
# BMT CTN 1902 / MM CAR-T TO UPGRADE RESPONSE

# IND#: 26844

# STATISTICAL ANALYSIS PLAN

Version 4.0

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# VERSION HISTORY

| Version # | Creation/ Revision Date (DDMMMYYYY) | Approved By | Approval Date (DDMMMYYYY) | Reason for Change |
|---|---|---|---|---|
| 1.0 | 27JUL2020 | Maggie Wu | 20SEP2021 | Initial document |
| 2.0 | 17OCT2022 | Maggie Wu | 20OCT2022 | Protocol Amendment from V2.0 to 3.0 |
| 3.0 | 05NOV2024 | Brent Logan | 13NOV2024 | Clarifications; Change reference timepoint from LD chemotherapy to infusion |
| 4.0 | 22JUL2025 | Brent Logan | 05AUG2025 | Clarifications of CAR T-cell expansion and persistence analyses |

# ABBREVIATIONS/DEFINITIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ASTCT | American Society for Transplantation and Cellular Therapy Transplantation |
| AUC | Area Under the Curve |
| ALC | Alternate Level of Care |
| BCMA | anti-B Cell Maturation Antigen |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CAR | Chimeric Antigen Receptor |
| CRS | Cytokine Release Syndrome |
| CIBMTR | Center for International Blood and Marrow Transplant Research |
| CR | Complete Response |
| CBC | Complete Blood Count |
| CT | Computed Tomography |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| CD | Cluster of Differentiation |
| DSMB | Data Safety Monitoring Board |
| DNA | Deoxyribonucleic Acid |
| EDC | Electronic Data Capture |
| ECHO | Echocardiogram |
| FDA | Food and Drug Administration |
| FCBP | Females of Child-Bearing Potential |
| FLC | Free Light Chains |
| HCT | Hematopoietic Cell Transplant |
| $H_0$ | Null Hypothesis |
| $H_a$ | Alternate Hypothesis |
| IV | Intra Venous |

| Abbreviation | Definition |
|---|---|
| ICE | Immune-Effector Cell Encephalopathy |
| ICF | Informed Consent Form |
| INR | International Normalized Ratio |
| ICANS | Immune-Effector Cell Associated Neurotoxicity Syndrome |
| LDH | Lactate Dehydrogenase |
| LD | Lympho Depleting |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| MR | Minimal Response |
| MRD+/- | Minimum Residual Disease Positive/Negative |
| MM | Multiple Myeloma |
| MRD | Minimal Residual Disease |
| MOP | Manual of Procedures |
| MUGA | Multiple-Gated Acquisition |
| NRM | Non-Relapse Mortality |
| NGS | Next Generation Sequencing |
| NHLBI | National Heart Lung and Blood Institute |
| OS | Overall Survival |
| OOS | Out of Specification |
| PR | Partial Response |
| PET | Positron Emission Tomography |
| PFS | Progression Free Survival |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PTT | Partial Thromboplastin Time |
| PT | Preferred Term |
| qPCR | quantitative Polymerase Chain Reaction |
| SAE | Serious Adverse Event |
| SCR | Stringent Complete Response |
| SAP | Statistical Analysis Plan |

| Abbreviation | Definition |
|---|---|
| SPEP | Serum Protein Electrophoresis |
| SOC | System Organ Class |
| SPD | Sum of Product of the Perpendicular Diameters |
| SD | Stable Disease |
| TNF | Tumor Necrosis Factor |
| US | United States |
| UPEP | Urine Electrophoresis |
| VGPR | Very Good Partial Remission/Response |

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# 1 PROTOCOL

BMT CTN protocol #1902 is titled “Phase II Multicenter Trial of anti-B Cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy for Multiple Myeloma Participants with Sub-Optimal Response After Autologous Hematopoietic Cell Transplantation and Maintenance Lenalidomide”. The version of the protocol used to develop this SAP is version 3.0 dated March 10, 2022.

# 2 GENERAL REVIEW OF STUDY DESIGN AND PROCESS

## 2.1 STUDY OBJECTIVE

BMT CTN #1902 is a single arm, Phase II, open-label, multi-center trial designed to assess BCMA CAR T-Cells (bb2121) to improve post autologous HCT responses among participants with MM. Primarily, the study aims to evaluate the efficacy of BCMA CAR T-Cell therapy to improve the response in participants who received an upfront autologous HCT and lenalidomide maintenance and failed to achieve at least a VGPR after first-line therapy (induction followed by high-dose melphalan, autologous stem cell transplant and maintenance lenalidomide). Prior to enrollment, participants must have had an autologous HCT and initiated lenalidomide-based maintenance with a response of less than CR (i.e., VGPR or less) (in comparison to pre-induction status).

