A Study to Evaluate the Safety of bb2121 in Subjects With High Risk, Newly Diagnosed Multiple Myeloma (NDMM)

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT04196491	RECRUITING	DECEMBER 12, 2019	SEPTEMBER 16, 2020

STUDY DESCRIPTION

Brief Summary

This is a multicenter, open-label, phase 1, single arm study intended to determine the optimal target dose and safety of bb2121 in subjects with HR (R-ISS Stage III per IMWG criteria) NDMM. Subjects should have received 3 Cycles of standard induction therapy prior to undergoing leukapheresis procedure to collect autologous mononuclear cells for manufacture of the drug product (bb2121). Following manufacture of the drug product, subjects will receive fourth cycle of induction therapy followed by lymphodepleting therapy with fludarabine and cyclophosphamide prior to bb2121 infusion. Maintenance therapy is recommended for all subjects who have received bb2121 infusion and should be initiated upon adequate bone marrow recovery or from 90-day post-bb2121 infusion, whichever is later.

Condition or Disease: Multiple Myeloma

Intervention/treatment: Biological: bb2121 carfilzomib
Drug: Fludarabine
Drug: Cyclophosphamide
Drug: Lenalidomide

Phase: Phase 1

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 60 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 1, Open-label, Multicenter Study to Evaluate the Safety of bb2121 in Subjects With High Risk, Newly Diagnosed Multiple Myeloma (KarMMa-4)

Actual Study Start Date: May 2020

Estimated Primary Completion Date: January 2025

Estimated Study Completion Date: January 2025

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Dose Escalation bb2121 autologous CAR T cells will be infused at a dose ranging from 150 - 800 x 10^6 CAR+ T cells after receiving lymphodepleting chemotherapy with a planned starting dose of 450 x 10^6 CAR+ T cells. Lenalidomide maintenance therapy is recommended for all patients and should be initiated upon adequate bone marrow recovery or from 90-day post-bb2121 infusion, whichever is later	Biological: bb2121 carfilzomib CAR-T Cell Therapy Drug: Fludarabine Lymphodepleting Chemotherapy Drug: Cyclophosphamide Lymphodepleting Chemotherapy Drug: Lenalidomide Maintenance Therapy

OUTCOME MEASURES

Primary Outcome Measures: 1. Adverse Events (AEs) [Time Frame: Up to approximately 5 years after first subject bb2121 infused]
An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE.
2. Dose-limiting toxicity (DLT) rates [Time Frame: Up to approximately 2 years after first subject bb2121 infused]
DLTs will be assessed during the DLT interval (ie, within 21 days immediately after bb2121 infusion). DLTs are defined as any bb2121 related Grade 3 to 5 toxicity.

Secondary Outcome Measures: 1. Proportion of subjects who achieved Complete Response (CR) Rate [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as proportion of subjects who achieved CR or better according to IMWG Uniform Response Criteria for Multiple Myeloma for multiple myeloma will be determined by an Investigator assessment.
2. Overall Response Rate (ORR) [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as proportion of subjects who achieved PR or better according to IMWG Uniform Response Criteria for Multiple Myeloma as determined by an Investigator assessment

3. Duration of Response (DoR) [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as time from first documentation of response (PR or better) to first documentation of progressive disease (PD) or death from any cause, whichever occurs first, for responders.
4. Time to Complete Response (TCR) [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as time from bb2121 infusion date to first documentation of CR for responders (Complete Response (CR) or better).
5. Time to start maintenance [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as time to start lenalidomide maintenance therapy post-bb2121 infusion
6. Feasibility of initiating maintenance [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Number of subjects starting the maintenance or on maintenance between D90 and D110
7. Progression-free Survival (PFS) [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as time from bb2121 infusion date to first documentation of PD, or death due to any cause, whichever occurs first.
8. Overall Survival (OS) [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Is defined as time from bb2121 infusion date to time of death due to any cause
9. Pharmacokinetics - Cmax [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Maximum transgene level
10. Pharmacokinetics - Tmax [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Time to peak transgene level
11. Pharmacokinetics - AUC [Time Frame: Approximately 2.5 years after first subject bb2121 infused]
Area under the curve of the transgene level

