Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre (Version January 2024)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFECTS OF EDP-938 IN HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS WITH ACUTE RESPIRATORY SYNCYTIAL VIRUS INFECTION OF THE UPPER RESPIRATORY TRACT

Protocol: RSVTx Study

Inclusion Criteria

1. Age: 18-75
2. Allo or Auto SCT with any conditioning regimen
3. ALC < 500 cells/micL
4. Lab confirmed Dx.
5. New onset of URTI within 3 days before signing consent
6. No pneumonia in Chest XR/CT
7. O2 ≥92 % on room air.
8. BMI: ≥18 kg/m2 and ≤40 kg/m2.
9. Childbearing age women: negative pregnancy test, should agree to use 2 contraception methods
10. Males with childbearing-age wife: should agree to use 2 contraception methods
11. No sperm donation until 90 days after last dose
12. Autos <6 months (upcoming amendment)

Exclusion Criteria

1. Pneumonia
2. Other viral infection within 7 days before consent
3. Other significant IDs within 14 days before consent
4. HIV, pregnant, drug use, alcohol abuse
5. Prolonged QT in ECG: Fridericia's (QTcF) that is >500 milliseconds
6. Medications affecting CYP3A4 (except azole antifungals)
7. Any anti-RSV Ab in previous 30 day
8. EGFR< (MDRD) <50 mL/min

Contact: Dr. Christine Chen– **Open for Enrollment**

AN OPEN-LABEL, 2-ARM, MULTICENTER, RANDOMIZED PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ELRANATAMAB (PF-06863135) + DARATUMUMAB + LENALIDOMIDE VERSUS DARATUMUMAB + LENALIDOMIDE + DEXAMETHASONE IN TRANSPLANT-INELIGIBLE PARTICIPANTS WITH NEWLY-DIAGNOSED MULTIPLE MYELOMA.

Protocol Number: C1071006 (MAGNETISMM-6)

Inclusion Criteria

1. Participant's age ≥18 years at screening visit.

2. Diagnosis of MM as defined according to IMWG criteria, including measurable disease based on IMWG criteria as defined by at least 1 of the following (as assessed by the central laboratory for Part 2):

- Serum M-protein ≥0.5 g/dL;
- Urinary M-protein excretion ≥200 mg/24 hours;
- Involved FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

3. **Part 1 only**: Participant with NDMM or RRMM. NDMM participant must be transplant-ineligible as defined by age ≥65 years or transplant-ineligible as defined by age <65 years with comorbidities impacting the possibility of transplant.
Participants with RRMM must have received 1-2 prior lines of MM therapy including at least one IMiD and one PI.

Part 2 only: Participant has NDMM and is transplant-ineligible as defined by age ≥65 years or is transplant-ineligible as defined by age <65 years with comorbidities impacting the possibility of transplant.

4. Eastern Cooperative Oncology Group (ECOG) performance status <2.

5. BM function characterized by the following:
   a. ANC ≥1.0 × 109/L (use of G-CSFs is permitted if completed at least 7 days prior to planned start of dosing);
   b. Platelet count ≥75,000/μL if <50% of BM nucleated cells are plasma cells, or ≥50,000/μL if ≥50% of BM nucleated cells are plasma cells (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and
   c. Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing).

6. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L), or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

7. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.

Exclusion Criteria

Medical Conditions:

1. Smoldering MM or MGUS or Waldenströms Macroglobulinemia or Plasma cell leukemia defined as ≥20 % circulating plasma cells in the peripheral blood with an absolute plasma cell count of more than 2 × 109/L, or Systemic light chain amyloidosis, or POEMS Syndrome.

2. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:

   a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);

   b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);

   c. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);

   d. Prolonged QT syndrome (or QTcF >470 msec at screening).

   e. LVEF <40% as determined by a MUGA scan or ECHO.

3. Ongoing Grade 3 or higher peripheral sensory or motor neuropathy, history of GBS or GBS variants, or history of any Grade >3 peripheral motor polyneuropathy.

4. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) COVID-19/SARS-CoV-2, HBV, HCV, and known HIV or AIDS-related illness. Active infections must be resolved at least 14 days prior to enrollment. Comments regarding specific circumstances

follow.

a. **HIV:** In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes could be considered eligible. Potential eligibility for a specific HIV positive protocol candidate should be evaluated and discussed with the Sponsor prior to any screening, based on current and past CD4 and T-cell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions will be taken into consideration.

b. **HBV/HCV:** Relevant laboratory tests should be performed at screening. Refer to CDC website (https://www.cdc.gov/hepatitis/index.htm) for further details.

c. HBV:

i. This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis).
ii. However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.
iii. Participants with positive anti-HBcAb but negative HBsAg and anti-HBsAb profile are eligible if HBV DNA is not detected.

d. **HCV:** Positive HCV antibody is indicative of infection but may not necessarily render a potential participant ineligible, depending on clinical circumstances. If exposure to HCV is recent, HCV antibody may not have yet turned positive. In this circumstance it is recommended to test HCV RNA. Refer to CDC website for further details (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).

5. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ, or Stage 0/1 with minimal risk of recurrence per investigator.

6. Participants with known or suspected hypersensitivity to the study interventions or any of their excipients.

7. Participants with known or suspected CNS or clinical signs of myelomatous meningeal involvement.

8. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

- Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap band surgery. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed (assuming no drug interaction potential).

Prior/Concomitant Therapy:

9. Part 1 only:

a. Previous treatment with a BCMA-directed therapy, anti-CD38-directed therapy within 6 months preceding the first dose of study intervention in this study, or refractory to prior anti-CD38-directed therapy (disease progression while on therapy or within 60 days of the last dose of therapy or participants who have not achieved at least a MR on prior anti-CD38-directed therapy).
b. Primary refractory MM, defined as participants who have never achieved at least a MR with any prior anti-MM therapy based on investigator assessment using IMWG criteria.
c. Stem cell transplant ≤3 months prior to first dose of study intervention or active GVHD.

10. Participants who are unable to tolerate lenalidomide, daratumumab, or discontinued prior lenalidomide or daratumumab due to treatment-related toxicity (Part 1 only).

11. **Part 2 only:** Previous systemic treatment for MM except for a short course of corticosteroids (ie, up to 4 days of 40 mg dexamethasone or equivalent before the first dose of study intervention).

12. Live attenuated vaccine administered within 4 weeks of the first dose of study intervention.

Prior/Concurrent Clinical Study Experience:

13. Administration of investigational product (eg, drug or vaccine) concurrent with study intervention or within 30 days (or as determined by the local requirement) preceding the first dose of study intervention used in this study. A participant may be eligible if they are in the follow-up phase of an investigational study if they meet the criterion for time elapsed from previous administration of investigational product. Cases must be discussed with Sponsor's medical monitor to judge eligibility.

Diagnostic Assessments:

14. Hepatic and renal function characterized by the following:

    a. Total bilirubin >1.5 × ULN (>3 × ULN if documented Gilbert's syndrome);

    b. AST >2.5 × ULN and ALT >2.5 × ULN.

    c. **Part 1 only (NDMM and RRMM population):** Renal function defined according to local institutional standard method: eGFR <60 mL/min/1.73 m2 using the 2021 CKD-EPI 2021 Creatinine Equation* or estimated CrCl <60 mL/min using Cockcroft Gault formula. If both formulae are calculated, the higher of the two values may be used. A 24-hour urine collection for CrCl may also be used in equivocal cases where amyloidosis is suspected.
    *https://www.kidney.org/content/ckd-epi-creatinine-equation-2021

    Part 2 only (NDMM population): Renal function defined according to local institutional standard method: eGFR <30 mL/min/1.73 m2 using the 2021 CKDEPI Creatinine Equation* or estimated CrCl <30 mL/min using Cockcroft Gault formula. If both formulae are calculated, the higher of the two values may be used. A 24-hour urine collection for CrCl may also be used in equivocal cases where amyloidosis is suspected.
    *https://www.kidney.org/content/ckd-epi-creatinine-equation-2021

Contact: Dr. Suzanne Trudel /Naomi Kimbriel – **Open Enrollment**

A RANDOMIZED, 2-ARM, PHASE 3 STUDY OF ELRANATAMAB (PF-06863135) VERSUS LENALIDOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA WHO ARE MINIMAL RESIDUAL DISEASE-POSITIVE AFTER UNDERGOING AUTOLOGOUS STEM-CELL TRANSPLANTATION

Protocol Number: C1071007 (MAGNETISMM-7)

Inclusion Criteria

1. Participant's age ≥ 18 years (or the minimum country-specific age of consent if >18) at Visit 1 (Screening).
2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Male participants and female participants of childbearing potential must agree to use methods of contraception according to the lenalidomide approved country label.

4. Diagnosis of MM as defined according to IMWG criteria (Rajkumar et al, 2014).
   - History of 3 to 8 cycles of induction therapy for newly diagnosed MM, followed by high-dose therapy and ASCT. Randomization must occur within 120 days from the stem cell transplant. For participants who receive consolidation therapy after ASCT, randomization must occur within 60 days of consolidation and within 6 months from ASCT.
5. PR or better according to IMWG criteria at the time of randomization.

6. MRD positive (≥10-5) at screening by central laboratory NGS test (Adaptive Biotechnologies clonoSEQ® assay).

- **Must have an archived bone marrow aspirate sample(s) that identifies the dominant malignant (index) clone that is used to track MRD status by central laboratory assessment (Adaptive Biotechnologies clonoSEQ® assay). This sample should preferably be collected before induction treatment (e.g., at diagnosis) or before transplant.** A sample collected after transplant may be accepted with sponsor approval. If a participant has an Adaptive Biotechnologies' clonoSEQ® MRD assay result from previous testing that identifies the index multiple myeloma clone, and the result is retrievable and useable in this study, an archival sample will not be required.
- **A bone marrow aspirate sample collected during screening is required to determine MRD status.**

7. Eastern Cooperative Oncology Group (ECOG) performance status grade ≤1.
8. LVEF ≥40% as determined by a MUGA scan or ECHO.

9. Adequate hepatic function characterized by the following:
   - Total bilirubin ≤2 × ULN (≤3 × ULN if documented Gilbert's syndrome);
   - AST ≤2.5 × ULN; and
   - ALT ≤2.5 × ULN.

10. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft-Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method).

11. Adequate post-ASCT recovery of BM function characterized by the following:
    - ANC ≥1.0 × 109/L (use of G-CSF is permitted if completed at least 7 days prior to planned start of dosing, G-CSF should not be used to reach this level);
    - Platelets ≥75 × 109/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and
    - Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing).
12. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L).

13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤ 1.

<u>Exclusion Criteria</u>

15. Plasma cell leukemia
16. POEMS syndrome
17. Systemic amyloid light chain amyloidosis
18. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
    - Acute myocardial infarction or acute coronary syndromes (e.g., unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);
    - Clinically significant cardiac arrhythmias (e.g., uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
    - Thromboembolic or cerebrovascular events (e.g., transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);
    - Prolonged QT syndrome or QTcF ≥470 msec at screening.

19. Ongoing Grade ≥ 3 peripheral sensory or motor neuropathy.
20. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
21. Live attenuated vaccine within 4 weeks of the first dose.
22. Known or suspected hypersensitivity to the study interventions or any of its excipients.
23. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
24. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the

participant inappropriate for the study.
25. Previous MM maintenance treatment.
26. Prior treatment with BCMA targeted therapy.
27. Previous administration with an investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
28. Serum pregnancy test (for females of childbearing potential) positive at screening.

29. Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness. Comments regarding specific circumstances follow.
    - COVID-19/SARS-CoV-2: This protocol excludes patients with active infections, as noted above. While SARS-CoV-2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a patient has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, he/she is excluded.
    - HIV: In equivocal cases, participants whose viral load is negative may be eligible. HIV seropositive participants who are otherwise healthy and at low risk for AIDS-related outcomes could be considered eligible. Potential eligibility for a specific HIV positive protocol candidate should be evaluated and discussed with the sponsor prior to any screening, based on current and past CD4 and T-cell counts, history (if any) of AIDS defining conditions (e.g., opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions will be taken into consideration.
    - HBV/HCV: Relevant laboratory tests should be performed at screening and added to the table in Appendix 2 Clinical Laboratory Tests. Refer to CDC website (https://www.cdc.gov/hepatitis/index.htm) for further details.
    - HBV:
        - This criterion excludes participants with a positive HBsAg (i.e., either acute or chronic active hepatitis).
        - However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.
        - Patients with positive anti-HBcAb but negative HBsAg and anti-HBsAb profile may, depending on clinical circumstances, be eligible. Discussion with the sponsor is indicated.

    a. HCV
        - Positive HCV antibody is indicative of infection but may not necessarily render a potential candidate ineligible, depending on clinical circumstances. Discussion with the sponsor is indicated. If exposure to HCV is recent, HCV antibody may not have yet turned positive. In this circumstance it is recommended to test for HCV RNA. Refer to CDC website for further details (https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf).

Contact: Dr. Suzanne Trudel /Olga Levina – **Open Enrollment**

A PHASE 1/2, MULTICENTER, OPEN-LABEL, STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN, AND EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF CC-92480 IN COMBINATION WITH STANDARD TREATMENTS IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM) AND NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

Protocol Number: CC-92480-MM-002

Inclusion Criteria:

1. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Females of childbearing potential (FCBP) must:

    a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.

    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with two reliable forms of contraception as defined in the Pregnancy Prevention Plan (PPP) without interruption, 28 days prior to starting CC-92480, during the study treatment (including

during dose interruptions), and for 28 days after the last dose of CC-92480 or 90 days after the last dose of BTZ (**for Cohorts A, D and G**) or DARA (**for Cohorts B and E**) or 6 months after the last dose of CFZ (**for Cohorts C and F**), whichever is later.

Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point and, 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 (ie, has had menses at any time in the preceding 24 consecutive months).

3. Male subjects must:

a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use of a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study (even during dose interruptions) and for at least 3 months following study treatment discontinuation, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and coitus interruptus (withdrawal) are not acceptable methods of contraception.

4. Males must agree to refrain from donating sperm or semen while on study treatment, and for at least 3 months following last dose of study treatment. Females must refrain from egg cell (ova) donation while on study treatment, and for 28 days after the last dose of CC-92480.

5. All subjects must agree to refrain from donating blood while on study treatment and for 28 days after the last dose of study treatment.

6. All male and female subjects must follow all requirements defined in the PPP (Pregnancy Prevention Plan: study nurse will train the subjects on this)

For subjects in Cohorts A, B, C, D, E and F, the following inclusions will also apply:

7. Subject has documented diagnosis of MM and measurable disease, defined as:

a. M-protein quantities ≥ 0.5 g/dL by serum protein electrophoresis (sPEP) or ≥ 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP) and/or

b. Serum free light chain (FLC) levels > 100 mg/L (10 mg/dL) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in subjects without measurable disease in the serum or urine

8. Subject has received 2 to 4 (**for Cohorts A, B, and C**) or 1 to 3 (**Cohorts D, E and F**) prior anti-myeloma regimens. Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered as one regimen.

