS clinical

management/treatment decisions in the absence of other clinical signs and symptoms of CRS; for example, a subject with an elevated CRP but no concomitant symptoms may not require intervention. Thus, close observation of these subjects is strongly recommended.

Table I2: American Society of Blood and Marrow Transplant (ASBMT) CRS Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
With Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[2] Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg., CPAP, BiPAP, intubation and mechanical ventilation)

Adapted from Lee 2018[28]. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[1] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2] CRS grade is determined by more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

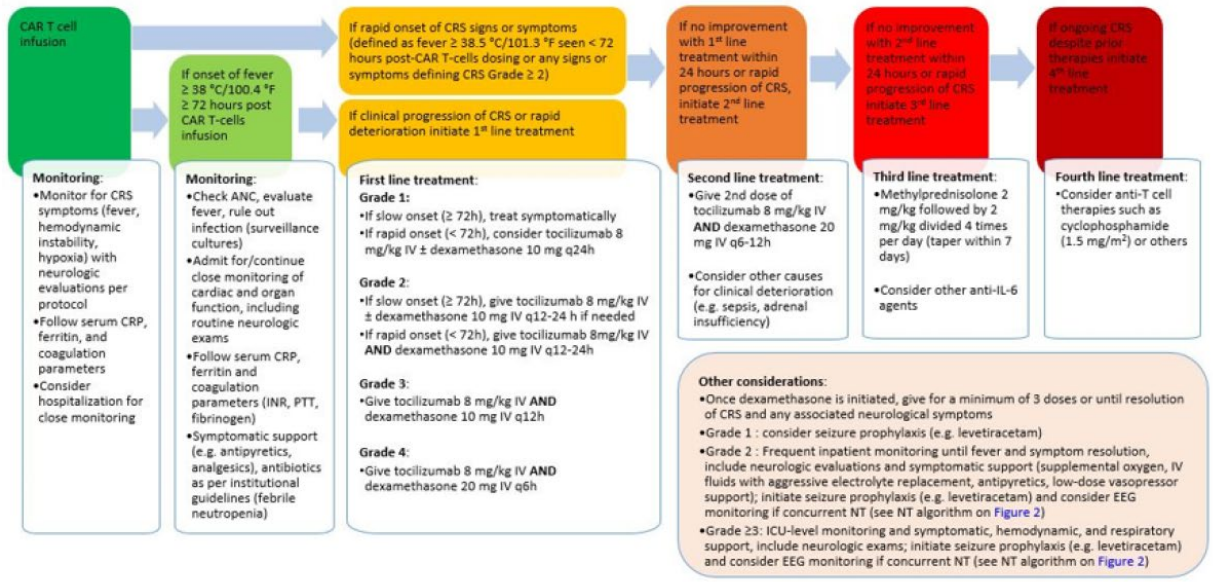
Detailed CRS management guidelines are shown in **Figure I1**. Treatment should be individualized for each subject's clinical needs. This guidance emphasizes the importance of early intervention for grade 2 CRS, or in the setting of a rapid onset or rapid progression of CRS symptoms, to prevent the development of severe (grade 3 or greater) CRS and neurotoxicity.

In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe CRS. Please refer to the currently approved tocilizumab (Actemra®) prescribing information. Tocilizumab (Actemra®) has been approved by the Food and Drug Administration (FDA) for the treatment of CAR T cell-induced severe or life-threatening CRS in adults. The preferred dose to intervene in adult subjects with CRS is 8 mg/kg (maximum 800 mg) IV. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, additional doses of tocilizumab may be administered.

Other anti-IL-6 agents, if available, should be considered in the event of severe CRS not responding to tocilizumab and corticosteroids. Dosing of any other anti-IL-6 agent should be per prescribing information.

In the most unresponsive cases additional treatment with T cell depleting therapies such as cyclophosphamide should be considered.[66]

Figure I1: Cytokine Release Syndrome (CRS) Treatment Algorithm



Abbreviations: ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CRP = C-reactive protein; CRS = cytokine release syndrome; EEG = electroencephalogram; ICU = intensive care unit; IL-6 = interleukin 6; INR = international normalized ratio; IV = intravenous; NT = neurotoxicity; PTT = partial thromboplastin time; q = every.