Additionally, the study will include assessment of disease progression, best disease response to treatment as determined by improved clinical disease response and conversion to MRD negativity, non-relapse mortality, PFS, incidence of CRS, incidence of prolonged cytopenias, and incidence of neurotoxicity.

Furthermore, the study will assess exploratory objectives which will include incidence of toxicities greater than or equal to grade 3 per the 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 and immune reconstitution.

### 2.1.1 PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the efficacy of BCMA CAR T-Cell therapy to improve the response in participants who received an upfront autologous HCT and lenalidomide maintenance.

### 2.1.2 SECONDARY OBJECTIVES

The clinical secondary objectives of the study include:

- Progression of disease
- Best disease response as described by conversion to MRD negativity and upgrade in clinical disease response
- Non-relapse mortality (NRM)
- Progression-free survival (PFS)
- Incidence of cytokine release syndrome (CRS)
- Incidence of prolonged cytopenias
- Incidence of neurotoxicity (ICANS)Feasibility of reinitiations of lenalidomide maintenance

### 2.1.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study include:

- Incidence of toxicities greater than or equal to grade 3 per CTCAE version 5.0
- Incidence of infections per protocol-specific MOP
- Overall survival (OS)
- CAR T-Cell expansion
- CAR T-Cell persistence
- BCMA expression
- Immune reconstitution

## 2.2 STUDY DESIGN AND PROCEDURES

### 2.2.1 PRIMARY HYPOTHESIS AND PRIMARY ENDPOINT

The primary hypothesis of the study is that infusion of bb2121 will result in a significant reduction in myeloma tumor burden as documented by the achievement of a complete response in participants who failed to achieve at least a VGPR after high dose of melphalan, autologous stem cell transplant, and maintenance therapy.

### 2.2.2 ACCRUAL PLAN

The target sample size of the study is 40 participants. The study plans to enroll 40 participants on this trial in order to get at least 33 evaluable participants receiving the final selected dose of bb2121 infusion. There will be a safety run-in with staggered enrollment to assess for excess early toxicity of CAR T cells in this new clinical setting or prolonged cytopenias that limit resumption of maintenance lenalidomide.

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.

This run-in will start with the standard CAR T cell dose of 450 x 106 cells and may include up to 6 participants at this dose, if still there are toxicity concerns the dose will be reduced to 300 x 106 cells which will then be the selected dose for this study. If the lower dose is still toxic, the trial will be paused for reconsideration. Only participants 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 approximately 40 total participants at that dose, including those in the run-in. Assuming the potential for dose de-escalation after the first 6 participants were enrolled in the run-in phase and 1 participant dropping out from enrollment before initiation of LD chemotherapy, this will result in at least 33 evaluable participants 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.

The estimated accrual period is 22 months.

### 2.2.3 DURATION OF FOLLOW-UP

Participants will be followed on this protocol for 12 months post CAR T-Cell infusion. Participants who withdraw from the study treatment for any reason prior to 12 months from infusion will continue to be followed per protocol for 12 months post infusion unless the participant withdraws consent for study follow up.

Considering long term follow up, all participants will be followed for 15 years using the CIBMTR cellular therapy registry. Data regarding study participant's clinical situation, including follow up after 1 year to year 15, may be obtained from the CIBMTR, which captures information on all US transplants and cellular therapies. Such long-term follow up data is NOT within the scope of this SAP and analysis on these long-term follow up data is not part of the primary analysis.

## 2.3 INCLUSION/EXCLUSION CRITERIA AND TREATMENT DESCRIPTION

Participants must meet specified eligibility criteria outlined prior to initial enrollment. Additional criteria must also be met to continue to successive stages of the protocol.

Refer to protocol section 2.3 for participant eligibility criteria.

There are some updates regarding Inclusion and Exclusion Criteria in protocol amendment from version 2.0 to version 3.0 of the protocol.

The final criteria will be incorporated in the final analysis should be more amendments prior to the final database lock.

## 2.4 TREATMENT DESCRIPTION

### 2.4.1 TREATMENT PRIOR TO ENROLLMENT

Please refer to protocol section 2.4.1 for details of treatment prior to enrollment. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

### 2.4.2 LEUKAPHERESIS

Please refer to protocol section 2.4.2 for details of leukapheresis. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

### 2.4.3 CAR T-CELL (BB2121) MANUFACTURING

Please refer to protocol section 2.4.3 for details CAR T-Cell manufacturing. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

### 2.4.4 LD CHEMOTHERAPY

Please refer to protocol section 2.4.4 for details of LD chemotherapy. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

### 2.4.5 CAR T-CELL BB2121 INFUSION

Please refer to protocol section 2.4.5 for details of CAR T-Cell bb2121 infusion. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

### 2.4.6 MAINTENANCE TREATMENT

Please refer to protocol section 2.4.6 for details of maintenance treatment. Should there be more amendments prior to the final database lock, the final version will be incorporated in the final data analysis report.