9. Subject has received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles.

10. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.

11. Subject must have documented disease progression during or after their last anti-myeloma regimen.

12. **Cohort F**: Prior therapy with a proteasome inhibitor (PI), excluding carfilzomib, is allowed as long as the subject had at least a PR to prior PI therapy, was not removed from PI therapy due to toxicity, and will have at least a 6-month PI treatment-free interval from last dose received until first study treatment (Subjects may receive maintenance therapy with drugs that are not in PI class during this 6-month treatment free interval).

For subjects in Cohort G, the following inclusions will also apply:

13. Considered by the investigator to be eligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT) according to the institution's criteria based on age, medical history, cardiac and pulmonary status, overall health and condition, co-morbid condition(s), physical examination, and laboratory.

14. Subject must have documented diagnosis with previously untreated symptomatic MM as defined by the criteria below (Rajkumar, 2016):

- MM diagnostic criteria;
  - Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma*
  - Any one or more of the following myeloma defining events:
    - one or more of the following Myeloma-related organ dysfunction (at least one of the following);
      - [C] Calcium elevation (serum calcium > 0.25 mmol/L [> 1 mg/dL] higher than the upper limit of laboratory normal or > 2.75 mmol/L (> 11 mg/dL))
      - [R] Renal insufficiency (serum creatinine > 2 mg/dl) [> 177 μmol/L] or creatinine clearance < 40 ml/min
      - [A] Anemia (hemoglobin < 10 g/dl or > 2 g/dL below the lower limit of laboratory normal)
      - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT
    - one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage* ≥ 60%
- Abnormal serum free light-chain ratio ≥ 100 (involved kappa) or < 0.01 (involved lambda) and involved FLC level must be ≥ 100 mg/L
- >1 focal lesion detected by magnetic resonance imaging (MRI) (at least 5 mm in size)

IN ADDITION, have measurable disease, as assessed by central laboratory, defined by any of the following:

- Immunoglobulin (Ig)G myeloma: serum M-protein level ≥ 1.0 g/dL or urine Mprotein level ≥ 200 mg/24 hours; or
- IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in serum or urine: serum FLC ≥ 100 mg/L and abnormal kappa lambda (κ/λ) ratio

Exclusion criteria:

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 any of the following laboratory abnormalities:
   a. Absolute neutrophil count (ANC) < 1,000/μL (for Phase 1 without growth factor support for ≥ 7 days [≥ 14 days for pegfilgrastim])
   b. Platelet count: < 75,000/μL (it is not permissible to transfuse a subject to reach this level)
   c. Hemoglobin < 8 g/dL (< 4.9 mmol/L)
   d. Creatinine clearance (CrCL) < 45 mL/min
   e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
   f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN
   g. Serum total bilirubin > 1.5 x ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
   h. Prothrombin time (PT)/international normalized ration (INR) > 1.5 x ULN or partial thromboplastin time (PTT) > 1.5 x ULN, (for subjects not receiving therapeutic anticoagulation).

Note: Subjects receiving therapy for a thromboembolic event that occurred >3 months prior to enrollment are eligible as long as they are on a stable regimen of anticoagulation with warfarin, low-molecular weight heparin or other approved therapeutic anticoagulation regimen.
5. Subject has peripheral neuropathy ≥ Grade 2
6. Subject with gastrointestinal disease that may significantly alter the absorption of CC-92480.
7. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies:

- 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 TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative

8. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or clinically significant amyloidosis.
9. Subject with known central nervous system (CNS) involvement with myeloma.
10. Subject has received immunosuppressive medication within the last 14 days of initiating study treatment. The following are exceptions to this criterion:

- Intranasal, inhaled, topical or local corticosteroid injections (e.g., intra-articular injection).
- Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent.
- Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication).

11. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:

- Left ventricular ejection fraction (LVEF) < 45% as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan at Screening.
- Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiogram (ECG) finding at Screening
- A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval > 470 milliseconds (msec) using Fridericia's QT correction formula; a history of or current risk factors for Torsades de Pointe

(eg, heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval
- Congestive heart failure (New York Heart Association Class III or IV).
- Myocardial infarction within 12 months prior to starting study treatment.
- Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris
- History of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, pericardial disease or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker

12. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment.
13. Concurrent administration of strong CYP3A modulators. For full list of modulators, refer to: https://drug-interactions.medicine.iu.edu/MainTable.aspx
14. Subject is a female who is pregnant, nursing or breastfeeding, or who intends to become pregnant during the participation in the study.
15. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B, or active hepatitis A or C.
16. Subject has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, pomalidomide, BTZ (**for Cohorts A, D and G**), DARA (**for Cohort B**), CFZ (**for Cohort C**) or dexamethasone.
17. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480, BTZ (**for Cohorts A, D and G**), DARA (**for Cohorts B and E**), CFZ (**for Cohorts C and F**) or dexamethasone.
18. Contraindications to the standard treatment regimens, per local prescribing information.
19. Subject is unable or unwilling to undergo protocol required thromboembolism prophylaxis.

For subjects in Cohorts A, B, C, D, E and F, the following exclusions will also apply:
20. Subject received any of the following within the last 14 days of initiating study treatment:
    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 systemic anti-myeloma drug therapy
21. **Cohorts A and D**: Subjects who had progression during treatment or within 60 days of the last dose of BTZ or discontinued BTZ due to toxicity.
22. **Cohort B**: Subjects who had progression during treatment or within 60 days of the last dose of DARA or discontinued DARA due to toxicity.
23. **Cohort C**: Subjects who had progression during treatment or within 60 days of the last dose of CFZ or discontinued CFZ due to toxicity.
24. **Cohorts D, E and F**: Previous treatment with pomalidomide (POM).
25. **Cohort E:** Previous treatment with DARA.
26. **Cohort F**: Previous treatment with CFZ.
27. Subject used any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment.
28. **Cohorts B and E**: Subject has received previous allogeneic stem cell transplantation or received autologous stem cell transplantation within 12 weeks prior to starting study treatment.
29. **Cohorts B and E**: Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal.
30. **Cohorts B and E**: Subject has known moderate or severe persistent asthma, or currently has uncontrolled asthma of any classification.
31. **Cohorts C and F**: Subject has mild hepatic impairment defined as elevated bilirubin > 1.0 but < 1.5 x ULN or normal bilirubin with any elevation of AST.

For subjects in Cohort G, the following exclusion criteria will also apply
32. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of initiating study treatment]).

Contact: Dr. Suzanne Trudel/Trina Wang – **Open for enrollment**

A PHASE 2 MULTI-CENTER, OPEN LABEL STUDY OF ISATUXIMAB ADDED TO STANDARD CYBORD INDUCTION AND LENALIDOMIDE MAINTENANCE TREATMENTS IN NEWLY DIAGNOSED, TRANSPLANT ELIGIBLE MULTIPLE MYELOMA

Protocol CMRG 008

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Males or females, age 18 to 75 years of age.
2. ECOG performance status score of 0, 1 or 2.
3. Life expectancy of at least 9 months
4. Measurable disease according to the IMWG criteria defined as
a. Serum monoclonal paraprotein (M-protein) ≥ 10 g/L (if IgG) or ≥5g/L (if IgA, D, E or M)
b. Urine M-protein ≥ 200 mg/24 h
c. Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/L and an abnormal serum free light chain ratio (< 0.26 or > 1 .65) if no M-protein detected in serum or urine
5. Newly Diagnosed Symptomatic Multiple Myeloma by IMWG criteria (Appendix 8)
6. The following laboratory results must be met within 10 days of first study drug administration:
a. ANC ≥ 1.0 x 109/L
b. Hemoglobin ≥ 80 g/L (transfusions permitted)
c. Platelets ≥ 70 x 109/L (or ≥50 x 109/L if ≥50% plasmacytosis in bone marrow.
d. Calculated CrCl ≥ 30 mL/min
e. AST and ALT ≤ 3.0 x ULN
f. Total bilirubin ≤ 2 x ULN unless known to have Gilbert's disease
g. Corrected serum calcium ≤ 3.5 mmol/L

Exclusion Criteria

1. Prior exposure to Isatuximab (or other anti-CD38 monoclonal antibody)
2. Prior treatment for Multiple Myeloma (MM) with the exception of corticosteroids not exceeding a total dose specified below:
3. Subjects who have received steroids within 2 weeks prior to starting study treatment or who have not recovered from side effects of such therapy. Concomitant therapy medications that include corticosteroids are allowed if subject receive ≤10 mg of prednisone per day, or equivalent, as indicated for other medical conditions, or up to 100 mg of hydrocortisone as pre-medication for administration of certain medications or blood products prior to enrolment in this study.
4. Prior history of malignancies, other than MM, unless the subject has been free of the disease for 3 years or longer. Exceptions include the following:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix or breast
    c. Adenocarcinoma of the prostate (TNM stage of T1 a or T1 b)
    5. Other concurrent severe and/or uncontrolled medical conditions (i.e. uncontrolled diabetes, active or uncontrolled infection, acute diffuse pulmonary disease, pericardial disease, uncontrolled thyroid dysfunction or uncontrolled severe arterial hypertension) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
    6. History of or current uncontrolled cardiovascular disease including:
    a. Unstable angina, myocardial infarction, or known congestive heart failure Class III/IV (Appendix 5) within the preceding 12 months
    b. Transient ischemic attack within the preceding 3 months, pulmonary embolism within the preceding 2 months.
    c. Any of the following: sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, cardiac arrest, Mobitz II second degree heart block or third-degree heart block; known presence of dilated, hypertrophic, or restrictive cardiomyopathy.
    d. QTc prolongation as confirmed by ECG assessment at screening (QTc >470 milliseconds).
    e. Poorly controlled severe arterial hypertension.
    7.Known HIV positivity or active infectious hepatitis B or C
    8. Known allergies, hypersensitivity to mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Isatuximab PM), or known sensitivity to mammalian-derived products, if not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents.
    9. Known CNS involvement, plasma cell leukemia or amyloidosis.

Contact: Dr. Sita Bhella/ Elena Talovikova – **Open for Enrollment**

STUDY TITLE: DOES FRAILTY ASSESSMENT PREDICT IMMEDIATE POST-TRANSPLANT TOXICITY IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANT? A PILOT STUDY
Protocol Short Name: Frailty Assessment Pre-ASCT in Myeloma

Non-Interventional

Inclusion criteria:

1. Newly diagnosed MM patients, who are eligible and cleared to proceed with their first ASCT, as determined by the Princess Margaret autologous transplant team
2. Age ≥ 18 years at the time of signing the consent
3. Able to understand the consent and agrees to participate in the study.
4. Subsequent follow up visits must be at Princess Margaret Cancer Centre

Exclusion criteria:

1. Patient deemed unfit or ineligible to proceed with ASCT.
2. Concurrent *plasma cell disorder such as amyloid or POEMS*, or other hematological malignancy
3. Any serious medical condition or psychiatric illness that would prevent the subject from signing the informed consent form.
4. Declined to participate
5. Unable to speak or understand English, necessary for completing the questionnaire and follow instructions

Contact: Dr. Christine Chen/Harjot Vohra -**Open for Enrollment**

IDENTIFICATION OF PATIENTS WITH AGE-RELATED CLONAL HEMATOPOIESIS (ARCH) AMONG CANCER SURVIVORS
PROTOCOL SHORT NAME: ARCH-001

Non-Interventional

Inclusion criteria:

1. Age ≥ 60
2. Completed chemotherapy and/or radiation therapy and are being followed at University Health Network.
3. Patient must be in remission after completing chemotherapy or radiation
4. Peripheral blood counts must have returned to normal as defined by:
    a. Platelets ≥ 100 x 10^9/L
    b. PMN ≥ 1 x 10^9/L
    c. Ongoing treatment for malignancy allowed, if does not involve the use of conventional cytotoxic chemotherapeutic agents **OR**
5. Prior to chemotherapy and/or radiation therapy at the University Health Network, or prior to a myeloablative dose of chemotherapy such as autotransplant, even if already commenced treatment with chemotherapy and/or radiation at non-myeloablative doses.
6. All histologically/cytologically proven tumour types (solid tumours and hematologic malignancies) will be eligible.
7. Received or will receive regimens of chemotherapy or radiation with doses expected to produce transient myelosuppression (PMN<1.0x10^9/L) (The identification and definition of appropriate myelosuppressive chemotherapy and radiation regimens will be at the discretion of the treating physician and will vary among disease sites).
8. Patients must have the ability to understand the requirements of the study and provide written informed consent, which includes authorization for release of protected health information
9. Patient must be willing to provide a peripheral blood sample.

Exclusion criteria:

1. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

Contact: Dr. Christine Chen/Harjot Vohra -**Open for Enrollment**

HEALTH-RELATED QUALITY OF LIFE AND CAREGIVER BURDEN ASSESSMENT IN MULTIPLE MYELOMA AND LYMPHOMA PATIENTS AND THEIR CAREGIVERS UNDERGOING OUTPATIENT AUTOLOGOUS STEM CELL TRANSPLANTATION AS COMPARED TO INPATIENT TRANSPLANTATIONS: A NEEDS ASSESSMENT

Non-Interventional

Inclusion criteria:

1. Males or females aged 18 years or older undergoing an autologous stem cell transplant for multiple myeloma, or Hodgkin or Non-Hodgkin Lymphoma
2. Able to provide consent
3. Able to read, write and speak English
4. Available primary caregiver for the caregiver QOL and burden component of study who is able to provide consent and read, write and speak English

Exclusion criteria:

1. Geographically inaccessible/will not be followed at Princess Margaret Cancer Centre for the 100d period post-transplant.
2. Unable to provide consent.

Contact: Dr. Anca Prica -**Open for Enrollment**

THE TERRY FOX PAN-CANADIAN MULTIPLE MYELOMA MOLECULAR MONITORING COHORT STUDY (THE M4 STUDY)

Non-Interventional

Inclusion criteria:

1. Age ≥ 19 ye
2. Ability to give informed co
3. Diagnosed with active multiple myeloma (refer to Appendix I for IMWG definition);
4. Also enrolling in the CMM-DB project; and
5. Previously untreated and eligible for autologous stem-cell transplantation (ASCT).
6. Patients who are going to be treated on a clinical trial are also eligible to participate in this study if they meet the other eligibility criteria.

Contact: Dr. Donna Reece/Harjot Vohra -**Open Enrollment**

DETECTION OF AL AMYLOID FIBRILS AND OLIGOMERS IN BLOOD PLASMA OF MULTIPLE MYELOMA AND RELATED PLASMA CELL DYSCRASIAS USING IMMUNO-GOLD ELECTRON MICROSCOPY

Non-Interventional

Inclusion criteria:

1. Patients must have or be suspected of a diagnosis of AL amyloidosis, MM, or related clonal plasma cell disorder (PCD) such as smoldering myeloma or MGUS.
2. Patient must be ≥ 18 years old.
3. Patients are undergoing standard of care blood draw.
4. All patients must have signed and dated an informed consent form.

