Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM)

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03651128	RECRUITING	AUGUST 29, 2018	AUGUST 11, 2020

STUDY DESCRIPTION

Brief Summary

This is a multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of bb2121 versus standard regimens in subjects with relapsed and refractory multiple myeloma (RRMM). The study is anticipated to randomize approximately 381 subjects with RRMM. Approximately 254 subjects will be randomized to Treatment Arm A and approximately 127 subjects will be randomized to Treatment Arm B.

Condition or Disease: Multiple Myeloma

Intervention/treatment: Biological: bb2121
Drug: Daratumumab
Drug: Pomalidomide
Drug: Dexamethasone
Drug: Bortezomib
Drug: Ixazomib
Drug: Lenalidomide
Drug: Carfilzomib
Drug: Elotuzumab

Phase: Phase 3

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 381 participants

Intervention Model : Parallel Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)

Actual Study Start Date: October 2018

Estimated Primary Completion Date: May 2022

Estimated Study Completion Date: November 2025

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Arm A - Administration of bb2121 bb2121 autologous CAR T cells will be infused at a dose ranging from 150 - 450 x 10^6 CAR+ T cells after receiving lymphodepleting chemotherapy	Biological: bb2121 bb2121
Experimental: Arm B- standard regimens as per Investigator's discretion The participants will receive one of following regimens dependent on the subject's most recent anti-myeloma treatment regimen: Daratumumab (DARA) in combination with pomalidomide (POM) and low-dose dexamethasone (dex) (DPd) OR DARA in combination with bortezomib (BTZ) and low-dose dex (DVd) OR Ixazomib (IXA) in combination with lenalidomide (LEN) and low-dose dex (IRd) OR Carfilzomib (CFZ) in combination with low-dose dexamethasone (Kd) OR Elotuzumab (ELO) in combination with POM and low-dose dexamethasone (EPd)	Drug: Daratumumab Daratumumab Drug: Pomalidomide Pomalidomide Drug: Dexamethasone Dexamethasone Drug: Bortezomib Bortezomib Drug: Ixazomib Ixazomib Drug: Lenalidomide Lenalidomide Drug: Carfilzomib Carfilzomib Drug: Elotuzumab Elotuzumab

OUTCOME MEASURES

Primary Outcome Measures:
1. Progression-free Survival (PFS) [Time Frame: Minimum of 5 years from randomization]
Time from randomization to the first documentation of progressive disease based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma assessed by an independent response committee (IRC) or death due to any cause, whichever occurs first.