(2) Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. The start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) [62] after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

(2.1) Pathophysiology of Neurologic Toxicities

The pathogenesis of neurotoxicity is poorly defined. Subjects with NHL who have high baseline tumor burden (measured by SPD or high serum LDH (≥ 500 U/L) prior to the start of lymphodepletion) also have a higher risk of developing neurotoxicity.[65] In addition, severe neurotoxicity has also been reported in subjects with B-cell ALL and higher disease burden at the time of CD19 directed CAR T cell infusion.[67]

Peak levels of IL-6, IFN-γ, ferritin, and CRP are significantly higher in subjects who develop any grade or grade ≥3 neurotoxicity.[68, 69] In a study treating NHL subjects with a CD19-directed CAR using a CD28 costimulatory domain, development of grade ≥3 neurologic events and CRS correlated with elevation of various cytokines, including IL-6, IL-15, and IL-2Rα. Subjects with CRS-independent grade ≥3 neurologic events had higher CAR T cell levels and specific cytokines, including IL-2, GM-CSF, and ferritin.[31] Protein levels in the cerebrospinal fluid (CSF) are usually elevated in patients with neurotoxicity, compared to baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunction (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy.[70] In another study, it has been reported that evidence for cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood-brain barrier disruption allowing transit of high concentrations of systemic cytokines into the CSF.[67]

Current American Society of Blood and Marrow Transplant (ASBMT) Consensus Grading refers neurotoxicity observed CAR T cell therapy as immune effector cell-associated neurotoxicity syndrome (ICANS).[28]

(2.1) Clinical Management of Neurologic Toxicities

The optimal management of CAR T cell-induced neurotoxicity is unknown at this time. These management guidelines represent the current state of knowledge. Management should also be guided as per institutional or standard clinical practice, and as determined by the investigator or treating physician and/or consulting neurologist. A thorough neurologic evaluation, including electroencephalogram (EEG), magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain and diagnostic lumbar puncture and frequent monitoring of cognitive function should be considered. Please refer to **Table I2** for encephalopathy assessment tool for grading of ICANS, and **Table I3** for the ASBMT ICAN Consensus Grading for adults.

Table I2: Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [70]	ICE
Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points	Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (e.g. point to clock, pen, button): 3 points	Naming: ability to name 3 objects (e.g. point to clock, pen, button): 3 points
Writing: ability to write a standard sentence (e.g. "Our national bird is the bald eagle"): 1 point	Writing: ability to write a standard sentence (e.g. "Our national bird is the bald eagle"): 1 point
Attention: ability to count backwards from 1000 by 10: 1 point	Attention: ability to count backwards from 1000 by 10: 1 point
	Following commands: ability to follow simple commands (e.g. "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point

Adapted from Lee 2018 [28]. CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Scoring: 10, no impairment;
7-9, grade 1 ICANS:
3-6, grade 2 ICANS:
0-2, grade 3 ICANS:
0 due to patient unarousable or unable to perform ICE assessment, grade 4 ICANS.

Table I3: ASBMT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[1]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed levels of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[3]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure (ICP)/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[4]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Adapted from Lee 2018[28]ICANS grading is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
[2] Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication).
[3] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[4] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Treatable causes of neurologic dysfunction, such as infection or hemorrhage should be ruled out. Common manifestations of neurotoxicity (e.g. confusion, seizure, aphasia), can also be seen with infection, electrolyte imbalances, metabolic acidosis, uremia, concomitant medication use (e.g. narcotics), and other medical conditions. Other causes for such symptoms should be considered.