Healthy Subject Inclusion Criteria

1. 18-60 years old

2. 110 lbs. and above
3. Not pregnant
4. Not known to be anemic

Contact: Dr. Rodger Tiedemann/Harjot Vohra-**Open Enrollment**

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

SECOND LINE THERAPY

AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF LINVOSELTAMAB (REGN5458; ANTI-BCMA X ANTI-CD3 BISPECIFIC ANTIBODY) VERSUS THE COMBINATION OF ELOTUZUMAB, POMALIDOMIDE, AND DEXAMETHASONE (EPD), IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (LINKER-MM3)

Protocol Number: R5458-ONC-2245

Inclusion Criteria

1. ≥18 years of age.
2. ECOG 1 or 0. Medical Monitor may allow ECOG 2 if solely due to local symptoms of myeloma (e.g. pain).
3. Patient with Multiple Myeloma (MM) who have received 1 to 4 prior lines of MM therapies including lenalidomide and a proteasome inhibitor. Has disease progression on or after the last therapy per 2016 IMWG criteria. Patients who have received only 1 line of MM therapy must be lenalidomide refractory (includes patients with progression on or within 60 days of the last dose of lenalidomide given as maintenance).
4. Measurable disease at screening as defined by 2016 IMWG criteria as having 1 or more of the following:
   - Serum M-protein ≥5g/L (5% population enrollment cap for those between >5g/L and <10g/L)
   - Urine M-protein ≥0.2g/24 hr
   - Free light chain (FLC) assay with involved FLC level ≥100mg/L and an abnormal serum FLC ratio (normal ratio 0.26 to 1.65)
   - Quantitative immunoglobulin levels of ≥5g/L (IgA and IgD myeloma only).

   In addition, participants must have evidence of adequate bone marrow reserves and adequate hepatic, renal, and cardiac function
5. Adequate hematologic function within 7 days of randomization as measured by:
   - **Platelet count ≥75 x 10^9/L** for participants in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count **≥50 x 10^9/L**. No platelet transfusion within 7 days.
   - **Absolute neutrophil count (ANC) ≥1.0 x 10^9/L.** No granulocyte colony stimulating factor within 2 days.
   - **Hemoglobin ≥80g/L.** Red blood cell transfusions are permitted in order to meet this requirement.
6. Adequate hepatic function within 7 days of randomization, defined as:
   - **Total bilirubin ≤1.5 x ULN.** Participants with Gilbert syndrome do not need to meet this total bilirubin requirement provided that the total bilirubin is unchanged from baseline.
   - **Transaminase (ALT, AST) ≤2.5 x ULN**
7. Serum creatinine clearance by Cockcroft Gault >30 mL/min within 7 days of randomization.
8. **Corrected serum calcium ≤3.5 mmol/L** or **free ionized calcium <6.5 mg/dL** within 7 days of randomization
9. Life expectancy of at least 6 months
10. Recovery to grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and grade 2 peripheral neuropathy.
11. Able to understand and complete study-related questionnaires

Exclusion Criteria

1. Diagnosis of plasma cell leukemia, amyloidosis (including myeloma associated amyloidosis), Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or POEMS syndrome.
2. Prior treatment with elotuzumab and/or pomalidomide

3. Participants with known MM brain lesions or meningeal involvement
4. Treatment with any systemic anti-cancer therapy within 5 half-lives or within 28 days before first administration of study drug, whichever is shorter
5. History of allogeneic stem cell transplantation within 6 months, or autologous stem cell transplantation within 12 weeks of the start of study treatment
6. Prior treatment with BCMA directed immunotherapies, including BCMA bispecific antibodies and BiTEs (Bispecific T-cell engagers) and BCMA CAR T-cells. Note: BCMA antibody-drug conjugates are allowed.
7. Treatment with systemic corticosteroid treatment with more than 10 mg per day of prednisone or steroid equivalent within 72 hours of start of study drug
8. History of neurodegenerative condition or CNS movement disorder.
9. History of seizure within 12 months before randomization.
10. Uncontrolled psychiatric illness, or psychiatric illness requiring hospitalization within the prior 12 months
11. Live or live attenuated vaccination within 28 days before first study drug administration with a vector that has replicative potential.
12. Has received a COVID-19 vaccination within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations (initial series or booster[s]) would not be completed 1 week prior to start of study drug
13. Myelodysplastic syndrome or another malignancy in the past 3 years, except for nonmelanoma skin cancer that has undergone potentially curative therapy, in situ carcinoma that has been deemed to be effectively treated with definitive local control and with curative intent with no evidence of recurrence, thyroid cancer that has been surgically treated with curative intent or low-risk early stage prostate adenocarcinoma (T1-T2aN0M0 and Gleason score ≤6 and prostate-specific antigen (PSA) ≤10 ng/mL) for which the management plan is active surveillance.
14. Has any medical condition, comorbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator renders the participant unsuitable for participation in a clinical study due to high safety risks and/or potential to affect interpretation of results
15. Cardiac ejection fraction <40% by echocardiogram or multi-gated acquisition (MUGA) scan
16. Significant cardiovascular disease (e.g., New York Heart Association Class III or IV cardiac disease, myocardial infarction, stroke, or transient ischemic attack within the previous 6 months, unstable arrhythmias or unstable angina) and/or significant pulmonary disease (e.g., obstructive pulmonary disease and history of symptomatic bronchospasm or pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.)
17. Any infection requiring hospitalization or treatment with intravenous (IV) anti-infectives within 2 weeks of first administration of study drug
18. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C; or another uncontrolled infection (such as cytomegalovirus [CMV]). Additional guidelines for HIV, Hepatitis B, and Hepatitis C are:
    - Participants with HIV who have controlled infection (undetectable viral load and CD4 count above 350 cells/μL, either spontaneously or on a stable antiviral regimen) are permitted
    - Participants with hepatitis B surface antigen (HBsAg+) who have controlled infection (serum hepatitis B virus DNA polymerase chain reaction [PCR] that is below the limit of detection AND receiving antiviral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of study drug.
    - Participants who are hepatitis C virus (HCV) antibody positive who have controlled infection (undetectable HCV RNA by PCR, either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted
19. History of severe allergic reaction attributed to any study drug or excipient. A severe allergic reaction is defined for this purpose as requiring hospitalization and/or treatment with epinephrine
20. Known hypersensitivity to both allopurinol and rasburicase
21. Is committed to an institution by virtue of an order issued either by judicial or administrative authorities
22. Is currently receiving treatment in another interventional study
23. Radiation therapy other than local therapy for myeloma-associated bone lesions within 14 days prior to randomization
24. Any active gastrointestinal dysfunction interfering with the participant's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment.
25. Members of the clinical site study team and/or his/her immediate family unless prior approval granted by the Sponsor.
26. Pregnant or breastfeeding women.
27. Women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose.
28. Has a history of tuberculosis or systemic fungal diseases.

Contact: Dr. Keith Stewart /Olga Levina – **Open Enrollment**

A PHASE 3, TWO-STAGE, RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY COMPARING CC-92480 (BMS-986348), CARFILZOMIB, AND DEXAMETHASONE (480KD) VERSUS CARFILZOMIB AND DEXAMETHASONE (KD) IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM).
Protocol Number: CA057-008

Inclusion Criteria

1. Age: ≥ 18 years of age
2. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
3. Must have either of the following:
   - Participant has received at least 1 prior line of anti-myeloma therapy. (Note: One line can contain several phases, eg, induction, (with or without) hematopoietic stem cell transplant, (with or without) consolidation, and/or (with or without) maintenance therapy)
   - Participant must have received prior treatment with lenalidomide and at least 2 cycles of an anti-CD38 monoclonal antibody. Note: Patients who were intolerant of an anti-CD38 mAb and received < 2 cycles are still eligible.
   - Participant achieved minimal response (MR) or better to at least 1 prior anti-myeloma therapy.
   - Participant must have documented disease progression during or after their last anti myeloma regimen.

4. Measurable disease at screening as defined by any of the following:
   - M-protein ≥ 0.5 g/dL by serum protein electrophoresis (sPEP) or
   - M-protein ≥ 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP) or,
   - For participants without measurable disease in sPEP or uPEP: sFLC levels > 100 mg/L (10 mg/dL) involved light chain and an abnormal κ/λ FLC ratio.
5. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1 or 2 at screening and C1D1.

Exclusion Criteria

30. Participant who has had prior treatment with CC-92480 or Carfilzomib
31. Participant who has had any investigational agents within 28 days or 5 half-lives (whichever is shorter) of initiating study intervention
32. Participant has received any of the following:
    - Plasmapheresis within the last 28 days of initiating study intervention.
    - Major surgery (as defined by the Investigator) within 28 days of initiating study intervention.
    - Radiation therapy, other than local palliative therapy, for myeloma-associated bone lesions within 14 days of initiating study intervention.
    - Use of any systemic anti-myeloma drug therapy within 14 days of initiating study intervention.
33. Participant has previously received allogeneic stem cell transplantation at any time during prior therapy or received autologous stem cell transplantation within 12 weeks of initiating study intervention.
34. Participant has plasma cell leukemia, Waldenstrom Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or clinically significant light-chain amyloidosis
35. Participant with known central nervous system (CNS) involvement with myeloma.
36. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 14 days for mild or asymptomatic infections or 28 days for severe/critical illness prior to initiating study intervention.
37. Participant has any of the following laboratory abnormalities:
    - **Absolute neutrophil count** (ANC) < 1,000/μL. It is not permissible to administer GCSF to achieve minimum ANC levels within 7 days prior to screening complete blood count (CBC) (Or within 14 days prior for pegfilgrastim).
    - **Platelet count**: < 75,000/μL for participants in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 50,000/μL for participants in whom ≥ 50% of bone marrow nucleated cells are plasma cells. Platelet transfusions are **not** permitted within **7 days** prior to screening complete blood count (CBC).
    - **Hemoglobin** < 8 g/dL (< 4.9 mmol/L)
    - **Estimated glomerular filtration** rate (eGFR) < 30 mL/min or requiring dialysis. eGFR will be calculated using the Modification of Diet in Renal Disease.
    - **Corrected serum calcium** > 13.5 mg/dL (> 3.4 mmol/L)
    - Serum aspartate aminotransferase (**AST**) or alanine aminotransferase (**ALT**) > 2.5× upper limit of normal (ULN)

- **Serum total bilirubin** > 1.5× ULN; < 3.0 mg/dL is allowed for participants with documented Gilbert's syndrome.

38. Participant with gastrointestinal disease or surgery (eg, gastric bypass surgery) that may significantly alter the absorption of CC-92480 and/or other oral study intervention.
39. Participant has received immunosuppressive medication within the last 14 days of initiating study intervention
40. Participant has uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment.
41. Participant who has had a live vaccine within 3 months of start of study therapy).
42. Participant is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B, active hepatitis A, or active hepatitis C.
43. Participant has impaired cardiac function or clinically significant cardiac disease, including any of the following:
    a. Myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function.
    b. Uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities, including prolongation of QT interval on Screening ECG as defined by a QTc interval > 470 msec using Fridericia's QT correction formula
    c. Left ventricular ejection fraction < 40% as assessed by transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA)
44. Participant has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide (including ≥ Grade 3 rash during prior thalidomide or lenalidomide therapy), Carfilzomib or dexamethasone, any CELMoD agents.
45. Participant has prior history of malignancies, other than MM, unless the participant has been free of the disease for ≥ 5 years.
46. Administration of strong CYP3A modulators; administration of proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) within 2 weeks of starting study intervention

Contact: Dr. Donna Reece / Guillaume Cheung – **Open for Enrollment**

A PHASE 1B/2 DOSE-ESCALATION AND COHORT-EXPANSION STUDY TO DETERMINE THE SAFETY AND EFFICACY OF BGB-11417 AS MONOTHERAPY, IN COMBINATION WITH DEXAMETHASONE AND CARFILZOMIB/DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND t(11;14)

Protocol Number: BGB-11417-105

Inclusion Criteria

1. ≥ 18 years old
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
3. A confirmed diagnosis of multiple myeloma (must have an M-component in serum and/or urine)
4. Measurable disease defined as:
    a. M-spike ≥ 500 mg/dL, or
    b. Urine protein M-spike of ≥ 200 mg/day, or
    c. Serum free light chains ≥ 10 mg/dL, and an abnormal κ:λ ratio
5. Participant has documented relapsed or progressive MM on or after any regimen or who are refractory to the most recent line of therapy.

    Note:

    - Relapsed MM is defined as previously treated MM that progresses and requires initiation of salvage therapy but does not meet the criteria for refractory MM.
    - Refractory MM is defined as disease that is nonresponsive (failure to achieve minimal response or development of progressive disease) while on primary or salvage therapy or progresses within 60 days of last therapy.
        a. Patients in Part 1 should have failed all other available options including having had ≥ 3 prior lines of therapy including a proteasome inhibitor, IMiD agent, and an anti-CD38 monoclonal antibody.
        b. Patients in Part 2 should have had and failed ≥ 1 but ≤ 7 prior lines of therapy and will have had prior treatment with both a proteasome inhibitor and an IMiD agent.

Note: A line of therapy consists of greater ≥ 1 complete cycle of a single agent, a regimen consisting of combination of several drugs, or a planned sequential therapy of various regimens. Induction therapy with consolidation and maintenance following stem cell transplant is considered a single line of therapy.

c. Prior treatment with carfilzomib is allowed but the patient must not be considered carfilzomib refractory and not have had carfilzomib within the past 6 months.