**Below are the follow up schedules:**

**Table 1: Follow up schedule after enrollment**

| Study Visit | Target Day |
|---|---|
| Pre-Enrollment Screening | < 30 days prior to enrollment unless |
| Leukapheresis | approximately 14 days post- |
| Screening to Initiate LD | < 7 days prior to Initiating LD |
| Initiation of LD Chemotherapy | 5 days prior to planned bb2121 |
| Screening for bb2121 Infusion | Day of bb2121 infusion |
| bb2121 Infusion[1] | < 7 days after the planned date of bb2121 infusion |
| Pre-Maintenance Screening | < 14 days prior to maintenance |
| Maintenance Start | Day 30-180 post bb2121 infusion |

[1] *bb2121 Infusion 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.*

**Table 2: 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 | +/- 7 days |
| Day 180, 270, 365 | +/- 28 days |

Should there be more amendments prior to the final database lock that would impact the follow up schedule, the final version will be incorporated in the final data analysis report.

**Please refer to the BMT CTN 1902 protocol for the Study Schema.**

## 2.5 RESPONSE VARIABLES AND DATA COLLECTION TIME POINTS

### 2.5.1 RESPONSE VARIABLES

The response variables for this study include the primary, secondary, exploratory and safety endpoints. 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 participants with suboptimal disease responses after an autologous HCT and lenalidomide maintenance.

**Secondary endpoints include:**

- Disease progression
- Disease response
- Non-relapse mortality (NRM)
- Incidence of cytokine release syndrome (CRS)
- Incidence of prolonged cytopenias
- Incidence of neurotoxicity (ICANS)
- Progression free survival (PFS)
- Feasibility of re-initiation of lenalidomide maintenance

**Exploratory endpoints include:**

- Incidence of toxicities grade >=3 per CTCAE version 5.0
- Incidence of infections per protocol-specific MOP
- Overall survival (OS)
- CAR T-Cell expansion
- CAR T-Cell persistence
- BCMA expression
- Immune reconstitution

Definitions for the primary, secondary, and exploratory endpoints are described in detail in Section 3 of Protocol version 3.0 as well as Section 5 of this SAP.

**Safety endpoints that will trigger a DSMB review include:**

- Occurrence of at least two cases of grade 4 CRS
- Occurrence of at least one event of grade 4 ICANS
- Occurrence of two or more non-relapse deaths within 28 days of infusion
- Occurrence of one bone marrow failure requiring CT rescue
- 15% of participants are unable to start lenalidomide maintenance by Day 60 after CAR-T infusion
- 15% of participants who are able to start lenalidomide maintenance are unable to sustain therapy due to cytopenia-driven interruption

Safety monitoring will be conducted per protocol schedule. Adverse events will be reported per the BMT CTN MOP.

### 2.5.2 DATA COLLECTION TIME POINTS

Participants are evaluated for pre-enrollment assessments at initial study enrollment, at leukapheresis, at Pre-LD Chemotherapy Screening, and prior to the start of bb2121 infusion (Day 0). Post bb2121 infusion, participants are evaluated over a 12 month period at the following time points: Day 4 (+/- 2 days), Day 7 (+/- 2 days), Day 10 (+/- 2 days), Day 14 (+/- 2 days), Day 21 (+/- 2 days), Day 30 (+/- 7 days), Day 60 (+/- 7 days), Day 90 (+/- 7 days), Day 180 (+/- 7 days), Day 270 (+/- 7 days) and Day 365 (+/- 7 days).

Death, relapse/progression, infections, hospitalizations, and adverse events are reported on event-driven forms. Data on occurrence of these events are recorded per the BMT CTN MOP.

Pre-enrollment evaluations must be completed within 30 days prior to enrollment. Participants must have received initial systemic anti- myeloma therapy consisting of induction therapy and consolidation with high-dose melphalan (>140 mg/m2) followed by an auto HCT (minimum cell dose of 2x106 CD34+ cells/kg (actual body weight) within 12 months from initiation of systemic anti-myeloma therapy. Participants 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. Participants 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.

Following the screening assessments and enrollment, participants 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.

LD chemotherapy will be initiated 5 days prior to planned bb2121 infusion (Day 0). Sample collection for ancillary studies and for future research use are performed prior to initiation of lymphodepleting LD chemotherapy and at the time of disease progression (if applicable).

Participant data related to primary and secondary endpoints are collected through Advantage eClinical up to 28 days after the last maintenance dose or 1 year post bb2121 infusion depending on participant's compliance to the lenalidomide. The specimens collected for immunologic endpoints are being tracked in Advantage eClinical and GlobalTrace. Samples will be shipped to BMT CTN Biorepository or institutional laboratories based on the purpose of specimen. All unexpected grades 3-5 AEs are required to be reported using the expedited AE reporting system in Advantage eClinical through 1 year post maintenance. Other follow up data after 1 year post maintenance initiation until 15 years post maintenance initiation may be obtained from the CIBMTR.