MRI and CT scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in subjects treated with CAR T cell therapy, although rare cases of reversible T2/fluid attenuation inversion recovery (FLAIR) MRI hyperintensity involving the thalami, dorsal pons, and medulla, and cerebral edema have been reported.[70]

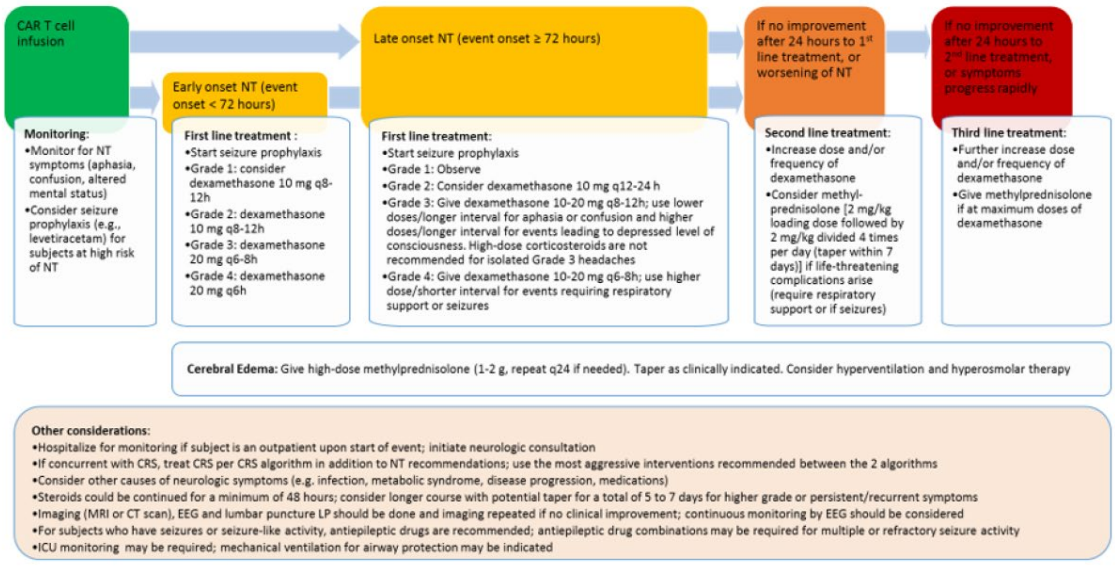
For subjects who have neurologic toxicity in the present of CRS, the CRS should be managed following the guidelines provided in **Figure I1**.

Neurotoxicity should be evaluated following the guidelines in **Figure I2**. For concurrent CRS and neurotoxicity, the most aggressive intervention recommended by either guideline should be employed (if the recommendations for steroid doses differ, use the highest dose and/or frequency). For subjects with grade 4 neurotoxicity with cerebral edema, high-dose corticosteroids, hyperventilation and hyposmolar therapy has been recommended.[70]

Note: Tocilizumab is not recommended for the treatment of neurotoxicity related to CAR T cell therapy unless CRS or MAS/HLH is also present. Results from 2 studies, one of preemptive use of tocilizumab, shortly after anti-CD19 CAR T cell therapy in relapsed/refractory NHL subjects,[71] and the other mandatory use of tocilizumab at first fever (≥ 38.5 °C) in pediatric ALL patients treated with anti-CD19 CAR T cells,[59] demonstrated that early tocilizumab use either increased overall neurotoxicity and grade ≥ 3 neurotoxicity rates (85% vs 62% overall; 35% vs 26% grade ≥ 3) or provided no improvement in neurotoxicity rates, respectively. These findings support the hypothesis that tocilizumab does not improve any may worsen isolated neurotoxicity.[71]

Neurotoxicity management guidelines are provided in **Figure I2**.

Figure I2: Neurotoxicity Treatment Algorithm



Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; LP = lumbar puncture; MRI = magnetic resonance imaging; NT = neurotoxicity; q = every.

APPENDIX J

MANAGEMENT GUIDELINES FOR CYTOPENIAS

Management guidelines for neutropenia:

Guidelines below refer to filgrastim use, but filgrastim biosimilars or pegfilgrastim may also be used where filgrastim use is specified below according to investigator discretion and local institutional practice.