6. Positivity for t(11;14) by a validated fluorescence in situ hybridization (FISH) assay in a predefined central laboratory:
    a. A fresh bone marrow aspirate sample must be collected at screening and sent to central laboratory for t(11;14) FISH testing.
    b. Enrollment requires centrally confirmed t(11;14) results.
7. Either > 100 days after autologous stem cell transplant or ≥ 6 months after allogeneic transplant and without active graft-versus-host disease (i.e., requiring treatment)
8. > 2 months after chimeric antigen receptor T-cell therapy with resolution of ongoing toxicity to less than Grade 2 (except for alopecia).
9. Adequate organ function defined as:
    a. Hemoglobin ≥ 8.0 g/dL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
    b. Platelet count ≥ 75,000/μL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
    c. Absolute neutrophil count (ANC) ≥ 1000/mm^3 [ANC = (% of segmented neutrophils + % of segmented bands) x total WBC count] within 7 days before first dose of study treatment
    NOTE: The screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim (or other pegylated myeloid growth factors) and at least 7 days following the most recent administration of filgrastim or other myeloid growth factors
    d. ALT and AST ≤ 3 x upper limit of normal (ULN) and total bilirubin ≤ 2.0 x ULN
    e. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 45 mL/min/1.73 m^2 calculated by the MDRD-6 formula. Web-based calculator available at:
    https://qxmd.com/calculate/calculator_141/mdrd-egfr-6-variable
10. Women of childbearing potential must have a negative serum pregnancy test ≤ 7 days before the first dose of study drug. In addition, they must use a highly effective method of birth control initiated before the first dose of study drug, for the duration of the study treatment period, and for ≥ 6 months after the last dose of study drug. See Appendix 10 for highly effective methods of birth control and the definition of childbearing potential.
11. Nonsterile men must use a highly effective method of birth control along with barrier contraception for the duration of the study treatment period and for ≥ 90 days after the last dose of study drug. During this same period, they must not donate sperm. Sterile men must use barrier contraception. In addition, partners of these men who could become pregnant should also utilize a highly effective method of birth control. See Appendix 10 for highly effective methods of birth control and the definition of sterile.
12. Life expectancy ≥ 6 months
13. Able to comply with the requirements of the study

Exclusion Criteria

1. Participant has any of the following conditions:
    a. Non secretory MM (Serum free light chains < 10 mg/dL)
    b. Solitary plasmacytoma
    c. Active plasma cell leukemia (i.e., either 20% of peripheral white blood cells or > 2.0 x 10^9/L circulating plasma cells by standard differential)
    d. Waldenstrom Macroglobulinemia
    e. Amyloidosis
    f. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome
2. Uncontrolled diabetes (HbA1c > 7% or 53 mmol/mol or requiring insulin at study entry [American Diabetes Association 2021])
3. Chronic respiratory disease that requires continuous oxygen
4. Significant cardiovascular disease, including but not limited to:
    a. Myocardial infarction ≤ 6 months before screening
    b. Ejection fraction ≤ 50%
    c. Unstable angina ≤ 3 months before screening
    d. New York Heart Association Class III or IV congestive heart failure (see Appendix 5)
    e. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
    f. Heart rate-corrected QT interval > 480 milliseconds based on Fridericia's formula

g. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
h. Uncontrolled hypertension at screening, defined as systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg by ≥ 2 consecutive measurements

5. Prior therapy with BGB-11417 or other agents inhibiting Bcl-2 activity (eg, Venetoclax)
6. Known infection with human immunodeficiency virus (HIV).
7. Serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if HBV DNA is undetectable (limitation of sensitivity < 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (limitation of sensitivity < 15 IU/mL).
8. Major surgery within 4 weeks prior to enrollment.
   Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, or meninges), the surgery is considered major.
9. Acute infections requiring antimicrobial therapy (antibiotic, antifungal, or antiviral) not resolved >14 days prior to Cycle 1 Day 1.
10. Peripheral neuropathy ≥ Grade 3 or ≥ Grade 2 with pain within 2 weeks prior to starting study drug.
11. Need for chronic corticosteroid therapy (> 10 mg prednisone or equivalent daily).
12. Any other medical condition that, in the opinion of the investigator, would adversely affect the participant's participation in the study or will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results.
13. Psychiatric or cognitive dysfunction precluding active participation with the study protocol.
14. Radiation therapy that could affect bone marrow (eg, encompassing ≥ 5% of total bone marrow).
15. Use of the following substances prior to the first dose of study drug:
    a. ≤ 30 days prior to the first dose of study drug
        - Any biologic and/or anti-CD38-based therapy
    b. ≤ 14 days prior to the first dose of study drug
        - Systemic chemotherapy or therapeutic radiation therapy (palliative radiation therapy for bone lesions is acceptable)
    c. ≤ 7 days prior to the first dose of study drug
        - Corticosteroid given with antineoplastic intent
        - Dexamethasone for any indication
        - BTK inhibitor, tyrosine kinase inhibitor, or other targeted small molecule (with 5 half-lives ≥ 7 days) given with antineoplastic intent
16. A history of other active malignancies, including myelodysplastic syndrome, within the past 2 years prior to study entry, with the following exceptions
    a. Adequately treated in situ carcinoma
    b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    c. Prostate cancer ≤ Gleason Grade 6 and with stable prostate-specific antigen levels off treatment
    d. Previous malignancy, > 2 years with no evidence of disease, confined and surgically resected (or treated with other modalities) with curative intent, and unlikely to impact survival during the duration of the study
17. If patient had prior allogeneic stem cell transplant, there is evidence of ongoing graft--versus-host disease.
18. Pregnant or lactating women.
19. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedure, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
20. Receiving any treatment with a moderate CYP3A4 inhibitor or strong CYP3A4 inhibitor or inducer ≤ 14 days (or 5 half-lives, whichever is longer) before first dose of BGB-11417. See Appendix 6 for guidance on CYP3A inhibitors and inducers.
21. History of hypersensitivity to excipient(s) of BGB-11417, carfilzomib, or dexamethasone.
22. Vaccination with a live vaccine ≤ 35 days before first dose of study drug.

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. A non-live COVID-19 vaccine may be administered if recommended per local practice.

Contact: Dr. Christine Chen / Olga Levina – **Open Enrollment**

AN EXPLORATORY PHASE 1B/2A MULTICENTER, OPEN-LABEL, NOVEL-NOVEL COMBINATION STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY EFFICACY OF CC-92480 (BMS-986348) IN NOVEL THERAPEUTIC COMBINATIONS IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CA057-003

Inclusion Criteria

1. MM with relapsed or refractory disease and must:
   i. Have documented disease progression by the International Myeloma Working Group (IMWG) Uniform Response Criteria during or after their last myeloma therapy
   ii. Be refractory to, intolerant to, or not a candidate for available, established therapies known to provide clinical benefit in MM.
2. Have measurable disease including at least 1 of the following criteria:
   i. M-protein quantities ≥ 1.0 g/dL by serum protein electrophoresis (sPEP)
   ii. M-protein quantities ≥ 200 mg/24 hour urine collection by urine protein electrophoresis (uPEP)
   iii. Serum free light chain (sFLC) levels > 100 mg/L of the involved light chain and an abnormal kappa/lambda (κ/λ) ratio in participants without measurable serum or urine M-protein
   iv. Immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 1 g/dL
3. Participant consents to serial bone marrow aspirations (BMAs) and/or biopsies (BMBs) during screening and study treatment, and may consent to BMA and/or BMB at the end of treatment
4. ECOG Performance Status of 0 or 1
5. ≥18 years of age
6. Female of childbearing potential must have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy.
7. Female of Child Bearing Potential participants and all male participants must follow study pregnancy prevention contraception requirements and Pregnancy Prevention Program. Varies depending on study treatment.
8. Male participant must agree to refrain from donating sperm or semen while on study treatment, during dose interruptions, and for up to 4 months after last dose of study treatment (duration dependent on study drug).
9. Female of Child Bearing Potential participants must agree to refrain from donating eggs or breastfeeding while on study treatment and up to 7 months after last dose of study treatment (duration dependent on study drug)
10. Must agree to refrain from donating blood while on study treatment, during dose interruptions, and for ≥ 28 days following last dose of study treatment.

Exclusion Criteria

1. Current or history of central nervous system involvement of MM
2. Plasma cell leukemia; Waldenstrom's macroglobulinemia; polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome; or clinically significant light-chain amyloidosis.
3. Cannot tolerate oral medications and/or has gastrointestinal disease that may significantly alter the absorption of oral study treatments
4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   i. Left ventricular ejection fraction (LVEF) < 45% as determined by echocardiography (ECHO) or multi-gated acquisition (MUGA) scan at screening
   ii. Complete left bundle branch, bifascicular block, or other clinically significant abnormal electrocardiographic finding at screening
   iii. A prolongation of QT interval on screening electrocardiogram (ECG) as defined by corrected QT interval (QTc) > 480 ms using Fridericia's QT correction formula; a history of or current risk factors for Torsades de Pointe (eg, heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval
   iv. Congestive heart failure (New York Heart Association Class III or IV)
   v. Myocardial infarction or stroke ≤ 6 months prior to starting study treatments
   vi. Unstable angina or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris
5. HIV positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if:
   i. They have received antiretroviral therapy (ART) for at least 4 weeks prior to starting study treatment as clinically indicated while enrolled on study.

ii. They continue taking ART as clinically indicated and while enrolled on study.
iii. CD4 counts and viral load are monitored per standard of care by a local health care provider.

6. History of hepatitis B or C virus or has virologic or serological evidence of hepatitis A, B, or C virus infection. Participants who had hepatitis C virus (HCV) but have received an antiviral treatment and show no detectable HCV viral ribonucleic acid (RNA) for 6 months are eligible.
7. History of concurrent second cancer requiring ongoing systemic treatment.
8. Prior malignancy other than MM, except if the participant has been free of disease for ≥ 3 years or the participant had 1 of the following non-invasive malignancies treated with curative intent without known recurrence:
   i. Basal or squamous cell carcinoma of the skin
   ii. Carcinoma in situ of the cervix or breast
   iii. Stage 1 bladder cancer
   iv. Incidental histological findings of localized prostate cancer such as tumor Stage 1a or 1b (T1a or T1b) using the tumor, nodes, and metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent
9. Participant has active, uncontrolled, or suspected infection.
10. SARS-CoV-2 infection within 14 days for asymptomatic or mild symptomatic infections or 28 days for severe/critical illness prior to Cycle 1 Day 1 (C1D1). Acute symptoms must have resolved. There are no sequelae that would place the participant at a higher risk of receiving study treatment
11. Medical condition including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study.
12. Pregnant, nursing, or breastfeeding, or who intend to become pregnant during participation in the study
13. Inability to comply with restrictions and prohibited treatments as listed in protocol Section 7.7
14. For Part 1: Participant received prior therapy with CC-92480. For Part 2: Participant received prior therapy with CC-92480, tazemetostat, BMS-986158, or trametinib.
15. Previously received allogeneic stem-cell transplant at any time or received autologous stem-cell transplant within 12 weeks of initiating study treatment.
16. Received any of the following within 14 days prior to initiating study treatment:
   i. Plasmapheresis
   ii. Major surgery (as defined by the investigator)
   iii. Radiation therapy other than local therapy for myeloma associated bone lesions
   iv. Use of any systemic anti-myeloma drug therapy
17. Used any investigational agents within 28 days or 5 half-lives (whichever is shorter) prior to study treatment.
18. Received immunosuppressive medication within 14 days prior to initiating study treatment. The following are exceptions to this criterion:
   i. Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection)
   ii. Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent
   iii. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
19. COVID-19 vaccine within 14 days prior to C1D1. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to C1D1.
20. Live/attenuated vaccine, including live vaccines for COVID-19, within 30 days prior to initiating study treatment
21. Concurrent administration of strong CYP3A modulators including within 14 days prior to initiating study treatment
22. Concurrent administration of proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole; etc.) including within 14 days prior to initiating study treatment.
23. Unable or unwilling to undergo protocol-required thromboembolism prophylaxis
24. Evidence of organ dysfunction or any clinically significant deviation from normal by physical examination or in vital signs, by ECG, or by clinical laboratory determinations beyond what is consistent with the target population and in addition to the specific criteria above and below
25. Participant has any of the following laboratory values (determined by local lab); qualifying laboratory value must occur at most recent measurement prior to cohort assignment and must be no more than 14 days prior to cohort assignment:
   i. **Absolute neutrophil count (ANC)** < 1.0 x 10^9/L (< 1000/μL) without growth factor support within 7 days prior to screening complete blood count (CBC) (14 days if pegfilgrastim is used)
   ii. **Platelets** < 75 x 10^9/L (< 75,000/μL) and no platelet transfusions within the 7-day period leading up to the screening CBC
   iii. **Hemoglobin** < 8 g/dL (< 4.9 mmol/L) and no RBC transfusions are allowed within the 72-hour period leading up to the screening CBC
   iv. **Potassium** outside normal limits and cannot be corrected with supplements
   v. **Corrected serum calcium** > 13.5 mg/dL (> 3.4 mmol/L)
   vi. **Serum AST/serum glutamic oxaloacetic transaminase (SGOT**) and **ALT/serum glutamic pyruvic transaminase (SGPT)** > 3x ULN
   vii. **Serum bilirubin** > 1.5x ULN; > 3.0 mg/dL is allowed for participants with documented Gilbert's Syndrome
   viii. **Estimated glomerular filtration rate (eGFR)** < 45 mL/min/1.73 m^2 calculated using the Modified Diet in Renal Disease (MDRD) formula (see Appendix 7)

ix. **International normalized ratio (INR)** ≥ 1.5x ULN and **partial thromboplastin time (PTT)** ≥ 1.5x ULN (only for participants who are not on anticoagulants). Note: Participants receiving therapy for a thromboembolic event that occurred > 3 months prior to enrollment are eligible as long as they are on a stable regimen of anticoagulation with warfarin, low-molecular weight heparin, or another approved therapeutic anticoagulation regimen

26. History of severe allergic or anaphylactic reactions or hypersensitivity to a CRBN-modulating agent, BETi, EZH2i, MEKi, or any of their excipients
27. Current or recent (within 3 months of study intervention administration) gastrointestinal disease that could impact upon the absorption of study intervention
28. Any gastrointestinal surgery that could impact upon the absorption of study intervention

Contact: Dr. Donna Reece / Rebecca Noronha – **Open Enrollment**

ELRANATAMAB (PF-06863135) MONOTHERAPY EXPANDED ACCESS PROTOCOL FOR TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WHO ARE REFRACTORY TO AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY DRUG AND ONE ANTI-CD38 ANTIBODY AND HAVE NO ACCESS TO OTHER COMPARABLE/ALTERNATIVE THERAPY.
Protocol Number: Pfizer C1071017 (MAGNETISMM-17)

Inclusion Criteria

1. Male or female participants age ≥18 years.
    a. A female participant is eligible to participate if she is not pregnant or breastfeeding.

2. Prior diagnosis of MM as defined according to IMWG criteria.

3. Participants who are ineligible for participation in any ongoing clinical trial of elranatamab, including lack of access due to geographical limitations, and who have exhausted all other treatment options.

4. Measurable disease based on IMWG criteria as defined by at least 1 of the following:
    a) Serum monoclonal protein (M-protein) level ≥ 0.5 g/dL (≥ 5 g/L);
    b) Urinary M-protein excretion ≥200 mg/24 hours;
    c) Involved FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

5. Refractory to at least one IMiD, one PI, and one anti-CD38 antibody.

6. Relapsed/refractory to last anti-MM regimen.

7. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0-1.

8. Adequate BM function characterized by the following:
    a) ANC ≥1.0 × 109/L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing);
    b) Platelets ≥25 × 109/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and
    c) Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).

9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.

Exclusion Criteria

1. Smoldering MM; plasma cell leukemia; POEMS syndrome; Waldenström's macroglobulinemia; amyloidosis; stem cell transplant within 12 weeks prior to enrollment or active GVHD.

2. Previous treatment with BCMA directed therapy;

3. Ongoing Grade ≥2 peripheral sensory or motor neuropathy; history of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy; known active CNS involvement or clinical signs of meningeal involvement of MM;

4. SARS-CoV2, HIV, HBV, HCV or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.

5. Known or suspected hypersensitivity to the study intervention or any of its excipients.

6. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ or Stage 0/1 with minimal risk of recurrence per investigator.

7. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

8. Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.

9. Previous administration with an investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

10. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
    a) Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);
    b) Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
    c) Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with acentral venous access complication] or pulmonary embolism);
    d) Prolonged QT syndrome (or QTcF >470 msec at screening);
    e) LVEF <40% as determined by a MUGA scan or ECHO.