The schedule of assessments is provided in Table 3 and 4.

Should there be more amendments prior to the final database lock that would impact the schedule of assessments, the final version will be incorporated in the final data analysis report.

## **Table 3.** Participant 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** (+/- 28 days) | **270** (+/- 28 days) | **365** (+/- 28 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 | X[12] | X[11] | X[6] | X | X | X[13] | X[6] | X | X[6] | X | X | X[6] | X[6] |

| **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** (+/- 28 days) | **270** (+/- 28 days) | **365** (+/- 28 days) | |
| functions, and blood chemistries[1] | | | | | | | | | | | | | |
| 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** | |
| Local assessment of unilateral bone | | | **X**[10] | | | | **X** | | **X** | **X** | **X**[3] | **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** (+/- 28 days) | **270** (+/- 28 days) | **365** (+/- 28 days) | |
| marrow aspirate and biopsy | | | | | | | | | | | | | |
| Coagulation Panel including PTT, INR, and fibrinogen | **X**[12] | | **X** | | | | | | | | | | |
| Evaluation for CRS/ICANS | | | | | | **X** | **X** | **X** | **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 H)
[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: 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 (5 mL) | | X | | | | | | | X | X | | X | X |
| CAR-T Cell expansion and persistence (2mL) | | X | | | | | X | | X | | | X | X |
| Optional Repository Sample for Future Research (6mL) | | 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 participants that have disease progression while in study follow up.
[2]Only Immune Profiling Assessment done from Day 30 sample.

## 2.6 STUDY ENDPOINT DEFINITIONS

Until disease progression, all disease classifications are relative to the participant'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.

**Table 5: Study Endpoint Definitions[1]**

| Study Endpoint Definitions | |
|---|---|
| Response Categories | |
| Stringent Complete Response (sCR): | sCR requires, in addition to CR (defined below), all of the following:<br>• 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 participants, respectively, after counting ≥100 plasma cells. |
| Complete Response (CR): | CR requires all of the following:<br>• 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.<br>• Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.<br>• No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)[1].<br>• Disappearance of soft tissue plasmacytomas.<br><br>Participants 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 participants in whom routine electrophoresis is negative but in whom immunofixation has not been performed.<br>[1]*If not clinically indicated, radiographs are not required to document CR.* |
| Very Good Partial Remission (VGPR) | VGPR requires, in addition to PR (defined below), all of the following:<br>• Serum or urine paraprotein detectable by immunofixation but not on electrophoresis.<br>OR<br>• Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein less than 100 mg/24hrs.<br>• For free light chain only disease, VGPR requires a 90% reduction of involved light chain. |

| Study Endpoint Definitions | |
|---|---|
| Response Categories | |
| Partial Response (PR) | PR requires one of the following:<br>• 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.<br>• 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.<br>• 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%.<br>• Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas if present at baseline (by radiography or clinical examination)[1].<br><br>[1]*Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For* participants *with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.* |
| 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%.<br>• 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) | Participants who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease above are considered to have stable disease (SD). |
| Disease Progression Definitions | |
| Progressive Disease (PD) from CR or sCR | Progression from CR or sCR requires one or more of the following:<br>• A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.<br>• 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.<br>• Abnormal FLC levels of greater than 10 mg/dl, only in participants without measurable paraprotein in the serum and urine.<br>• At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.<br>• Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.<br>• Development of new bone lesions or soft tissue plasmacytomas.<br>• Development of hypercalcemia (corrected serum Ca greater than11.5 mg/dL or greater than 2.8 mmol/L) not attributable to any other cause. |

| Study Endpoint Definitions | |
|---|---|
| Response Categories | |
| Progressive Disease (PD) for Participants not in CR or sCR | For participants not in CR or sCR, progressive disease requires one or more of the following:<br>• 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.<br>• 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.<br>• Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be greater than 10 mg/dl), only in participants without measurable paraprotein in the serum and urine.<br>• 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%.<br>• Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.<br>• Development of new bone lesions or soft tissue plasmacytomas.<br>• Development of a compression fracture does not exclude continued response and may not indicate progression.<br>• 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. |

[1] *From the 1902 study protocol, Section 3.1.1*

# 3 GENERAL STATISTICAL CONSIDERATIONS

## 3.1 SAMPLE SIZE AND POWER CALCULATIONS

The primary objective of this clinical trial is to estimate the proportions of participants achieving CR or better 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 participants not in CR after autologous HCT and 6 months of maintenance therapy will get into CR within a subsequent 6 months of maintenance therapy. The trial will use hypothesis testing to assess the potential efficacy of the addition of bb2121 cells to upgrade post autologous transplant responses. The trial will test the null hypothesis that the 6-month probability of achieving CR or better is less than or equal to 10% against the alternative that it is greater than 10%, using a one-sided 5% significance level.