Secondary Outcome Measures:
1. Progression-free survival after next line therapy (PFS2) [Time Frame: Minimum of 5 years from randomization]
Time from randomization to second objective disease progression or death from any cause, whichever is first
2. Overall Survival (OS) [Time Frame: Minimum of 5 years from randomization]
Time from randomization to time of death due to any cause
3. Event-free Survival (EFS) [Time Frame: Minimum of 5 years from randomization]
Time from randomization to the first documentation of progressive disease, first day when subject receives another anti-myeloma treatment or death due to any cause, whichever occurs first
4. Overall Response Rate (ORR) [Time Frame: Minimum of 5 years from randomization]
Percentage of subjects who achieved partial response (PR) or better according to IMWG Uniform Response Criteria for Multiple Myeloma as assessed by an IRC
5. Minimal Residual Disease (MRD) [Time Frame: Minimum of 5 years from randomization]
Percentage of MRD evaluable subjects that are MRD negative (defined at a minimum of 1 in 10^5 nucleated cells) using flow cytometry (EuroFlow) and next generation sequencing (NGS)
6. Complete Response (CR) Rate [Time Frame: Minimum of 5 years from randomization]
Percentage of subjects who achieved CR or better according to IMWG Uniform Response Criteria for Multiple Myeloma as assessed by an IRC
7. Duration of Response (DOR) [Time Frame: Minimum of 5 years from randomization]
Time from first documentation of response (PR or better) to first documentation of disease progression or death from any cause, whichever occurs first
8. Time to Response (TTR) [Time Frame: Minimum of 5 years from randomization]
TTR is calculated as the time from randomization to the initial documented response (PR or better) based on IMWG guideline for responders
9. Adverse Events (AEs) [Time Frame: Minimum of 5 years from randomization]
Number of participants with adverse events
10. Pharmacokinetics- Cmax [Time Frame: Minimum 5 years after bb2121 infusion]
Maximum peak in bb2121 chimeric antigen receptor (CAR) T cells
11. Pharmacokinetics- tmax [Time Frame: Minimum 5 years after bb2121 infusion]
Time to peak of bb2121 CAR T cells
12. Pharmacokinetics- AUC [Time Frame: Minimum 5 years after bb2121 infusion]
Area under the curve of CAR T cells
13. Pharmacokinetics- t-last [Time Frame: Minimum 5 years after bb2121 infusion]
Time to last measurable CAR T cells
14. Pharmacokinetics- AUC0-28days [Time Frame: Minimum 5 years after bb2121 infusion]
Area under the curve of CAR T cells from time zero to Day 28
15. Subject-reported outcomes as measured by European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC-QLQ-C30) [Time Frame: Minimum of 5 years from randomization]
Questionnaire will be used as a measure of health-related quality of life
16. Subject-reported outcomes as measured by EuroQoL Group European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) Health Questionnaire [Time Frame: Minimum of 5 years from randomization]
Is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal
17. Subject-reported outcomes as measured by European Quality of Life Multiple Myeloma Module (EORTC-QLQ-MY20) [Time Frame: Minimum of 5 years from randomization]
Is a 20-item myeloma module intended for use among patients varying in disease stage and treatment modality
18. Time to next antimyeloma treatment [Time Frame: Minimum of 5 years from randomization]
Time from randomization to first day when subject receives another anti-myeloma treatment