11. Impaired hepatic function characterized by the following:
    a) Total bilirubin >2 x ULN (>3 x ULN if documented Gilbert's syndrome);
    b) AST >2.5 x ULN; and
    c) ALT >2.5 x ULN

12. Impaired renal function defined according to local institutional standard method:
    a) eGFR <30 mL/min/1.73 m2 using CKD-EPI 2021 equation23 or estimated CrCl <30 mL/min using Cockcroft Gault formula. If both formulae are calculated, the higher of the two values may be used. A 24-hour urine collection for CrCl may also be used in equivocal cases where amyloidosis is suspected.

Contact: Dr. Suzanne Trudel /Elena Talovikova– **Open Enrollment**

A RANDOMIZED, PHASE 3, OPEN LABEL STUDY EVALUATING SUBCUTANEOUS VERSUS INTRAVENOUS ADMINISTRATION OF ISATUXIMAB IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE IN ADULT PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Protocol Number: EFC15951

Inclusion Criteria

1. ≥18 years of age.
2. Participants with measurable disease defined as at least one of the following:
-Serum M-protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis and/or
-Urine M-protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis and/or

-Serum free light chain (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
3. Participants must have received at least 1 prior line of anti-myeloma therapy, which must include at least 2 consecutive cycles of lenalidomide and a PI (bortezomib, carfilzomib or ixazomib) given alone or in combination.
4. Participants must have documented evidence of progressive disease, as defined by 2016 IMWG criteria on or after the last regimen.
5. Participants who received only one prior line of therapy must have progressed on or within 60 days after end of the lenalidomide therapy before signing the informed consent form (ICF), i.e., lenalidomide refractory.

Exclusion Criteria

1. Primary refractory multiple myeloma defined as: participants who have never achieved at least a minimal response (MR) with any treatment during the disease course.
2. Inability to tolerate thromboprophylaxis or excess risk of bleeding.
3. Participants with prior anti-CD38 treatment are excluded if: a) Progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least MR to treatment (i.e., Refractory to anti-CD38) with a washout period inferior to 9 months before randomization or, b) Intolerant to the anti-CD38 previously received.
4. Prior therapy with pomalidomide.
5. Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone.
6. Prior allogenic HSC transplant with active graft versus host disease (GvHD) (GvHD any grade and/or being under immunosuppressive treatment within the last 2 months prior to randomization).
7. Any major procedure within 14 days before the initiation of the study treatment.
8. Plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy.
9. Received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever is shorter.
10. **COUNTS as follows:**
    - Platelets <50000 cells/µL. Platelet transfusion is not allowed within 7 days before the screening hematological test.
    - ANC <1000 µL (1 x 109/L). The use of granulocyte-colony stimulating factor (G-CSF) is not allowed to reach this level.
11. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m2 (modification of diet in renal disease MDRD Formula).
12. Hypersensitivity to IMiDs (thalidomide or lenalidomide) defined as any hypersensitivity reaction leading to stop IMiDs within the 2 first cycles or reaction which does meet intolerance definition.
13. Known intolerance or hypersensitivity to dexamethasone, to any of isatuximab SC formulation excipients (L-histidine; L-histidine hydrochloride monohydrate, L-arginine monohydrochloride, sucrose, polysorbate 80, and poloxamer 188), or to any of the components study therapy that are not amenable to premedication with steroids, or H2 blockers, that would prohibit further treatment with these agents.
14. Participants with contraindication to dexamethasone, and/or contraindication to pomalidomide, and/or
15. ≥Grade 2 peripheral neuropathy.
16. Known acquired immunodeficiency syndrome (AIDS)-related illness or known human immunodeficiency virus (HIV).
17. Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide.
18. Concomitant plasma cell leukemia.

Contact: Dr. Donna Reece / Naomi Kimbriel – **Open Enrollment**

THIRD LINE THERAPY

A PHASE 1B/2 DOSE ESCALATION AND EXPANSION STUDY OF THE COMBINATION OF THE BISPECIFIC T CELL REDIRECTION ANTIBODIES TALQUETAMAB AND TECLISTAMAB IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: 64007957MMY1003

Inclusion Criteria

1. ≥18 years of age.
2. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
3. Must have either of the following:

Part 3:

- Relapsed or refractory disease, and exposed to a PI, IMiD and an anti-CD38 mAb.
- Documented evidence of progressive disease based on investigator's determination of response by IMWG criteria on or after their last regimen.

4. Measurable disease at screening as defined by any of the following:

Part 3:

- Documented relapsed or refractory multiple myeloma with 1 or more focus of EMD meeting the following criteria: extramedullary plasmacytoma not contiguous with a bone lesion at least 1 lesion >2cm (at its greatest dimension) diameter on PET-CT, and not previously radiated.

5. Part 3: Eastern Cooperative Oncology Group (ECOG) performance status grade of 0,1, or 2 at screening and immediately before the start of the study drug administration

6 Clinical laboratory values:

Part 3: Clinical laboratory values meeting the following criteria during the Screening phase and within 72 hours Of the first dose of study treatment.

- **Hemoglobin** ≥ 8.0 g/dL (≥5 mmol/L) (without RBC transfusion in the prior 7 days; recombinant human erythropoietin use is permitted)
- **Platelets** ≥50×109/L (without transfusion support in the prior7 days)
- **Absolute Neutrophil Count (ANC)** ≥1.0×109/L (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF or 14 days for pegylated-G-CSF)
- **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)**≤2.5×ULN
- **Creatinine clearance** ≥30 mL/min/1.73 m2 based upon Modified Diet in Renal Disease formula calculation
- **Total bilirubin** ≤1.5 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5×ULN is required)
- **Serum calcium corrected for albumin** ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium<6.5 mg/dL (<1.6 mmol/L)

7. For all parts, a participant of child bearing potential must have a negative serum pregnancy test at screening and within 72 hours of the start of the study treatment and must agree to further serum or urine pregnancy tests during the study

Exclusion Criteria

47. All Parts: Prior/concurrent exposure to any of the following in the specified time frame prior to enrollment:
    - Targeted therapy, epigenetic therapy, or treatment with an investigational treatment or an invasive medical device within 21 days or at least 5 half-lives, whichever is less.
    - Investigational vaccine other than SARS-CoV-2 vaccine approved/in use under emergency approval within 4 weeks.
    - Monoclonal antibody treatment within 21 days
    - Cytotoxic therapy within 21 days.
    - PI therapy within 14 days.
    - IMiD therapy within 7 days.
    - Radiotherapy within 21 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
    - Gene modified adoptive cell therapy (e.g., chimeric antigen receptor modified T cells, NK cells) within 3 months

    Part 3:
    - Cannot have received a prior BCMA targeted bispecific antibody therapy
    - Cannot have received any prior GPRC5D targeted therapy
48. A cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drugs.
49. Live, attenuated vaccine within 4 weeks prior to the first dose of study drug unless approved by sponsor.
50. Non-hematological toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade ≤1 (except alopecia [any grade] or peripheral neuropathy Grade ≤3).
51. Stem cell transplantation:
    - Subjects who received an allogeneic transplant must be off all immunosuppressive medications for ≥42 days without signs of graft-versus-host disease
    - Autologous stem cell transplantation ≤12 weeks before the first dose of study drug
52. Active central nervous system involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, brain magnetic resonance imaging (MRI) and lumbar cytology are required.
53. Active plasma cell leukemia (>2.0 x 109/L plasma cells by standard differential), Waldenstrom's Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or primary amyloid light chain amyloidosis.
54. Known to be seropositive for human immunodeficiency virus (H/O HIV antibody positive)

55. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants who are HBsAg negative with antibodies to total anti-HBc with or without the presence of anti-HBs must be screened using RT-PCR measurement of HBV DNA levels.
56. Active hepatitis C infection as measured by positive hepatitis C virus (HCV)-RNA testing. Subjects with a history of Hepatitis C virus antibody positivity must undergo HCV-RNA testing
57. Known allergies, hypersensitivity, or intolerance to daratumumab (Part 1 and Part 2 only), Talquetamab and Teclistamab or their excipients
58. Other malignancies:
    Part 3: Myelodysplastic syndrome or active malignancies other than relapsed/ refractory malignancies except non-muscle invasive bladder cancer, skin cancer, non-invasive cervical cancer, breast cancer, localized prostate cancer and other malignancy that is considered cured with minimal risk of recurrence.
59. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures
60. Pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study drug.
61. Major surgery within 2 weeks of the first dose, will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to be treated in the study.

Contact: Dr. Donna Reece / Naomi Kimbriel – **Open Enrollment**

An Open-label Phase 1b Study of ORIC-533 in Patients with Relapsed or Refractory Multiple Myeloma

Protocol Number: ORIC-533-01

Inclusion Criteria

1. At least 18 years of age at the time of signing the informed consent
2. Documented diagnosis of multiple myeloma (MM) with relapsed or refractory disease according to IMWG Criteria
3. Refractory to or not eligible for, in the opinion of the treating physician, MM treatment regimens that are known to provide clinical benefit, including but not limited to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, with documented disease progression
4. Agreement and ability to undergo on-study biopsies, through a procedure that is deemed to be clinically feasible and not carry significant risk
5. Measurable disease at screening, including at least 1 of the criteria below:
    - Serum M-protein >0.5 g/dL
        - Patients with IgA myeloma in whom serum M protein is unreliable due to comigration of normal serum proteins may be considered eligible if total IgA >400 mg/dL
    - Urine M-protein >200 mg/24 hours
    - Serum free light chains (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) *and an abnormal serum FLC ratio (<0.26 or >1.65)*
    - Measurable bone or extramedullary plasmacytoma
6. ECOG performance status ≤2
7. Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function defined as:
    - Estimated glomerular filtration rate □40 mL/min/1.73 m2 (calculated using the Cockcroft-Gault equation (Cockcroft and Gault 1976). A 24-hour urine collection for creatinine clearance may be used at the investigator's discretion
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels both ≤3 times of upper limit of normal, unless there is suspected disease in the liver, in which case, no limit is set provided serum bilirubin is within eligibility criterion
    - Total bilirubin <1.5 × upper limit of normal (ULN), except in study participants with Gilbert's syndrome
    - Platelet count >40,000/μL (platelet transfusions not permitted within 7 days of qualifying lab result)
    - Absolute neutrophil count (ANC) >1000/μL (G-CSF not permitted within 7 days of qualifying lab result)

- Left ventricular ejection fraction (LVEF) >45% as assessed by echocardiogram (ECHO) or multiple gated acquisition (MUGA). ECHO/MUGA results performed within 6 months before screening and at least 28 days after the last cancer treatment may be acceptable if the study participant has not received any treatment with cardiotoxicity risks
- Baseline oxygen saturation >92% on room air

8. Male: must agree to the following during the treatment period and for at least 3 months after the last dose of study treatment:
   - Refrain from donating sperm; AND either
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent; OR
   - Use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

   Female: not pregnant, not breastfeeding, and at least one of the following conditions apply:
   - Is not a woman of childbearing potential (WOCBP); OR
   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) with low user dependency, as described in Section 5.5.7 during the treatment period and for at least 3 months after the last dose of study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment
   - A WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours before the first dose of study treatment
9. Capable of giving signed informed consent as described in Section 12.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Exclusion Criteria:

1. Diagnosed or treated for another malignancy within 3 years prior to enrollment, with the exception of basal cell carcinoma or squamous cell carcinoma of the skin, low risk prostate cancer after curative therapy, an in situ malignancy, or any other low risk malignancy that is not anticipated to interfere with the assessment of safety and efficacy.
2. Previous or concurrent plasma cell leukemia, AL amyloidosis, or POEMS (polyneuropathy, organomegaly, endocrinopathy, and skin changes) syndrome
3. Known central nervous system (CNS) involvement
4. Evidence of hyperviscosity syndrome
5. Treatment with the following therapies within the stated time frames prior to initiation of ORIC-533 therapy (i.e., wash-out periods for different therapies):
   - Previous cytotoxic therapies, including cytotoxic investigational agents (approved for other indications but not for MM) within 21 days (42 days for nitrosoureas)
   - The use of live vaccines within 28 days
   - IMIDs or PI within 14 days
   - Prior anti-BCMA or CAR T therapy within 28 days
   - Prior peripheral stem cell transplant within 12 weeks
   - Prior allogeneic stem cell transplantation with active graft-versus-host- disease
6. Receiving any investigational treatment with a novel investigational agent (i.e., no approved indication) within 28 days prior to the first dose of study drug
   - Clinical trials of FDA approved agents used for MM may have washout period as outlined in exclusion criteria 5 above
7. Not recovered or stabilized from all toxicities from prior anticancer therapies and/or radiotherapy to Grade <2 with the exception of peripheral neuropathy
8. Major surgery or radiation therapy within 14 days prior to first dose of study drug or incomplete recovery from adverse effects resulting from such procedure
   - Those who require limited course of radiation, as determined by the investigator, for management of bone pain for ≤14 days from initiation of therapy are not excluded
9. Infection requiring systemic antibiotic therapy or other serious infection within 14 days of starting therapy

- Those who are on prophylactic antibiotics only, or on antibiotics and have confirmation of resolution of active infection, are eligible

10. Daily requirement for corticosteroids (equivalent to >10 mg/day prednisone).
    Inhalation corticosteroids are exempt from this criterion
    - Exception: Corticosteroid dose equivalent >10 mg/day prednisone is acceptable if physiological levels require, so long as the dose is stable for at least 7 days prior to initiation of therapy
    - Lower amounts of corticosteroids that are not part of a daily requirement within 14 days prior to initiating therapy are also acceptable
11. Known seropositive for active viral infection with human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C virus (HCV). Those who are seropositive because of hepatitis B vaccine are eligible. Patients who are positive for HBV core antibody or HBV surface antigen must have a negative polymerase chain reaction (PCR) result prior to enrollment. Those who are PCR positive will be excluded.
12. History of class III or IV congestive heart failure or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months of first dose of study drug
13. QTcF >470 msec
14. Other concurrent serious uncontrolled medical, psychological, or addictive conditions that, in the opinion of the investigator, may interfere with protocol compliance or contraindicates participation in the study

Contact: Dr. Donna Reece /Elena Talovikova – **Open for enrollment**

FOURTH LINE OF THERAPY

A PHASE 1 STUDY OF KTX-1001, AN ORAL, FIRST-IN-CLASS, SELECTIVE, AND POTENT MMSET CATALYTIC INHIBITOR THAT SUPPRESSES H3K36ME2 IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol Number: K36MMSET-001