The study plans to enroll 40 participants in order to get at least 33 evaluable participants receiving the final selected doses of bb2121 infusion. Assuming the potential for dose de-escalation after the first 6 participants were enrolled in the run-in phase and at least 1 participant dropping out from enrollment before initiation of LD chemotherapy, this will result in at least 33 evaluable participants at the final selected dose. Assuming a 5% one-sided significance level, a sample size of 33 or more evaluable participants 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 33.

Since this is a Phase II trial, the sample size and power calculation used in the study design of the trial is not intended to provide definitive results but rather to detect any promising difference in response rates between the bb2121 infusion and maintenance therapy with lenalidomide in a multi-center setting for future trials consideration.

## 3.2 HANDLING MISSING DATA

Comprehensive data quality assurance will be conducted to reconcile data issues including missing data.

It is expected there will be minimal missing data (<5%) for the primary endpoint and secondary endpoints based on past experience with transplant and cellular therapy trials. For time-to-event variables, participants will be censored at the last observation for the endpoint if they have not had an event or competing risk event. Participants lost to follow up will be censored at the time of last contact date captured in eClinical.

For all other analyses, all available data will be used, and no imputation will be done on missing data, unless specified differently elsewhere in this SAP.

## 3.3 MULITPLE COMPARISONS

Adjustments will be made to reduce the significance level for the multiplicity of outcomes for the exploratory endpoints of CAR T-cell expansion, CAR T-cell persistence, and BCMA expression which will use a significance level of 0.01.

## 3.4 INTERIM ANALYSES AND STOPPING GUIDELINES

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

Assuming the trial will enroll at least 33 patients, additional 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:

- The occurrence of one bone marrow failure requiring CT rescue and
- If 15% of participants are unable to start lenalidomide maintenance by Day 60 after CAR T-Cell infusion.

A DSMB review will also be triggered if 15% of participants 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 protocol table 2.4.6, and details of 15% stopping rule for being unable to start or sustain lenalidomide maintenance are given below in Table 7.

**Table 6: Stopping rule for participants unable to start or sustain lenalidomide maintenance or unable to sustain therapy due to cytopenia-driven interruption**

| # of Participants | # 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.

## 3.5 TIMING OF ANALYSIS

The first round of the analysis will be for the primary endpoint, which is when all participants complete 6 months follow up post bb2121 infusion and data is locked.

A topline analysis will be conducted to include the primary endpoint and secondary endpoints to facilitate abstract submission of the primary results. These analyses will only include data through 6 months. Study enrollment, participant demographics and baseline data will also be included in the topline analysis.

A data freeze for the first round of analysis will be done upon the completion of related data quality assurance after all participants have completed 6 months follow up post bb2121 infusion.

The second round of the analysis will be the final analysis which will include all the study endpoints with complete 12 months follow up post bb2121 infusion. This comprehensive analysis will include the primary endpoint, secondary endpoints and exploratory endpoints and is conducted to facilitate the primary manuscript submission of the study. Correlative immunologic endpoints that are defined in the protocol will be included in this comprehensive analysis report.

## 3.6 SOFTWARE

All analyses will be conducted using SAS 9.4 or higher software, or R version 3.1.0 or higher.

## 3.7 ANALYSIS POPULATIONS

### 3.7.1 ENROLLED POPULATION

All participants who were enrolled in the study will be counted in the enrolled population. Demographic and baseline characteristics will be summarized for this population.

### 3.7.2 PRIMARY ANALYSIS POPULATION

All participants 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 infusion.

Primary analyses for the primary, secondary, and exploratory endpoints will use the primary analysis population. Analyses of each endpoint will follow the analysis plan as described below in Section 4 of this SAP. Note that if there is a dose de-escalation in the run-in phase before selecting the final dose, analyses as described below will apply to the final selected dose, while participants at the higher dose will be summarized separately in a descriptive manner due to the small numbers of participants at that dose. If any patients are enrolled but not infused, they will be described separately.

### 3.7.3 SAFETY ANALYSIS POPULATION

The primary analysis population will be used for all analyses of safety data. The primary analysis population will also be used for all analyses of safety data at the selected dose.

The reporting of serious adverse events will be consistent with standard BMT CTN procedures and compliant with additional requirements from Celgene Corporation who supplies lenalidomide for the study with the addition of any anticipated SAE related to the study drug or treatment/procedure. All reported serious adverse events potentially associated with study drug or treatment/procedure will be carefully examined with respect to the severity and relationship to study drug. The type and severity of adverse events will be described. Safety data will be summarized using MedDRA Coding version 5.0 or 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. 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).