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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 the following criteria to be enrolled in the study:
1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements within this protocol and for a subject randomized to Treatment Arm A, subject agrees to continued follow-up for up to 15 years as mandated by the regulatory guidelines for gene therapy trials.
4. Subject has documented diagnosis of MM and measurable disease, defined as:
- M-protein (serum protein electrophoresis [sPEP] or urine protein electrophoresis [uPEP]): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours and/or
- Light chain MM without measurable disease in the serum or urine: Serum immunoglobulin free light chain ≥ 10 mg/dL (100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio
5. Subject has received at least 2 but no greater than 4 prior MM regimens.
6. Subject has received prior treatment with DARA, a proteasome inhibitor- and an immunomodulatory compound-containing regimen for at least 2 consecutive cycles.
7. Subject must be refractory to the last treatment regimen. Refractory is defined as documented progressive disease during or within 60 days (measured from the last dose of any drug within the regimen) of completing treatment with the last anti-myeloma regimen before study entry.
8. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.
9. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Recovery to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 peripheral neuropathy.
11. Adequate vascular access for leukapheresis
12. Females of childbearing potential (FCBP) must:
a. Have negative pregnancy test(s) as verified by the Investigator. This applies even if the subject practices true abstinence from heterosexual contact.
b. Either practice true abstinence from heterosexual contact or agree to use, and be able to comply with, effective measures of contraception without interruption.
c. Agree to abstain from breastfeeding during study participation. d. Refrain from tissue donation including egg cell donation or any other tissue/blood/organ donations.
13. Male subjects must:
a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, even if he has undergone a successful vasectomy.
b. Refrain from tissue donation including sperm or any other tissue/blood/organ donations.
14. Only subjects that would be considered for any of the 5 proposed standard regimens (DPd, DVd, IRd, Kd, or EPd), as judged by the investigator, should be included in the study.
Exclusion Criteria:
The presence of any of the following will exclude a subject from enrollment:
1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject has nonsecretory multiple myeloma (MM).
5. Subject has any of the following laboratory abnormalities:
a. Absolute neutrophil count (ANC) < 1,000/µL b. Platelet count: < 75,000/µL in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/µL in subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level) c. Hemoglobin < 8 g/dL (< 4.9 mmol/L) (it is not permissible to transfuse a subject to reach this level) d. Serum creatinine clearance (CrCl) 13.5 mg/dL (> 3.4 mmol/L) f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN) g. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome h. International normalized ratio (INR) or activated partial thromboplastin time (aPTT) > 1.5 × ULN, or history of Grade ≥ 2 hemorrhage within 30 days, or subject requires ongoing treatment with chronic, therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors)
6. Subject has inadequate pulmonary function defined as oxygen saturation (SaO2) < 92% on room air. 7. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years • Basal cell carcinoma of the skin • Squamous cell carcinoma of the skin - Carcinoma in situ of the cervix - Carcinoma in situ of the breast - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system) or prostate cancer that can be treated with curative intent 8. Subject has active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome or amyloidosis. 9. Subject with known central nervous system (CNS) involvement with myeloma. 10. Subject has clinical evidence of pulmonary leukostasis and disseminated intravascular coagulation. 11. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. 12. Subject has a 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. 13. Subject was treated with DARA in combination with POM with or without dex (DP±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DPd as bridging therapy but may receive DVd, IRd, Kd or EPdas bridging as per Investigator's discretion if randomized to Treatment Arm A. 14. Subject was treated with DP±d as part of their most recent anti-myeloma treatment regimen, cannot receive DPd if randomized to Treatment Arm B but may receive DVd, IRd, Kd, or EPd as per Investigator's discretion. 15. Subject was treated with DARA in combination with BTZ with or without dexamethasone (DV±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DVd as bridging therapy but may receive DPd, IRd, Kd, or EPd as bridging as per Investigator's discretion if randomized to Treatment Arm A. 16. Subject was treated with DV±d as part of their most recent anti-myeloma treatment regimen, cannot receive DVd if randomized to Treatment Arm B but may receive DPd, IRd, Kd, or EPd as per Investigator's discretion. 17. Subject was treated with IXA in combination with LEN with or without dexamethasone (IR±d) as part of their most recent anti-myeloma treatment regimen, cannot receive IRd as bridging therapy but may receive DPd, DVd, Kd, or EPd as bridging as per Investigator's discretion if randomized to Treatment Arm A. 18. Subject was treated with IR±d as part of their most recent anti-myeloma treatment regimen, cannot receive IRd if randomized to Treatment Arm B but may receive DPd, DVd, Kd, or EPd as per Investigator's discretion. 19. Previous history of an allogeneic hematopoietic stem cell transplantation, treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy. 20. Subject has received autologous stem cell transplantation (ASCT) within 12 weeks prior to randomization. 21. Subject has received any of the following within the last 14 days prior to randomization: a. Plasmapheresis b. Major surgery (as defined by the Investigator) c. Radiation therapy other than local therapy for myeloma-associated bone lesions d. Use of any investigational agents and systemic anti-myeloma drug therapy 22. Echocardiogram (ECHO) or multigated acquisition (MUGA) with left ventricular ejection fraction (LVEF) < 45%. 23. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled or intranasal corticosteroids are allowed. 24. Subject is positive for human immunodeficiency virus (HIV-1 and HIV-2), chronic or active hepatitis B or active hepatitis A or C. 25. Subject has uncontrolled systemic fungal, bacterial, viral or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management. 26. Subject has a history of class III or IV congestive heart failure (CHF) or severe nonischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months prior to randomization. 27. Hypersensitivity to DARA, thalidomide, lenalidomide, POM, BTZ, IXA, CFZ, ELO or dexamathasone. This includes rash ≥ Grade 3 during prior thalidomide, POM or lenalidomide therapy. 28. Subject with known hypersensitivity to any component of bb2121 product, cyclophosphamide, fludarabine, and/or tocilizumab or hypersensitivity to the excipients contained in the formulation of DARA, POM, LEN, IXA, BTZ, CFZ, ELO or dexamethasone. 29. Subject is a female who is pregnant, nursing, or breastfeeding 30. For a subject randomized to Treatment Arm B and will be on a POM- or LEN-containing regimen; unable or unwilling to undergo protocol required thromboembolism prophylaxis. 28 Subject is intolerant to bortezomib, or has acute diffuse infiltrative pulmonary and pericardial disease, subject cannot receive DVd as bridging therapy if randomized to Treatment Arm A or cannot receive DVd if randomized to Treatment Arm B. 31. Subject was treated with K±d as part of their most recent anti-myeloma treatment regimen, cannot receive Kd if randomized to Treatment Arm B but may receive DPd, DVd, IRd or EPd as per Investigator's discretion. 32. Subject was treated with EP±d as part of their most recent anti-myeloma treatment regimen, cannot receive EPd if randomized to Treatment Arm B but may receive DPd, DVd, Kd or IRd as per Investigator's discretion.

CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

United States, Alabama	University of Alabama Birmingham	Birmingham
United States, Arizona	Mayo Clinic Arizona	Scottsdale
United States, California	UCLA Medical Centre-Santa Monica Hematology and Oncology	Los Angeles
United States, Colorado	University of Colorado Anschutz Cancer Pavilion	Aurora
United States, Florida	Mayo Clinic - Jacksonville	Jacksonville
United States, Florida	Moffit Cancer Center	Tampa
United States, Georgia	Emory University Hospital	Atlanta
United States, Georgia	Blood and Marrow Transplant Group of Georgia	Atlanta
United States, Illinois	Northwestern University Feinberg School of Medicine	Chicago
United States, Indiana	Indiana University Health Melvin and Bren Simon Cancer Center	Indianapolis
United States, Kansas	The University of Kansas Hospital	Westwood
United States, Maryland	Greenebaum University of Maryland	Baltimore
United States, Massachusetts	Mass General	Boston
United States, Massachusetts	Dana Farber Cancer Institute (DFCI)	Boston
United States, Michigan	University of Michigan Comprehensive Cancer Center	Ann Arbor
United States, Minnesota	Mayo Clinic - Rochester	Rochester
United States, Missouri	Washington University School of Medicine, Siteman Cancer Center	Saint Louis
United States, New Jersey	Hackensack University Medical Center	Hackensack
United States, New York	Mount Sinai Medical Center	New York
United States, New York	New York Presbyterian Hospital Weil Cornell Medical College	New York
United States, North Carolina	Duke Clinical Research Institute Duke University School of Medicine	Durham
United States, Pennsylvania	Thomas Jefferson University	Philadelphia
United States, Pennsylvania	Fox Chase Cancer Center	Philadelphia
United States, Pennsylvania	University of Pittsburgh Medical Center - William M. Cooper Ambulatory Care Pavilion	Pittsburgh
United States, Tennessee	Sarah Cannon Research Institute Center for Blood	Nashville
United States, Texas	Baylor University Medical Center at Dallas	Dallas
United States, Texas	MD Anderson Cancer center	Houston
United States, Utah	University of Utah Huntsman Cancer Center	Salt Lake City
United States, Washington	Swedish Cancer Institute	Seattle
United States, Wisconsin	University of Wisconsin Carbone Cancer Center	Madison
Belgium	UZ Leuven	Leuven
Canada, Alberta	Tom Baker Cancer center	Calgary
Canada, Ontario	Princess Margaret Cancer Centre	Toronto
France	CHRU Lille	Lille Cedex
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France	Hospital Saint-Louis - APHP	Paris
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Spain	Hospital Universitario de Salamanca	Salamanca
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Sponsors and Collaborators

Celgene

Investigator

Study Director :	Steven Novick, MD	Celgene

MORE INFORMATION

Responsible Party :	Celgene
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Studies a U.S. FDA-regulated Device Product:	No
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