Inclusion Criteria

1. Voluntarily provide informed consent prior to initiation of study specific activities
2. ≥18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) score ≤ 2
4. Patients must have a confirmed diagnosis of RRMM (as per IMWG).
    - Patients must have received at least 3 prior lines of therapy as defined by IMWG, including a PI, an IMiD, and an anti-CD38 antibody
    - Patients must have exhausted available therapeutic options that are expected to provide a meaningful clinical benefit, either through disease relapse, treatment refractory disease, intolerance, or refusal of the therapy
    - *For expansion cohorts in Part B only:* Have t(4;14) confirmed by standard of care fluorescence in situ hybridization (FISH) testing or GOF mutation in MMSET confirmed by local sequencing test.
5. Measurable disease, including at least 1 of the following criteria:
    - Serum M protein (detected by serum protein electrophoresis [SPEP]) ≥ 0.50 g/dL
        - For patients with immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA ≥ 0.50 g/dL (IgA will similarly be used for response)
    - Urine M protein (detected by urine protein electrophoresis [UPEP]) ≥ 200 mg/24 h
    - Serum free light chain (sFLC) involved light chain ≥ 10 mg/dL (100 mg/L) provided sFLC ratio is abnormal
    - ≥ 1 extramedullary lesion on imaging, including ≥ 1 lesion that is ≥ 1 cm in size and able to be followed by imaging assessments (Dose Escalation Only)
    - Bone marrow plasma cells ≥ 10% (Dose Escalation Only)
6. Recovery to Grade ≤ 1 for any nonhematologic toxicities due to prior therapy, excluding alopecia or Grade 2 neuropathy
7. Ability and willingness to adhere to study visit schedule and protocol requirements

Exclusion Criteria

62. Treatment with the following therapies in the specified time period:

- Radiation, chemotherapy, immunotherapy, or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1 (C1D1)
- Cellular therapies (eg, chimeric antigen receptor T cell) ≤ 8 weeks prior to C1D1
- < 100 days post autologous transplant (prior to first dose)
- ≤ 6 months post allogenic transplant prior to C1D1 or if > than 6 months from allogenic transplant, no active graft-versus-host disease requiring treatment
- Major surgery ≤ 4 weeks from C1D1

63. History of or current plasma cell leukemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, and skin changes) syndrome, solitary bone lesion or bone lesions as the only evidence for plasma cell dyscrasia, myelodysplastic syndrome, or a myeloproliferative neoplasm or light chain amyloidosis.
64. Active central nervous system (CNS) disease: patients with previously treated stable CNS disease are eligible
65. Inadequate bone marrow function defined by:
    - Absolute neutrophil count (ANC) < 1000 cells/mm3
    - Platelets (PLT) < 75,000 cells/mm3
    - Hemoglobin < 8 g/dL (may be transfused provided no evidence of active bleeding)
66. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)
67. Direct bilirubin > 1.5 × ULN, > 2 × ULN for patients with documented Gilbert's syndrome
68. Prothrombin time (PT) or partial thromboplastin time (PTT) international normalized ratio (INR) > 1.5 × ULN, OR INR > 1.5 × ULN or within target range if on prophylactic anticoagulation
69. Creatinine clearance < 50 mL/min by Cockcroft-Gault formula
    - Active, ongoing, or uncontrolled systemic viral, bacterial, or fungal infection. Prophylactic medications, antimicrobials or antiretroviral therapies are permitted provided the agents are not prohibited
    - HIV-positive patients with CD4+ T-cell counts < 350 cells/μL or not on a stable antiretroviral regimen for > 4 weeks with a viral load > 400 copies/mL prior to enrollment may not be enrolled
    - Hepatitis C virus (HCV)-positive patients who have not completed curative antiviral treatment and have a quantifiable viral load may not be enrolled
    - Hepatitis B surface antigen (HBs-AG)-positive and hepatitis B core antigen (anti-HBc)-positive patients may be enrolled following a discussion with the Medical Monitor to discuss anti-hepatitis B virus (HBV) prophylaxis. Patients with chronic HBV infection should complete an anti-HBV therapy regimen with follow-up assessment
70. Use of prohibited medications, including acid reducing agents and strong inhibitors or inducers of CYP3A4, within 14 days or 5 half-lives prior to starting KTX-1001
71. Uncontrolled thromboembolic events or recent severe hemorrhage that, in the opinion of the Investigator or Medical Monitor would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion
72. Any history of pulmonary embolism or deep vein thrombosis (DVT) within 1 month of enrollment. Therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) is allowed for history of DVT if > 3 months from time of enrollment.
73. Active, unstable cardiovascular function; presence of any of the following:
    a. Symptomatic ischemia
    b. Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on antiarrhythmics are excluded; patients with first degree atrioventricular or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded)
    c. Congestive heart failure or New York Heart Association Class ≥ 3
    d. Myocardial infarction within 3 months prior to C1D1
    e. Uncontrolled hypertension
    f. QTc > 470 ms
74. Active malignancy not related to myeloma that has required therapy in the last 3 years prior to enrollment or is not in complete remission. Exceptions to these criteria include successfully treated nonmetastatic basal cell or squamous cell skin carcinoma, or prostate cancer that does not require therapy. Other similar malignant conditions may be discussed with and permitted by the Medical Monitor
75. Malabsorption syndrome or other condition affecting oral absorption
76. Men and women of reproductive potential who are unwilling to practice acceptable methods of effective birth control while on study through 6 months (women) or 3 months (men) after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (refraining from heterosexual intercourse; men, women); vasectomy; tubal ligation; or a condom with spermicide (men) in combination with barrier methods, hormonal birth control or intrauterine device (women)
    - Pregnancy, or females planning on becoming pregnant while on study or through 6 months after last study drug administration; or females who are lactating/breast feeding or who plan to breastfeed while on study through 6 months after last study drug administration

- Male patients must refrain from sperm donation, or attempt to conceive from study drug administration until 3 months after last dose of study drug

77. History or evidence of any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the Investigator or Medical Monitor would pose a risk to patient safety or interfere with the study evaluation, procedures or completion, including inability to find alternative concomitant medications that may be potential risk for drug-drug interaction (DDI)

Contact: Dr. Suzanne Trudel /Rebecca Noronha – **Open Enrollment**

A PHASE 1B/2, OPEN LABEL UMBRELLA STUDY OF ELRANATAMAB (PF-06863135), A B-CELL MATURATION ANTIGEN (BCMA) CD3 BISPECIFIC ANTIBODY, IN COMBINATION WITH OTHER ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH MULTIPLE MYELOMA
(Master protocol with two sub-studies A&B)
Protocol Number: C1071004 (MAGNETISMM-4)

Inclusion Criteria

1. Participant's age ≥ 18 years at the time of inform consent.
2. A female participant is eligible to participate if she is not pregnant or breastfeeding.
   a) Male participants and female participants of childbearing potential must agree to use methods of contraception according to the lenalidomide approved country label.
3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
4. Diagnosis of MM as defined according to IMWG criteria.
5. Measurable disease based on IMWG guidelines as defined by at least 1 of the following:
   a) Serum M-protein ≥ 0.5 g/dL by SPEP
   b) Urinary M-protein excretion ≥ 200 mg/24 hours by UPEP
   c) Serum immunoglobulin FLC ≥10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)
6. Refractory to at least one IMiD, proteasome inhibitor, and anti-CD38 antibody.
7. Relapsed or refractory to last prior anti-MM regimen.
   Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response. Relapsed MM is the recurrence of disease after a prior response, as defined by the IMWG criteria for clinical relapse evidenced by markers of increasing disease burden and/or end-organ dysfunction.
8. Received at least 3 prior MM lines of therapy for multiple myeloma.
9. Eastern Cooperative Oncology Group (ECOG) performance status grade 0-1.
10. LVEF ≥ 40% as determined by a MUGA scan or ECHO.
11. Adequate hepatic function characterized by the following:
    - Total bilirubin ≤1.5 × ULN (≤3 × ULN if documented Gilbert's syndrome)
    - AST ≤2.5 × ULN
    - ALT ≤2.5 × ULN
12. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (SSA) and ≥60 mL/min (SSB), (according to the Cockcroft-Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method).
13. Adequate bone marrow function characterized by the following at screening:
    - ANC ≥1,000/mm^3 (independent of growth factor support; use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing)
    - Platelets ≥25,000/mm^3 (SSA), and ≥30,000/mm^3 (SSB) (transfusion support is permitted if completed at least 7 days prior to planned start of dosing)
    - Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing)
14. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L).
15. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤ 1.

Exclusion Criteria

19. Active Plasma cell leukemia

20. Amyloidosis
21. Stem cell transplant within 12 weeks prior to enrollment, or active GVHD
22. POEMS syndrome
23. Ongoing Grade ≥2 peripheral sensory or motor neuropathy.
24. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (SSA).
25. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
26. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
    - Acute myocardial infarction or acute coronary syndromes (e.g., unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);
    - Clinically significant cardiac arrhythmias (e.g., uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
    - Thromboembolic or cerebrovascular events (e.g., transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);
    - Prolonged QT syndrome or QTcF ≥470 msec at screening.

27. Participants with active HBV, HCV, SARS-CoV-2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.
    a. COVID-19/SARS-CoV-2: While SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, he/she is excluded.
28. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
29. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
30. Known or suspected hypersensitivity to the study interventions or any of its excipients.
31. Primary refractory MM defined as participants who have never achieved at least a MR with any treatment during the disease course.
32. Participants who are unable to tolerate lenalidomide or discontinued prior lenalidomide due to treatment-related toxicity (SSB).
33. Previous treatment with an anti-BCMA bispecific antibody.
34. Prior treatment with anti-BCMA CAR-T and/or ADC therapy is permitted; however, the participant cannot be refractory to this therapy if it was administered as the last line prior to study enrollment (SSA).
35. Participant is currently using (within 7 days before the first administration of study intervention) drugs that are known strong inhibitors or strong inducers of cytochrome P450 3A4 (CYP3A4) (SSA).
36. Live attenuated vaccine within 4 weeks of the first dose of study intervention.
37. Previous administration with an investigational drug within 30 days or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
38. Intolerance to or participants who have had a severe (Grade ≥3) allergic or anaphylactic reaction to antibodies or therapeutic proteins.

SSA = Sub-Study A
SSB= Sub-Study B

Contact: Dr. Suzanne Trudel /Rebecca Noronha –**Enrollment on hold (pending amendment approval)**

A PHASE 1, MULTI-CENTER, OPEN-LABEL, DOSE FINDING STUDY OF CC-92328 IN SUBJECTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CC-92328-MM-001 (NK ENGAGER)

Inclusion Criteria

1. Subject must understand and voluntarily sign an informed consent form (ICF) prior to any study-related assessments/procedures being conducted.
2. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
3. Subject is ≥ 18 years of age the time of signing the ICF.
4. Subject has a history of MM with relapsed and/or refractory disease, and must:

- Have documented disease progression on or within 12 months from the last dose of their last myeloma therapy (subjects with documented disease progression who received CAR T cells as their last myeloma therapy are permitted to enroll beyond 12 months from CAR T infusion) and,
- Have received at **least 3 prior MM treatment regimens**, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody (e.g., daratumumab or isatuximab). Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen; and,
- Have failed treatment with, are intolerant to, or are not candidates for available therapies that are known to confer clinical benefit to patients with 4L+ relapsed and refractory MM. Prior treatment with BCMA targeted agents is allowed.

5. Subject must have measurable disease (as determined by the central lab), including at least one of the criteria below:
   - M-protein quantities ≥ 0.5 g/dL by serum protein electrophoresis (sPEP) or
   - M-protein quantities ≥ 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP) or
   - Serum FLC levels > 100 mg/L (milligrams/liter involved light chain) and an abnormal kappa/lambda (κ/λ) ratio in subjects without measurable serum or urine M-protein or for subjects with immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 0.50 g/dL.
6. Subject consents to serial bone marrow aspirations and/or biopsies during Screening, study treatment and at the end of treatment.
7. Subject has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.
8. Subject must have the following laboratory values (determined by local lab):
   - Absolute neutrophil count (ANC) ≥ 1.0 x 109/L without growth factor support for 7 days (14 days if pegfilgrastim)
   - Platelets ≥ 50 x 109/L without transfusion for 7 days
   - Potassium within normal limits or correctable with supplements
   - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 3 x upper limit of normal (ULN)
   - Serum bilirubin ≤ 1.5 x ULN
   - Estimated serum creatinine clearance of ≥ 45 mL/min using the Cockcroft-Gault equation or directly calculated from the 24-hour urine collection method
   - International normalized ratio (INR) < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN (for subjects not receiving therapeutic anticoagulation).
9. Females of childbearing potential (FCBP) must:
   - Either commit to true abstinence from heterosexual contact or agree to use, and be able to comply with, at least one highly effective method of contraception (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; or vasectomized partner), from signing the ICF, throughout the study, including dose interruptions, and for at least 9 weeks following the last dose of CC-92328. The selected contraceptive method will be reviewed and evaluated on a monthly basis, and this will be noted in source documents; and
   - Have two negative pregnancy tests as verified by the Investigator prior to starting CC-92328. She must agree to ongoing pregnancy testing during the course of the study, through 9 weeks following treatment discontinuation. This applies even if the subject practices true abstinence2from heterosexual contact. The subject may not receive IP until the Investigator has verified that the result of the pregnancy tests are negative.
   - a negative serum pregnancy test (sensitivity of at least 25 mIU/mL) at Screening
   - a negative serum or urine pregnancy test (Investigator's discretion) within 72 hours prior to the first dose (Cycle 1 Day 1) of study treatment, and within 72 hours prior to Day 1 of every subsequent cycle (note that the Screening serum pregnancy test can be used as the test prior to Cycle 1 Day 1 study treatment if it is performed within the prior 72 hours prior to the first dose of IP). A serum or urine pregnancy test (Investigators discretion) must also be performed at treatment discontinuation, and at 9 weeks following treatment discontinuation.
   - Avoid conceiving for 9 weeks after the last dose of CC-92328.
   - Agree to ongoing pregnancy testing during the course of the study, and after the end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
10. Males must practice true abstinence (which must be reviewed, evaluated and source documented on a monthly basis) or agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or a FCBP and will avoid conceiving from signing the ICF, while participating in the study, during dose interruptions, and for at least 9 weeks following CC-92328 discontinuation, even if he has undergone a successful vasectomy.