## 4 PARTICIPANT CHARACTERISTICS AND COMPLIANCE

### 4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Descriptive statistics for demographics and baseline characteristics will be presented. Characteristics to be examined include: age, gender, race/ethnicity, Karnofsky performance status, multiple myeloma subtype, myeloma risk, International Staging System at diagnosis (ISS), Revised- ISS, cytogenetics, , lines/types of initial systemic anti-myeloma therapy, interval from diagnosis of symptomatic MM to enrollment, interval from initial systemic therapy to enrollment and to CAR T cell infusion, , timing from transplant to enrollment and to CAR T-Cell infusion, duration of lenalidomide-based post transplant therapy (maintenance or consolidation), interval from leukapheresis to CAR T cell infusion and initial disease response status at enrollment. Myeloma risk defines high risk disease based on ISS 3 and or high risk cytogenetics (t(4;14), t(14;16), t(14;20), deletion 17p or p53 deletion or amplification of 1q). The date of initiation of first systematic MM treatment after MM diagnosis will be used as date of symptomatic MM.

### 4.2 PARTICIPANT COMPLIANCE

A table listing significant protocol deviations/violations will be provided. Compliance with protocol interventions will be evaluated as appropriate. Premature withdrawals will be described for each case.

A consort diagram will be provided to illustrate study accrual and follow up.

In the tables/figures, the number of included participants will be provided/described for each analysis.

# 5 ANALYSIS PLAN

## 5.1 ANALYSIS OF THE 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 participants with suboptimal disease responses after an autologous HCT and lenalidomide maintenance. Participant's disease status will be evaluated based on the International Uniform Response Criteria3.

If there is no censoring prior to 6 months post CAR T-cell infusion and prior achieving a CR, then the probability of CR by 6 months post CAR T-cell infusion 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 participants in CR/sCR by 6 months post CAR T-cell infusion against a null hypothesis or value of 10% will be conducted using a 5% one-sided significance level. A one-sided significance level of 0.05 will be used to assess whether 6-month probability of CR post CAR T-cell infusion is ≤10% or >10%.

The study will test the null hypothesis that the 6-month probability of CR/sCR post CAR T-cell infusion is less than or equal to 10% against the alternative that it is greater than 10%, using a one-sided 5% significance level.

H0: 6-month probability of CR/sCR is ≤10% vs. Ha: 6-month probability of CR/sCR is >10%.

If there is censoring present prior to 6 months post CAR T-cell infusion and prior to achieving a CR/sCR, then the probability of CR/sCR by 6 months post CAR T-cell infusion will be estimated using the cumulative incidence technique, with death as a competing risk and participants alive without CR/sCR at last contact considered censored. 90% confidence intervals for the cumulative incidence will be computed using the complementary log-log transformation. The cumulative incidence curves will be presented.

## 5.2 ANALYSIS OF THE SECONDARY ENDPOINTS

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

### 5.2.1 ALL SECONDARY ENDPOINT ANALYSES WILL UTILIZE THE PRIMARY ANALYSIS POPULATION. RESPONSE TO TREATMENT

Disease response will be assessed according to protocol section 3.1.1 and the categories also shown in Table 6 above. The disease response categories will be tabulated at each assessment period at Day -30, Day -14, Pre-LD Chemotherapy Screening (< 7 days prior to initiating LD Chemotherapy), Day 30 (+/- 7 days), Day 60 (+/- 7 days), Day 90 (+/- 7 days), Day 180 (+/- 7 days), Day 270 (+/- 7 days), Day 365 (+/- 7 days) post bb2121 infusion.

The following will be reported:

- The proportion of participants achieving an upgrade in their response following enrollment (SD to MR or greater, MR to PR or greater, or PR to VGPR or greater) at any time point. The assessment of responses are compared to biochemical assessments of disease burden at time of initiation of therapy as the reference point. The definition of response depends on the percent decrease in the paraprotein or free light chain levels at the trial's time points (enrollment, at LD chemotherapy, day 30, 60, 90, 180, 270 and 365) in comparison with levels at initial diagnosis. 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.

- Durability of CR/sCR will be summarized using the Kaplan-Meier estimate, where death or loss of CR/sCR response are considered events, and the time to event is measured as the time from documentation of CR/sCR response to death, loss of CR/sCR response, or last contact.

- The proportion of participants who achieve conversion to MRD negativity at any time point. MRD will be assessed by multi-color flow at 10-5 level. The proportions of participants with MRD present (MRD+) will be described using frequencies at Pre-LD Chemotherapy, Day 90, Day 180, Day 365 and disease progression post bb2121 infusion.

