Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre (Version January 2022)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

A RANDOMIZED STUDY OF DARATUMUMAB PLUS LENALIDOMIDE VERSUS LENALIDOMIDE ALONE AS MAINTENANCE TREATMENT IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA WHO ARE MINIMAL RESIDUAL DISEASE POSITIVE AFTER FRONTLINE AUTOLOGOUS STEM CELL TRANSPLANT
Protocol Number: 54767414MMY3021 (AURIGA)

Inclusion Criteria

1. 18 to 79 years of age.
2. Newly diagnosed multiple myeloma with a history of a minimum of 4 cycles of induction therapy, have received ASCT within 12 months of the start of induction therapy, and be within 6 months of ASCT on the date of randomization
3. VGPR or better response assessed per IMWG 2016 criteria at the time of randomization.
4. Have an archived bone marrow samples collected before induction treatment (i.e., at diagnosis) or before transplant (eg, at the end of induction) or have existing results on the index MM clone based on Adaptive Biotechnologies' NGS-based MRD assay.
4. Must have residual disease as defined by detectable MRD (Adaptive Biotechnologies' NGS-based MRD assay).
5. ECOG performance status score of 0, 1, or 2
6. Pretreatment clinical laboratory values meeting the following criteria during screening
   - **Hemoglobin** ≥7.5 g/dL (≥4.65 mmol/L) (without RBC transfusion or recombinant human erythropoietin in prior 7 days)
   - **Absolute Neutrophil Count** (ANC) $\geq 1.0\times10^9$/L. Granulocyte colony stimulating factor use is permitted.
   - **Platelets** ≥50×109/L or $\geq 75\times10^9$/L for patients in whom <50% of bone marrow nucleated cells are plasma cells (without transfusion in prior 7 days)
   - **Aspartate aminotransferase** ≤2.5 folds of the upper limit of normal (ULN)
   - **Alanine aminotransferase** ≤2.5 folds of the ULN
   - **Total bilirubin** ≤2.0 folds of the ULN (except in patients with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤2.0 folds of the ULN)
   - **Estimated creatinine clearance** ≥30 mL/min. Creatinine clearance may be calculated using Cockcroft-Gault, estimated glomerular filtration rate (Modification of Diet in Renal Disease [MDRD]), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
   - **Corrected serum calcium** ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L)
8. If female, must follow study pregnancy prevention or not be of childbearing potential.

Exclusion Criteria

1. A history of malignancy (other than multiple myeloma) unless all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease before the date of randomization. Exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.
2. Must not have progressed on MM therapy at any time prior to screening.
3. Have had prior treatment/therapy with:
   a. Daratumumab or any other anti-CD38 therapies,
   b. Focal radiation therapy within 14 days prior to randomization with the exception of palliative radiotherapy for symptomatic management but not on measurable extramedullary plasmacytoma. Radiotherapy within 14 days prior to randomization on measurable extramedullary plasmacytoma is

not permitted even in the setting of palliation for symptomatic management
   c. Plasmapheresis within 28 days of randomization
4. Be exhibiting clinical signs of meningeal or central nervous system involvement due to multiple myeloma.
5. Have known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for patients with suspected COPD or asthma. Patients with FEV1 <50% of predicted normal (or for patients ≥65 years of age, old FEV1 <50% or Diffusing capacity of the lung [DLCO] <50%) on screening assessment must be excluded.
6. Have known moderate or severe persistent asthma within the past 2 years, or current uncontrolled asthma of any classification. Note that patients who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study, provided that FEV1 is ≥50% of predicted normal.
7. Have any of the following:
   a. Known history of seropositivity for human immunodeficiency virus (HIV).
   b. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Patients with resolved infection (i.e., patients who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time PCR measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Patients 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 PCR.
   c. Seropositive for hepatitis C (anti- hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response, defined as aviremia at least 12 weeks after completion of antiviral therapy).

   Note: Patients who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating HCV during screening may participate in the study. Such patients will be required to undergo regular assessments for HCV reactivation during the study and are to be withdrawn from the study if he/she test positive at any time during the study.
8. Have a concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease, Waldenstrom's Macroglobulinemia, POEMS syndrome [polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes], or light chain amyloidosis) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study and/or current or history of CNS involvement by the disease under investigation. 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).
9. Have any of the following:
   a. Myocardial infarction within 6 months of randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV),
   b. Uncontrolled cardiac arrhythmia
10. Have known allergies, hypersensitivity, or intolerance to boron or mannitol, sorbitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the IB) or known sensitivity to lenalidomide.
11. Be known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder).
12. Have any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Patient is taking any prohibited concomitant therapy per Section 8.3.
13. Be pregnant, or breast-feeding, or planning to become pregnant or breast-feed while enrolled in this study or within 3 months after the last dose of study treatment(s). Or, if male, planning to father a child while enrolled in this study or within 3 months after the last dose of study treatment(s).
14. Have had major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the patient is expected to participate in the study or within 2 weeks after the last dose of study treatment. Note: patients with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.
15. Have received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks or 5 pharmacokinetic half-lives, whichever is longer, before randomization or is currently enrolled in an interventional investigational study
16. Have contraindications to the use of lenalidomide or daratumumab, per local prescribing information.
17. Have gastrointestinal disease that may significantly alter the absorption of oral drugs.
18. Have received vaccination with live attenuated vaccines within 4 weeks of first study agent administration.