Exclusion Criteria

1. Subject has symptomatic central nervous system involvement of MM.
2. Subject has non-secretory multiple myeloma, plasma cell leukemia, Waldenstrom's Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis.
3. Subject is on chronic systemic immunosuppressive therapy or corticosteroids (e.g., prednisone or equivalent exceeding a total of 140 mg over the last 14 days) or subjects with clinically significant graft-versus-host disease. Intranasal, inhaled, topical, or local

corticosteroid injections (e.g., intra-articular injection), or steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are exceptions to this criterion.
4. Subject with a history of class III or IV congestive heart failure or severe non-ischemic cardiomyopathy, unstable angina, myocardial infarction, or any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
5. Inadequate cardiac function, defined as left ventricular ejection fraction (LVEF) < 45% as assessed by echocardiogram (ECHO) or multiple uptake-gated acquisition (MUGA) scan performed within 30 days of determination of eligibility.
6. Subject had a prior autologous stem cell transplant ≤ 90 days prior to starting CC-92328.
7. Subject had prior anti-CD38 antibody treatment ≤ 90 days prior to starting CC-92328.
8. Subject had a prior allogeneic stem cell transplant with either standard or reduced intensity conditioning ≤ 12 months prior to starting CC-92328.
9. Subject had prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting CC-92328, whichever is shorter. Subjects must have recovered from any clinically significant non-hematologic toxicities (i.e., to Grade ≤ 1) of prior systemic anti-cancer directed treatments unless otherwise specified.
10. Subject had major surgery ≤ 2 weeks prior to starting CC-92328. Subjects must have recovered from any clinically significant effects of recent surgery.
11. Subject is a pregnant or lactating female.
12. Subject received live virus vaccines within at least 4 weeks prior to starting study drug.
13. Subject has known active human immunodeficiency virus (HIV) infection.
    - Subjects with well controlled HIV are eligible if they have CD4+ T-cell (CD4+) counts ≥ 350 cells/uL and have not had an opportunistic infection within the past 12 months
14. Subject has active hepatitis B or C (HBV/HCV) infection.
    - Subject with no active hepatitis B infection (e.g., HBsAg negative, anti-HBc positive) who are under adequate prophylaxis against HBV re-activation are eligible.
    - Subject who had HCV but have received a curative antiviral treatment and show no evidence of active HCV infection are eligible.
15. Subject has a history of a venous thromboembolic event (VTE) within 6 months prior to study entry (e.g., deep-vein thrombosis or pulmonary embolism).
    - Subjects with distant history of VTE (i.e., occurring > 6 months prior to study entry) who require ongoing treatment with chronic, therapeutic dosing of anti-coagulants (e.g., warfarin, low molecular weight heparin, Factor Xa inhibitors) are eligible for study entry.
16. Subject has a history of concurrent second cancers requiring active, ongoing systemic treatment.
17. Subjects with extramedullary disease with visceral involvement of vital organs (e.g., lung, renal, cardiac, liver) may be excluded from study entry. Such cases must be discussed with the Medical Monitor prior to enrollment.
18. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
19. Subject has any condition (e.g., active or uncontrolled infection) including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
20. Subjects with previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to C1D. Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving study treatment.
21. Previous SARS-CoV-2 vaccine within 14 days of C1D1. For vaccines requiring more than one dose, the full series (e.g., both doses of a two-dose series) should be completed by at least 14 days prior to C1D1 when feasible and when a delay in C1D1 would not put the study subject at risk.
22. Inadequate pulmonary function as defined as oxygen saturation (SpO2) < 92 % on room air.
23. Subject weight is ≤ 40 kg at screening

Contact: Dr. Donna Reece / Trina Wang – **Open for Enrollment**

AN OPEN-LABEL, MULTICENTER, PHASE Ib TRIAL EVALUATING THE SAFETY, PHARMACOKINETICS, AND ACTIVITY OF CEVOSTAMAB IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: GO42552

Key Inclusion Criteria

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Life expectancy of at least 12 weeks

- Diagnosis of R/R MM for which no established therapy for MM is appropriate and available, or intolerance to those established therapies
- Resolution of adverse events from prior anti-cancer therapy to Grade ≤ 1, with the following exceptions:
    - Any grade alopecia is allowed.
    - Peripheral sensory or motor neuropathy must have resolved to Grade ≤ 2.
- Measurable disease defined as at least one of the following:
    - Serum M-protein ≥0.5 g/dL (≥5 g/L)
    - Urine M-protein ≥ 200 mg/24 hr.
    - Serum free light chain (SFLC) assay: Involved SFLCs ≥10 mg/dL (≥100 mg/L) and an abnormal SFLC ratio (<0.26 or >1.65)
- Laboratory values as follows:
    - Hepatic function
        - AST and ALT ≤ 3 x ULN
        - Total bilirubin ≤ 1.5 x ULN; patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.

    - Hematologic function (requirement prior to first dose of cevostamab)
        - Platelet count ≥ 50,000/mm3 without transfusion within 7 days prior to first dose
        - ANC ≥ 1000/mm3
        - Total hemoglobin ≥ 8 g/dL

          Note: Patients may receive supportive care (e.g., transfusion, G-CSF, etc.) to meet hematologic function eligibility criteria.

          Patients who do not meet criteria for hematologic function because of MM-related cytopenias (e.g., due to extensive marrow involvement by MM) may be enrolled into the study after discussion with and with the approval of the Medical Monitor.

    - Creatinine ≤ 2.0 mg/dL and creatinine clearance (CrCl) ≥ 30 mL/min (either calculated using modified Cockcroft-Gault equation or per 24-hr urine collection)
    - Serum calcium (corrected for albumin) level ≤ 11.5 mg/dL (treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to Grade ≤ 1 with standard treatment)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Patients treated with cevostamab: Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period (including treatment interruptions) and for at least 3 months after the last dose of cevostamab was administered.

  Patients treated with tocilizumab (if applicable): Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of tocilizumab was administered. Women must refrain from breastfeeding during the same period.
  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgical sterilization (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

Men must remain abstinent or use a condom during the treatment period (including treatment interruptions), and for at least 60 days after the last dose of cevostamab or tocilizumab (if applicable) was administered to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Key Exclusion Criteria:

- Prior treatment with cevostamab or another agent with the same target
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the last dose of study drug
    - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate as anti-cancer therapy within 4 weeks before first study treatment, except for the use of non-myeloma therapy (e.g., denosumab for hypercalcemia is allowed).
- Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA 4, anti-PD-1, and anti-PD-L1 therapeutic antibodies within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first study treatment
- Prior treatment with CAR T-cell therapy within 12 weeks before first cevostamab infusion
- Known treatment-related, immune-mediated adverse events associated with prior checkpoint inhibitors as follows:
    - Prior PD-L1/PD-1 or CTLA-4 inhibitor: Grade ≥3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy
    - Grade 1-2 adverse events that did not resolve to baseline after treatment discontinuation
- Treatment with radiotherapy, any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first study treatment
- Autologous SCT within 100 days prior to first study treatment
- Prior allogeneic SCT
- Circulating plasma cell count exceeding 500/μL or 5% of the peripheral blood white cells
- Prior solid organ transplantation
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
- History of confirmed progressive multifocal leukoencephalopathy
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- Known history of amyloidosis (e.g., positive Congo Red stain or equivalent in tissue biopsy)
- Lesions in proximity of vital organs that may develop sudden decompensation/deterioration in the setting of a tumor flare
    - Patients may be eligible after discussion with the Medical Monitor.
- History of other malignancy within 2 years prior to screening, except those with negligible risk of metastasis or death (e.g., 5-year overall survival [OS]>90%), such as ductal carcinoma in situ not requiring chemotherapy, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, low-grade, localized prostate cancer (Gleason score ≤ 7) not requiring treatment or appropriately treated Stage I uterine cancer.
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
    - Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.
    - Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed.
- Significant cardiovascular disease (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, uncontrolled arrhythmias, or unstable angina) that may limit a patient's ability to adequately respond to a CRS event

- Patients may be eligible after discussion with the Medical Monitor.
- Symptomatic active pulmonary disease or requiring supplemental oxygen
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics where the last dose of IV antibiotics was given within 14 days prior to first study treatment
- Known or suspected chronic active EBV infection
  - Guidelines for diagnosing chronic active EBV infection are provided by Okano et al. (2005).
- Recent major surgery within 4 weeks prior to first study treatment
  - Protocol-mandated procedures (e.g., bone marrow biopsies) are permitted.
- Positive serologic or PCR test results for acute or chronic HBV infection
  - Patients whose HBV infection status cannot be determined by serologic test results (www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation.
- Acute or chronic HCV infection
  - Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Known history of HIV seropositivity
- Administration of a live, attenuated vaccine within 4 weeks before first study treatment or anticipation that such a live attenuated vaccine will be required during the study
  - Influenza vaccination may be given during influenza season (approximately October to May in the Northern Hemisphere; approximately May to October in the Southern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist) at any time during the study treatment period.

    SARS-CoV-2 vaccines, when available, may be given in accordance with the approved/authorized vaccine label and official/local immunization guidance, with approval of the Medical Monitor. SARS-CoV-2 vaccines must not be administered within 1 week before first study treatment or during Cycle 1.

    Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with any other non-live vaccines intended to prevent infectious diseases prior to study.

    Exceptions may be permitted with the approval of the Medical Monitor.

- Treatment with systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents), with the exception of corticosteroid treatment ≤ 10 mg/day prednisone or equivalent, within 2 weeks prior to first study treatment
  - The use of inhaled corticosteroids is permitted.
  - The use of mineralocorticoids for management of orthostatic hypotension is permitted.
  - The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any medical condition or abnormality in clinical laboratory tests that, in the investigator's or Medical Monitor's judgment, precludes the patient's safe participation in and completion of the study

Contact: Dr. Suzanne Trudel/Rebecca Noronha –**Open for Enrollment (Only Arm B)**

OPEN LABEL, MULTI-CENTER, PHASE 1B/2 CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF AUTOLOGOUS CAR-BCMA T CELLS (CT053) IN PATIENTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CT053-MM-02

Inclusion Criteria:

1. Patients must be ≥ 18 and ≤ 80 years old;
2. The patients have received at least 4 prior lines of therapy for MM,
3. The subjects must be exposed to at least one proteasome inhibitor, at least one IMiD, and at least one CD38-targeting antibody.
4. The patient should be refractory to the last line of therapy (progression on or within 60 days of discontinuing treatment).

5. The patients should have measurable disease based on at least one of the following parameters:
a. Serum M-protein ≥ **1.0 g/dL**
b. Urine M-protein ≥ **200 mg/24 hrs**
c. Serum free light chain (FLC): involved **FLC level ≥ 10 mg/dL (100 mg/L)** provided serum FLC ratio is abnormal.
6. Estimated life expectancy > 12 weeks
7. ECOG performance score 0-1
8. Subjects should meet the following without intensive supportive therapy:
a. Complete blood count (CBC) results:

- Screening absolute neutrophil count ANC ≥ 1.0 × 109/L, platelet count ≥ 75 × 109/L (If the proportion of plasma cells in the bone marrow is > 50%, subjects with platelet ≥ 50 × 109/L will be eligible), **Hb ≥ 7.5 g/dL**

Note: A maximum of one transfusion may be allowed within 7 days prior toleukapheresis if recommended by the treating physician.

- No growth factor support is allowed within 7 days of testing. Baseline (without transfusion and growth factor support within 7 days of testing): ANC ≥ 0.8 × 109/L, platelet count ≥ 45 × 109/L, Hb ≥ 6.5 g/dL.

b. Blood biochemistry:

- Screening: Creatinine clearance ≥ 45 mL/min (Cockcroft –Gault formula), alanine aminotransferase (ALT) ≤ 2.5 × upper limit normal (ULN), aspartate aminotransferase (AST) ≤ 2.5 × ULN, total bilirubin ≤ 2 × ULN (except patients with Gilbert's syndrome who must have a total bilirubin ≤ 3 × ULN)
- Baseline: Adequate renal function defined by creatinine clearance ≥ 30 mL/min; adequate hepatic function defined by AST and/or ALT ≤ 2.5 × ULN and total bilirubin ≤ 2 × ULN (except subjects with Gilbert's syndrome who must have a total bilirubin ≤ 3 × ULN).

9. Sufficient venous access for leukapheresis collection, and no other contraindications to leukapheresis.

Exclusion criteria:

1. Pregnant or lactating women
2. Patients with HIV, active hepatitis C virus (HCV), or active hepatitis B virus (HBV) infection. History of treated hepatitis B or C is permitted if the viral load is undetectable per qPCR and or nucleic acid testing
3. Patients with any uncontrolled active infection
4. Patients who have had either:

- Previous anti-BCMA therapy (antibody drug conjugate or bi-specific T cell engager) without response to treatment (≥PR);
- Previous anti-BCMA CAR-T therapy (with or without response to the treatment)
- Any other type of investigational cellular therapy within one year (such as CAR-T, TCR, NK, NKT, etc.).

5. Patients who have active acute graft versus host disease (GvHD) or chronic GvHD, or patients who had previous Grade 2 or higher GvHD
6. Left ventricular ejection fraction (LVEF) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan.

- Screening: LVEF < 50%
- Baseline: LVEF < 45% (for indicated subjects who require ECHO/MUGA re-evaluation)

7. Subjects who have one of the following pulmonary conditions:

- Forced expiratory volume in 1 second (FEV1) < 60%.
- Active obstructive chronic pulmonary disease.
- Require oxygen support to maintain oxygen saturation (finger detection) at
  - Screening: O2 saturation > 92%
  - Baseline: O2 saturation > 90%

8. Subjects who have received any of the following:

- Autologous stem cell transplantation within one year.
- Allogeneic stem cell transplantation within two years.

9. Subjects who have received radiation in which the field covers > 5% of the bone marrow 30 days before leukapheresis or 14 days before lymphodepletion. Subjects who have received any anticancer treatment other than radiation 14 days before leukapheresis or lymphodepletion. If the field of radiation covers ≤ 5% of the bone marrow, the subjects are eligible to participate in the study regardless of the radiotherapy end date.
10. Patients have received ≥ 20 mg prednisone daily or other equivalent dose of steroids within 14 days before leukapheresis or 72 hours prior to lymphodepletion
Note: Any steroid treatment encroaching into the 14-day washout period may be allowable if discussed with and approved by the study medical monitor.
11. Patients have received major surgery 7 days prior to leukapheresis or 21 days prior to lymphodepletion (excluding cataract and other local anesthesia)

12. Subjects who have significant neurologic disorders such as seizures or dementia or prior brain bleeding (subarachnoid or subdural hematoma within the past 5 years) and unable to safely stop anticoagulation treatment during the screening and treatment phase.
13. *Bridging Therapy:* The subjects shall not receive any bridging therapy within 14 days prior to start of lymphodepletion unless approved by the study medical monitor.
14. Patients with second malignancies in addition to MM are not eligible if the second malignancy has required treatment within the past 3 years or is not in complete remission. There are two exceptions to this criterion: successfully treated non-metastatic basal cell or squamous cell skin carcinoma.

Contact: Dr. Christine Chen/Trina Wang- **Enrollment on hold by the sponsor**

A PHASE I/II, RANDOMIZED, OPEN-LABEL PLATFORM STUDY UTILIZING A MASTER PROTOCOL TO STUDY BELANTAMAB MAFODOTIN (GSK2857916) AS MONOTHERAPY AND IN COMBINATION WITH ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) – DREAMM 5.