### 5.2.2 PROGRESSION-FREE SURVIVAL (PFS)

Progression free survival (PFS) is defined as progression of disease or death from any cause. PFS will be estimated using the Kaplan-Meier estimator. Progression of disease or death from any cause will be considered events and surviving participants 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 post bb2121 infusion.

### 5.2.3 NON-RELAPSE MORTALITY (NRM)

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

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 bb2121 infusion.

### 5.2.4 PROGRESSION OF DISEASE

Disease progression or initiation of off protocol anti-myeloma therapy is the event for this endpoint. Progression will be estimated using the cumulative incidence function, treating death prior to progression as a competing event. Patients alive without disease progression at last contact are considered censored for this event. A point estimate and 90% confidence interval will be provided for the probability of progression at 12 months post bb2121 infusion.

### 5.2.5 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 participants.

The CRS assessments will be done at Pre-LD Chemotherapy Screening (< 7 days prior to initiating LD Chemotherapy), Day 4 (+/- 2 days), Day 7 (+/- 2 days), Day 10 (+/- 2 days), Day 14 (+/- 2 days), and Day 21 (+/- 2 days) post bb2121 infusion.

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

### 5.2.6 INCIDENCE OF PROLONGED CYTOPENIAS

Overall incidence of prolonged cytopenias will be reported. Prolonged cytopenia is defined as failure to achieve ANC greater than 500/mm3 or platelet count greater than 20,000/mm3 (with or without support) by 30 days post CAR T-Cell infusion.

Proportions of participants who experience prolonged cytopenias will be tabulated.

### 5.2.7 INCIDENCE OF NEUROTOXICITY (ICANS)

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

This neurotoxicity assessment will be done at Pre-LD Chemotherapy Screening (< 7 days prior to initiating LD Chemotherapy), Day 4 (+/- 2 days), Day 7 (+/- 2 days), Day 10 (+/- 2 days), Day 14 (+/- 2 days), Day 21 (+/- 2 days), Day 30 (+/- 7 days), Day 60 (+/- 7 days), Day 90 (+/- 7 days), Day 180 (+/- 7 days), Day 270 (+/- 7 days), Day 365 (+/- 7 days) post bb2121 infusion.

The assessment will include a review of ICANS experienced during the entire assessment period and the highest grade during the assessment period will be recorded using CTCAE version 5.0.

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

### 5.2.8 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.

## 5.3 ANALYSIS OF THE EXPLORATORY ENDPOINTS

### 5.3.1 INCIDENCE OF TOXICITIES GRADE >=3 PER CTCAE VERSION 5.0

Toxicity assessments will be done at Pre-LD Chemotherapy Screening (< 7 days prior to initiating LD Chemotherapy), Pre-Maintenance Screening (< 14 days prior to maintenance initiation), Day 4 (+/- 2 days), Day 7 (+/- 2 days), Day 10 (+/- 2 days), Day 14 (+/- 2 days), Day 21 (+/- 2 days), Day

30 (+/- 7 days), Day 60 (+/- 7 days), Day 90 (+/- 7 days), Day 180 (+/- 7 days), Day 270 (+/- 7 days), Day 365 (+/- 7 days) post bb2121 infusion.

All Grade 3 or higher toxicities will be tabulated. All greater than or equal to grade 3 toxicities according to CTCAE version 5.0 will be categorized by SOC and PT using the MedDRA dictionary, and the number of AEs will be summarized by SOC, PT, and 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.

### 5.3.2 INCIDENCE OF INFECTIONS

Only grade 2 or higher infections are reported for this study.

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

The incidence of definite and probable viral, fungal and bacterial grade 2 or higher infections will be tabulated for each participant.

Grade 2 or higher definite and probable viral, fungal and bacterial infections will also be listed for each participant.

### 5.3.3 OVERALL SURVIVAL

The event is death from any cause. The time to this event is the time from initiation of LD chemotherapy to death, lost to follow up, or the end of the study, whichever comes first. Participants alive at the time of last observation are considered censored.

Overall survival will be estimated using the Kaplan-Meier estimator. Death from any cause will be the event and surviving participants 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 post LD chemotherapy initiation.

### 5.3.4 CAR T-CELL EXPANSION

Quantitation of CAR T-Cells in peripheral blood and/or bone marrow will be determined at specified time points by quantitative PCR assay, measured in copies/mcg genomic DNA.

Quantitative summaries of CAR T-Cell expansion measurements (number of participants n, Mean, Std. Dev., Median, Q1 (25%, 1st quartile), Q3 (75%, 3rd quartile), Minimum, Maximum) will be provided at pre-LD chemo, day 4, 7, 14, 21, 30, 60, 90, 180, 270, 365, and at time of progression. The data will also be presented in box plots and spaghetti plots by time point, as well as by time point and by achievement of CR/sCR at 6 mo. Peak CAR T-Cell expansion will be compared between participants who are and are not in CR/sCR at 6 months post-infusion using Mann-Whitney Wilcoxon tests. A significance level of 0.01 will be used to control for multiple testing. A patient level data listing of peak CAR T-cell expansion, presence of CAR T-cells at 6 mo, disease response status at 6 and 12 mo, and progression status at 6 and 12 mo will also be provided.