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
Subjects must satisfy all of the following criteria to be enrolled in the study:
1. Subject is newly diagnosed and has symptomatic Multiple Myeloma (MM) prior to initiating induction anti-myeloma therapy
2. Subject is ≥ 18 years of age at the time of initial diagnosis of MM
3. Subject has measurable disease at initial diagnosis by
- M-protein and/or
- Light chain MM without measurable disease in the serum or urine
4. Subject has high-risk MM at the time of initial diagnosis of MM per R-ISS Stage III as defined by IMWG:
- ISS Stage III and cytogenetic abnormalities with t(4; 14) and/or del(17p); and/or t(14:16) by iFISH; or;
- ISS Stage III and serum LDH > ULN
5. Subject has Eastern Cooperative Oncology Group performance ≤ 1
6. Subjects has received ≤ to 3 cycles of the following induction anti-myeloma therapy prior to enrollment:
- Cycle 1: one of the following regimens (RVd, KRd, CyBorD, D-RVd and D-KRd)
- Cycle 2 to Cycle 3: either KRd or RVd (Cycle 3 must be without dexamethasone)
Exclusion Criteria:
The presence of any of the following will exclude a subject from enrollment: The presence of any of the following will exclude a subject from enrollment:
At initial diagnosis, screening and prior to initiation of induction therapy for MM:
1. Subject has non-secretory MM
During Screening:
2. Subject received any treatments for MM other than up to 3 cycles of induction therapy per protocol
3. Subject has any of the following laboratory abnormalities:
1. Absolute neutrophil count < 1,000/µL 2. Platelet count < 50,000 mm3 3. Hemoglobin < 8 g/dL (< 4.9 mmol/L) 4. Serum creatinine clearance 13.5 mg/dL (> 3.4 mmol/L)
6. Serum aspartate aminotransferase or alanine aminotransferase > 2.5 × upper limit of normal
7. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
8. INR or aPTT > 1.5 × ULN
4. Subject has history or presence of clinically significant CNS pathology
5. Subjects has high risk for developing deep vein thrombosis or pulmonary embolus and are unable or unwilling to undergo anti-thrombotic therapy
6. Subject has peripheral neuropathy of > Grade 2 severity according to the NCI CTCAE Version 4.03 with bortezomib based induction regimen
7. Subjects has moderate or severe pulmonary hypertension
8. Subject has intolerance to components of induction regimen (KRd or RVd) or has any contraindication to one or the other drug
9. Subject has not recovered from induction therapy-related toxicities (non-hematologic) to < grade 1 CTCAE at the time of screening 10. Subject has prior history of deep vein thrombosis or pulmonary embolus (PE) within 6 months of starting study treatment 11. Subject has cardiac conditions such as: 1. Echocardiogram or multi gated acquisition assessment of left ventricular ejection fraction < 45% 2. Subject has a history of clinically significant cardiovascular disease or clinically significant ECG abnormalities 12. Subject has Pulmonary conditions such as: 1. Subject has known chronic obstructive pulmonary with a forced expiratory vol in 1 sec 50% of predicted normal. 2. Inadequate pulmonary function defined as oxygen saturation < 92 % on room air 13. Subject needs ongoing treatment with chronic immunosuppressants 14. Subject has history of primary immunodeficiency 15. Subject is seropositive for human immunodeficiency virus, chronic or active hepatitis B or active hepatitis A or C

CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

United States, Colorado	Colorado Blood Cancer Institute	Denver
United States, Florida	Mayo Clinic - Jacksonville	Jacksonville
United States, Georgia	Winship Cancer Institute of Emory University	Atlanta

United States, New Jersey	Hackensack University Medical Center	Hackensack
United States, Tennessee	Sarah Cannon Research Institute Center for Blood Cancers	Nashville

Sponsors and Collaborators

Celgene

Investigator

Study Director : Suresh Shelat, MD, PhD Celgene/BMS

MORE INFORMATION

Responsible Party :	Celgene
ClinicalTrials.gov Identifier :	NCT04196491
Other Study ID Numbers :	BB2121-MM-004, U1111-1243-5088
First Posted :	December 12, 2019
Last Update Posted :	September 16, 2020
Last Verified :	September 2020
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Yes
Plan Description:	Information relating to our policy on data sharing and the process for requesting data can be found at the following link: https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Supporting Materials:	Study Protocol, Statistical Analysis Plan (SAP), Informed Consent Form (ICF), Clinical Study Report (CSR), Analytic Code
Time Frame:	See Plan Description
Access Criteria:	See Plan Description
URL:	https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Keywords provided by Celgene:	*BB2121* *KarMMa-4* *Phase I* *NDMM* *High Risk* *R-ISS III* *RVd Dara-KRd* *Dara-RVd* *CyBorD* *BCMA* *KRd* *Multiple Myeloma* *Newly diagnosed multiple myeloma*
Additional relevant MeSH terms :	*Multiple Myeloma* *Neoplasms, Plasma Cell*