Patients should not receive filgrastim within 2 weeks of CAR T cell infusion. Beginning 2 weeks (day 15) after CAR T cell infusion, filgrastim may be administered according to local institutional practice to address neutropenia. Neutropenia is expected within 4 weeks of CAR T cell infusion and does not require filgrastim support, though filgrastim may be used between as early as day 15 after CAR T cell infusion at discretion of investigators. For persistent neutropenia at any individual post-infusion time point beyond 4 weeks, minimum support should include the following:

- If ANC less than 500/mm^3 (grade 4), administer filgrastim x 1, re-check within one week.
- If ANC is less than 500/mm^3 on re-check, administer daily filgrastim and re-check within one week.
- If ANC is less than 500/mm^3 after daily filgrastim x 1 week, bone marrow biopsy should be performed to assess etiology of persistent neutropenia.

Filgrastim may be administered for chronic neutropenia between 500/mm^3 and 1000/mm^3 (grade 3) but is not required by the protocol. If ANC is not consistently greater than 1000 by week 6 after CAR T cell infusion, bone marrow biopsy should be performed to assess the etiology of chronic neutropenia.

Management guidelines for thrombocytopenia:

Bone marrow biopsy to assess the etiology of thrombocytopenia should be performed if platelets are consistently less than 25,000/mm^3 (grade 4) at week 6 after CAR T cell infusion, less than 50,000/mm^3 (grade 3) at week 12 after CAR T cell infusion.

Guidelines for stem cell re-infusion:

Prolonged cytopenias have been reported after CAR T cell therapy. Cryopreserved autologous stem cells can be used to restore normal hematopoiesis in the circumstances defined below. The efficacy of this approach has not been well established, and the impact of this approach on the efficacy of CAR T cell therapy has not been studied.

The use of cryopreserved autologous stem cells in this protocol will be considered in the following circumstances:

1. Grade 4 thrombocytopenia with bleeding complications occurring more than 6 weeks after CAR T cell infusion
2. Grade 4 neutropenia lasting more than 6 weeks after CAR T cell infusion and not responding to or continuing to require growth factor support

3. Grade 3 or 4 cytopenias lasting more than 12 weeks post infusion
4. At ANY TIME in a patient with life threatening bleeding or infectious complications that in the view of the treating physician could only be reversed with rapid hematologic reconstitution.
5. Protracted transfusion requirements beyond 12 weeks post infusion not attributable to other causes.
6. Other indications as discussed with the protocol chairs and medical monitors.

The BMT CTN 1902 Protocol Chairs and Officer must be consulted prior to stem cell infusion. Prior approval from the BMT CTN Protocol Chairs or Office is required prior to stem cell re-infusion. Prior to stem cell reinfusion all patients should have the following tests performed to assess for other potential factors contributing to the cytopenias:

1. Viral PCR: HHV6, CMV, EBV, Adeno, Parvovirus
2. Thyroid function tests
3. Iron Studies
4. CRP and ESR
5. Bone marrow aspirate and biopsy to assess overall cellularity, adequacy of iron stores, myeloma burden, and to evaluate for myelodysplasia, hemophagocytosis, large granular lymphocyte (LGL) leukemia (by flow cytometry and morphology), and clonal cytogenetic abnormalities.
6. Autoimmune panel: ANA, ANCA panel, Antiplatelet antibodies, Coombs
7. Aspirate and biopsy samples should be sent to central biorepository

APPENDIX K

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APPENDIX L

INVESTIGATOR'S SIGNATURE

Phase II Multicenter Trial of anti-B Cell Maturation Antigen Chimeric Antigen Receptor T Cell Therapy for Multiple Myeloma Patients with Sub-Optimal Response After Autologous Hematopoietic Cell Transplantation and Maintenance Lenalidomide

BMT CTN PROTOCOL 1902

Version 2.0, April 16, 2021

I have read all pages of this clinical study protocol. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (MMDDYYYY)

Printed Name: .....

Address: .....

.....

.....