### 5.3.5 CAR T-CELL PERSISTENCE

Quantitation of CAR T-Cells in peripheral blood will be determined at day 30, 90, 180, 270, and 365 by quantitative PCR assay, measured in copies/mcg genomic DNA. Persistence will be measured in 2 ways:

- as an AUC over first 6 months post CAR T-Cell infusion and
- 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/sCR at 12 months. Last observation carried forward (LOCF) imputation method will be used to impute missing values for time points through 6 months for the calculation of $AUC_{6mos}$.

Persistence will be summarized on each participant using AUC over the first 6 months or using presence of detectable CAR T-Cells at 6 months post bb212 infusion. AUC will be compared between participants who are and are not in CR/sCR at 1 year using Mann-Whitney Wilcoxon tests. Presence of detectable CAR T-Cells at 6 months post infusion will be compared between participants who are and are not in CR/sCR at 1 year using chi-square test or Fisher's exact test as appropriate. A significance level of 0.01 will be used to control for multiple testing.

### 5.3.6 BCMA EXPRESSION

BCMA expression at specified time points 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. The BCMA expression and Immune Profiling Assessment (8mL) sampling will be done at Pre-LD Chemotherapy, Day 90 (+/- 7 days), Day 180 (+/- 7 days), Day 365 (+/- 7 days) post CAR T-Cell infusion and disease progression (only required for participants that progress while in study follow up).

BCMA expression will be compared between baseline and each post-CAR T-Cell infusion using Wilcoxon signed rank tests. The non-parametric Friedman test will be used to do a longitudinal analysis to see if there is any change from baseline. A significance level of 0.01 will be used to control for multiple testing.

### 5.3.7 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 specified time points by flow cytometry. The immune reconstitution sampling of 10mL will be done at Pre-LD Chemotherapy, Day 30 (+/- 7 days), Day 90 (+/- 7 days), Day 365 (+/- 7 days) post CAR T-Cell infusion and disease progression.

Quantitative summary measures (number of participants n, Mean, Std. Dev., Median, Q1 (25%, 1st quartile), Q3 (75%, 3rd quartile), Minimum, Maximum) will be provided for lymphocyte subsets at baseline and various time points after CAR T-Cell infusion.

## 5.4 DIFFERENCES BETWEEN THE SAP AND THE PROTOCOL

The following specifications in the SAP are different than in the protocol.

Primary Analysis Population is modified to be patients who receive a bb2121 infusion rather than those who start LD chemotherapy, and the clock for all analyses is modified to start at the time of infusion rather than the start of LD chemotherapy. As treated analysis is removed since it is now the same as the primary analysis population.

Baseline characteristics: ISS stage at diagnosis and R-ISS stage at diagnosis were added in place of myeloma risk status.

Peak CAR T-Cell expansion: These results will be displayed by visit and are not time-to-event analyses; the protocol did not specify the time to use for the analysis but since the visit target dates are based on infusion, this was updated to specify the analysis time points would be post-infusion.

The protocol has feasibility of reinitiations of lenalidomide maintenance as both a secondary and exploratory endpoint. We have removed it as an exploratory endpoint in the SAP.

# 6 TEMPLATE OF PROPOSED TABLE/FIGURE/LISTING (TFL) SHELLS

Table/Figure/Listing titles and layout are displayed in a separate Word file for illustration purposes only and may not be the final layout or wording chosen for publications or presentations. Actual format of the tables and figures may differ and will be subject to change in the final analysis report and/or publication.

# 7 REFERENCES

1 Kumar, S., et al., *International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma*. Lancet Oncol, 2016. 17(8): p. e328-e346.

# APPENDIX A:
# STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE PAGE

**BMT CTN 1902/MM CAR-T to Upgrade Response Statistical Analysis Plan**
**Reviewed and Accepted by:**

IND Sponsor:

| | | | |
|---|---|---|---|
| Signature: | | Date: | |
| Print Name: | Marcelo Pasquini, MD, MS | | MMDDDYYYY |
| Title: | IND Sponsor | | |

BMT CTN 1902:

| | | | |
|---|---|---|---|
| Signature: | | Date: | |
| Print Name: | Brent Logan | | MMDDDYYYY |
| Title: | BMT CTN Statistical Leadership | | |

BMT CTN 1902:

| | | | |
|---|---|---|---|
| Signature: | | Date: | |
| Print Name: | Ling Bai | | MMDDDYYYY |
| Title: | BMT CTN Emmes Biostatistician | | |