Protocol Number: 208887

Inclusion Criteria:

1. Participants who have histologically or cytologically confirmed diagnosis of MM, as defined by the International Myeloma Working Group.
2. Participants who have been treated with at least 3 prior lines of prior anti-myeloma treatments including an IMID (e.g. Lenalidomide), a proteasome inhibitor (e.g. Bortezomib) and an anti-CD38 monoclonal antibody. Lines of therapy are defined by consensus panel of the International Myeloma Workshop
3. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
   a. transplant was >100 days prior to screening
   b. no active infection(s)
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
5. Measurable disease defined as at least 1 of the following:
   - Serum M-protein ≥0.5 g/dL (≥5 g/L)
   - Urine M-protein ≥200 mg/24 hours
   - Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
6. Have organ system functions as defined by the following laboratory assessments:
   - Absolute neutrophil count (ANC >1.0 x109/L)
   - Hemoglobin >8.0 g/dL
   - Platelets >50 x109/L
   - Total bilirubin ≤1.5xULN (isolated bilirubin >1.5xULN is
   - acceptable if bilirubin is fractionated and direct
   - bilirubin <35%)
   - Alanine transaminase (ALT) <2.5xULN
   - Aspartate aminotransferase (AST) <2.5xULN
   - Estimated glomerular filtration rate (eGFR) 40 mL/min/1.73 m2
   - Spot urine (albumin/creatinine ratio) <500 mg/g (56 mg/mmol)
   - Left ventricular ejection fraction (LVEF) ≥ 50%
7. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI -CTCAE], version 5.0, 2017) must be Grade 1 at the time of screening except for alopecia (any grade), neuropathy (Grade 2), or endocrinopathy managed with replacement therapy (any grade).

Exclusion criteria:

1. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, Myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell Leukemia at the time of screening.
2. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent, or compliance with study procedures.
3. Current corneal epithelial disease except mild punctate keratopathy

4. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.

5. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM).

- Participants with curatively treated non-melanoma skin cancer are not excluded.

6. Evidence of cardiovascular risk including any of the following:
a. QTcF interval ≥480 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
b. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobiz Type II) or 3rd degree atrioventricular (AV) block.
c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting or bypass grafting, all within three months of Screening.
d. Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
e. Uncontrolled hypertension
f. Recent (within the past 6 months) history of symptomatic pericarditis.
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK'916 (belantamab mafodotin) or any of the components of the study treatment. History of severe hypersensitivity to other mAbs.
8. Active infection requiring antibiotic, antiviral, or antifungal treatment.
9. Any major surgery within the last four weeks prior to the first dose of study therapy
10. Presence of active renal condition. Subjects with isolated proteinuria resulting from MM are eligible.
11. Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
12. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
13. Current active liver or biliary disease
14. Evidence of any cardiovascular risk defined in the protocol

- QTcF interval ≥470 msecs
- Evidence of current clinically significant uncontrolled arrhythmias;
- History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
- Class III or IV heart failure as defined by the New York Heart Association functional classification system
- Uncontrolled hypertension
- Presence of cardiac pacemaker
- Abnormal cardiac valve morphology (≥Grade 2)

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or Pembrolizumab, or any of the components of the study treatment.
16. Known active infection requiring antibiotic, antiviral, or antifungal treatment
17. Active autoimmune disease that has required systemic treatment in past 2 years
18. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy

Contact: Dr. Suzanne Trudel/Olga Levina– **Open for enrollment**

AN OPEN-LABEL, MULTICENTER, PHASE I TRIAL EVALUATING THE SAFETY AND PHARMACOKINETICS OF ESCALATING DOSES OF BFCR4350A IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: G039775

Key Inclusion Criteria:

1. Patients must have R/R MM for which no established therapy for MM is appropriate and available or be intolerant to those established therapies
2. Agreement to provide bone marrow biopsy and aspirate samples as per protocol
3. Adverse events from prior anti-cancer therapy resolved to Grade ≤ 1, with the following exceptions:
    a. Any grade alopecia, peripheral sensory or motor neuropathy must have resolved to Grade ≤ 2
4. Measurable disease defined as at least one of the following:
    a. Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)

   b. Urine M-protein ≥ 200 mg/24 hr.
   c. Serum free light chain (SFLC) assay: Involved SFLCs ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (< 0.26 or > 1.65)
5. Laboratory values:
   a. Hepatic function: AST and ALT ≤ 3 × ULN; Total bilirubin ≤ 1.5 × ULN; patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
   b. Hematologic function: Platelet count ≥ 75,000/mm3 without transfusion within 14 days prior to first dose of BFCR4350A, ANC ≥ 1000/mm3, Total hemoglobin ≥ 8 g/dL
   c. Creatinine ≤ 2.0 mL/dL and creatinine clearance (CrCl) ≥ 30 mL/min (either calculated or per 24-hr urine collection)
   d. Serum calcium (corrected for albumin) level at or below the ULN
6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of BFCR4350A and tocilizumab (if applicable)
7. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm

Key Exclusion Criteria:

1. Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 4 weeks before first BFCR4350A infusion
2. Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA4, anti−PD-1, and anti−PD-L1 therapeutic antibodies, within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first BFCR4350A infusion
3. Treatment-related, immune-mediated adverse events associated with prior immunotherapeutic agents as follows:
   a. Grade ≥ 3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy
   b. Grade 1−2 adverse events that did not resolve to baseline after treatment discontinuation
4. Treatment with radiotherapy, any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first BFCR4350A infusion
5. Autologous stem cell transplantation (SCT) within 100 days prior to first BFCR4350A infusion
6. Prior allogeneic SCT
7. Primary or secondary plasma cell leukemia as defined by an absolute plasma cell count exceeding 2000/μL or 20% of the peripheral blood white cells
8. Prior solid organ transplantation
9. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
10. Patients with history of confirmed progressive multifocal leukoencephalopathy
11. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
12. History of other malignancy that could affect compliance with the protocol or interpretation of results. - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
    a. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to first BFCR4350A infusion.
13. Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
    a. Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.
    b. Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed.
14. Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
15. Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
16. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics within 4 weeks prior to first BFCR4350A infusion
17. Known or suspected chronic active EBV infection.
18. Recent major surgery within 4 weeks prior to first BFCR4350A infusion

19. Positive serologic or PCR test results for acute or chronic HBV infection: Patients whose HBV infection status cannot be determined by serologic test results
20. Acute or chronic HCV infection
21. Known history of HIV seropositivity
22. Administration of a live, attenuated vaccine within 4 weeks before first BFCR4350A infusion or anticipation that such a live attenuated vaccine will be required during the study.
23. Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of corticosteroid treatment ≤ 10 mg/day prednisone or equivalent within 2 weeks prior to first dose of BFCR4350A
    a. Patients who received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval of the Medical Monitor
    b. The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
24. History of illicit drug or alcohol abuse within 12 months prior to screening,

Contact: Dr. Suzanne Trudel/Rebecca Noronha– **(Enrollment on hold)**

AMYLOIDOSIS TRIALS:

A PHASE 2, MULTICOHORT STUDY OF DARATUMUMAB-BASED THERAPIES IN PARTICIPANTS WITH AMYLOID LIGHT CHAIN (AL) AMYLOIDOSIS

Protocol Number: 54767414AMY2009 AQUARIUS

Inclusion Criteria

1. ≥18 years of age.
2. New diagnosis of systemic AL amyloidosis based on both: (a) tissue deposition of amyloid in any organ other than bone marrow and (b) an underlying clonal plasma cell disorder as demonstrated by any one of the following:

- Clonal plasma cells in the bone marrow
- Monoclonal gammopathy in the serum or urine
- Abnormal free light chain ratio

Measurable disease at screening defined by:

- difference between iFLC and uninvolved FLC (dFLC) ≥40mg/L per central laboratory

Since other types of amyloidosis such as age-related amyloidosis or hereditary amyloidosis (ATTR mutation) may be encountered in specific populations, mass spectrometry typing of AL amyloid in a tissue biopsy is mandatory for:

- Male participants 70 years of age or older who have only cardiac involvement, or
- Black or African American participants

3. Cohort 1: Cardiac involvement (AL amyloidosis Mayo Cardiac Stage II and Stage IIIa; with or without other organ(s) involved.

Cohort 2: One or more organs impacted by systemic AL amyloidosis according to consensus guidelines

4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2.
5. Pre-treatment clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥8.0 g/dL (≥5 mmol/L); red blood cell transfusion allowed until 7 days before randomization/enrollment
Platelets	≥50×109 /L; platelet transfusions are allowed until 7 days before randomization/enrollment
Absolute Neutrophil count (ANC)	≥1.0×109 /L
Chemistry	
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5× ULN
Total bilirubin	≤1.5 × ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case

	direct bilirubin ≤2×ULN is required)
Estimated glomerular filtration rate (eGFR)	≥20 mL/min/1.73 m2 . Note: the eGFR is measured by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Abbreviations: ULN=upper level of normal

6. A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.
7. A female participant must be (as defined in Appendix 3: Contraceptive and Barrier Guidance) either of the following
   a. Not of childbearing potential
   b. Of childbearing potential and
      - practicing true abstinence.
      - or have a sole partner who is vasectomized.
      - or practicing at least 1 highly effective user independent method of contraception

   Contraception must begin 4 weeks prior to dosing and continue for 1 year after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. Note: If a woman becomes of childbearing potential after start of the study the woman must comply with point (b) as described above.
8. A male participant must wear a condom (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. His female partner, if of childbearing potential, must also be practicing a highly effective method of contraception

   If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/suppository), but his female partner is not required to use contraception
9. A female participant must agree not to donate eggs (ova, oocytes) or freeze for future use, for the purposes of assisted reproduction during the study and for a period of least 1 year after the last dose of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer.
10. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer.
11. Signed an informed consent form (ICF).
12. Cohort 2 only: self-identified racial and ethnic minorities, including Black or African American.
    Note: for Cohort 2, enrollment of Black or African American participants will be prioritized before the enrollment of other minorities to ensure a minimum of 15 participants with Black or African American. The Sponsor may consider pausing enrollment of other minority groups to ensure at least 15 Black or African American participants are included in Cohort 2. All minority participants may also be enrolled in Cohort 1 provided participants meet eligibility criteria for Cohort 1

Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Prior therapy for systemic AL amyloidosis or multiple myeloma including medications that target CD38, with the exception of 160 mg dexamethasone or equivalent corticosteroid maximum exposure prior to randomization/enrollment.
2. Previous or current diagnosis of symptomatic multiple myeloma per International Myeloma Working Group (IMWG) Criteria
3. Participant received any of the following therapies:
   a. treatment with an investigational drug or used an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less.
   b. vaccinated with an investigational vaccine (except for COVID-19), live attenuated or replicating viral vector vaccines within 4 weeks prior to randomization/enrollment.
      - participants who are taking strong CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of bortezomib
4. Stem cell transplantation –Planned stem cell transplant during the first 9 cycles of protocol therapy are excluded. Stem cell collection during the first 9 cycles of protocol therapy is permitted.
5. Grade 2 sensory or Grade 1 painful peripheral neuropathy.
6. Evidence of significant cardiovascular conditions as specified below:
   a. NT-ProBNP >8500 ng/L.
   b. NYHA classification IIIB or IV heart failure.

c. Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg, prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy.
d. Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass grafting within 6 months.
e. For participants with CHF, cardiovascular-related hospitalizations within 4 weeks prior to randomization/enrollment.
f. Participants with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ implantable cardioverter-defibrillator is indicated but not placed (Participants who do have a pacemaker/ implantable cardioverter-defibrillator are allowed on study).
g. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >500 msec. Participants who have a pacemaker may be included regardless of calculated QTc interval.
h. Supine systolic blood pressure 20 mm Hg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion.

7. Participant has an active malignancy (ie, progressing or requiring treatment change in the last 12 months) other than the disease being treated under study. The only allowed exceptions are:
    a. Non -muscle invasive bladder cancer treated within the last 12 months that is considered completely cured.
    b. Skin cancer (non-melanoma or melanoma) treated within the last 12 months that is considered completely cured.
    c. Non -invasive cervical cancer treated within the last 12 months that is considered completely cured.
    d. Localized prostate cancer (N0M0):
        - with a Gleason score of <6, regardless of treatment (active surveillance or active treatment) and has no biochemical recurrence (BCR),
        - with a Gleason score of 7 that has been treated more than 6 months prior to screening or did not get any treatment and has no BCR,
        - with a Gleason score 8-10 that has been treated more than 2 years prior to screening and has no BCR.
    e. Breast cancer:
        - adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
        - history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence
    f. Malignancy that is considered cured with minimal risk of recurrence.

8. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study treatment or its excipients, including bortezomib, boron, mannitol, or cyclophosphamide or any of its metabolites (refer to Investigator's Brochure and package inserts).
9. Known allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to IB), or known sensitivity to mammalian-derived products
10. Pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 year after discontinuation of cyclophosphamide or 100 days after the last dose of daratumumab, whichever is longer.
11. Plans to father a child while enrolled in this study or within 100 days after the last dose of study treatment
12. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1)
13. Moderate or severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification. (Note that participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).
14. Any of the following:
    a. Participant is known to be positive for human immunodeficiency virus (HIV), with 1 or more of the following:
    b. Not receiving highly active antiretroviral therapy (ART)
    c. Had a change in ART within 6 months of the start of screening
    d. Receiving ART that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment)
    e. CD4 count <350 at screening
    f. Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of start of screening
    g. Not agreeing to start ART and > 4 weeks plus having HIV viral load <400 copies/mL. at end of 4-week period (to ensure ART is tolerated and HIV controlled)

Note: enrollment of participants who meet the above criteria should be discussed with the medical monitor prior to enrollment

15. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HbsAg]). Participants with resolved infection (ie, participants who are HbsAg negative with antibodies to total hepatitis B core antigen [Anti-HBc] with or without the presence of hepatitis B surface antibodies [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of HBV- deoxyribonucleic acid (DNA) levels. Those who are real-time PCR positive will be excluded.
    EXCEPTION: Participants with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV-DNA by real-time PCR.
    a. Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

16. Any serious underlying medical or psychiatric condition or disease, that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:
    - Evidence of serious active viral or bacterial infection, requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection.
    - Active autoimmune disease or a history of autoimmune disease within 2 years. EXCEPTION: Participants with vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed
    - Disabling psychiatric conditions (e.g., alcohol or drug abuse), severe dementia, or altered mental status.

    Any other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the study site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
17. Major surgical procedure within 2 weeks before randomization/enrollment or has not fully recovered from an earlier surgical procedure, or has major surgical procedure planned during the time the participant is expected to participate in the study.
    Note: participants with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question about whether a procedure is considered a major surgical procedure, the investigator must consult with the Sponsor and resolve any issues before enrolling a participant in the study.
18. Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.

Contact: Dr. Donna Reece /Olga Levina – **Open Enrollment**

WALDESTROM'S MACROGLOBULINEMIA TRIALS:

THE USE OF PERIPHERAL BLOOD CELL-FREE DNA (CFDNA) FOR GENETIC PROFILING IN PATIENTS WITH LYMPHOPLASMACYTIC LYMPHOMA (LPL) AND WALDENSTROM'S MACROGLOBULINEMIA (WM)

Protocol Number: PM-WM001

Non-Interventional

Inclusion criteria:
1. Males or females aged 18 years or older at the time of signing consent
2. A confirmed diagnosis of lymphoplasmacytic lymphoma or Waldenstrom's Macroglobulinemia
3. Treatment-naïve or previously treated
4. Known to Princess Margaret Cancer Centre with routine standard of care laboratory testing available

Exclusion criteria:
1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form
2. Currently undergoing treatment for active malignancy, NOT indolent lymphoma

Contact: Dr. Christine Chen/Harjot Vohra -**Open Enrollment**

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