19. Be unable or unwilling to undergo antithrombotic prophylactic treatment.

Contact: Dr. Donna Reece /Olga Levina – **Enrollment temporarily on hold**

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 Number: 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

Subjects who meet any of the following exclusion criteria are not eligible for enrollment:
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/ Trisha Ramnanan – **Enrollment temporarily on hold**

A PHASE 3 RANDOMIZED STUDY COMPARING BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE (VRD) FOLLOWED BY CILTACABTAGENE AUTOLEUCEL, A CHIMERIC ANTIGEN RECEPTOR T CELL (CAR-T) THERAPY DIRECTED AGAINST BCMA VERSUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (VRD) FOLLOWED BY LENALIDOMIDE AND DEXAMETHASONE (RD) THERAPY IN PARTICIPANTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA FOR WHOM HEMATOPOIETIC STEM CELL TRANSPLANT IS NOT PLANNED AS INITIAL THERAPY

Protocol Number: 68284528MMY3004

Inclusion Criteria

1. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
2. Measurable disease at screening as defined by any of the following:
   - Serum monoclonal protein (M-protein) level ≥1.0 g/dLor Urine M-protein level ≥ 200 mg/24 hours;
   - Light chain multiple myeloma: Serum Ig free light chain (FLC) ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
3. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.
4 Clinical laboratory values:
   - **Hemoglobin** ≥ 8.0 g/dL (≥ 5 mmol/L), recombinant human erythropoietin use is permitted)
   - **Platelets** ≥75 ×109/L
   - **Absolute Neutrophil Count (ANC)** ≥ 1.0×109/L (prior growth factor support is permitted but must be without support in the 7 days prior to laboratory test.
   - **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)** ≤3.0×ULN
   - **Creatinine clearance** 40 mL/min/1.73 m2 based upon Modified Diet in Renal Disease formula (MDRD-4) calculation or a 24-hour urine collection.
   - **Total bilirubin** ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0×ULN is required)
5. Not considered for high-dose chemotherapy with ASCT due to:
   - Ineligible due to advanced age; or
   - Ineligible due to presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT; or
   - Deferral of high-dose chemotherapy with ASCT as initial treatment.

Exclusion Criteria

1. Frailty index of ≥ 2 according to Myeloma Geriatric Assessment score.
2. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:
   - non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.
   - skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
   - non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
   - localized prostate cancer (N0M0):
     - with a Gleason score of ≤ 6, treated within the last 24 months or untreated and under surveillance,
     - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence, or

- history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
- breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
- malignancy that is considered cured with minimal risk of recurrence.

3. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.
4. The following cardiac conditions:
- New York Heart Association Stage III or IV congestive heart failure
- Myocardial infarction or coronary artery bypass graft ≤6 months prior to enrollment
- History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
- History of severe non-ischemic cardiomyopathy
- Impaired cardiac function (left ventricular ejection fraction <45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed ≤ 8 weeks of apheresis)

5. Known active or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of MM.
6. Stroke or seizure within 6 months of signing ICF.
7. Plasma cell leukemia at the time of screening (>2.0 x 109/L plasma cells by standard differential), Waldenstrom's Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or primary amyloid light-chain amyloidosis.
8. Seropositive for human immunodeficiency virus (HIV).
9. Vaccinated with live, attenuated vaccine within 4 weeks prior to first dose of VRd.
10. In the event the Hepatitis B infection status is unclear, quantitative levels are necessary to determine the infection status
11. Hepatitis C infection defined as (anti-hepatitis C virus [HCV] antibody positive or detectable HCV-RNA) or known to have a history of hepatitis C.
NOTE: For participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is undetectable. For participants with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as undetectable HCV-RNA ≥24 weeks after completion of antiviral therapy.
12. Participant must not require continuous supplemental oxygen.
13. Contraindications, known life-threatening allergies, hypersensitivity, or intolerance to any of the study treatments (if known) or any of their excipients, including boron, mannitol and dimethyl sulfoxide.
14. Serious underlying medical condition, such as:
- Evidence of active viral or bacterial infection requiring systemic antimicrobial therapy, or uncontrolled systemic fungal infection; Active autoimmune disease
- Overt clinical evidence of dementia or altered mental status
- Any history of Parkinson's disease or other neurodegenerative disorder

15. Any prior therapy for MM or smoldering myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days, total of 160 mg dexamethasone or equivalent, or maximum 1 cycle of VRd therapy prior to enrollment, in a dosing regimen that is consistent with the protocol regimen for VRd induction.
16. Received a strong cytochrome P450 (CYP) 3A4 inducer within 5 half-lives prior to VRd induction therapy (see https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-andinducers).
17. Received an investigational treatment (including investigational vaccines) or used an invasive investigational medical device within 15 days prior to VRd induction therapy or is currently enrolled in an investigational study.
18. Major operations or surgical procedures within 2 weeks prior to VRd induction therapy, or has surgery planned during the study or within 2 weeks after study treatment administration. (Note: participants with planned surgical procedures to be conducted under local anesthesia may participate.)
19. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study and until 1 year after receiving cilta-cel infusion or for 4 weeks following discontinuation of lenalidomide (whichever is later).

Contact: Dr. Keith Stewart /Trina Wang – **Enrollment temporarily on hold**

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

<u>Exclusion criteria:</u>

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**

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/Harminder Paul -**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/Harminder Paul -**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/Rachel Aitken -**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/Harminder Paul -**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/Harminder Paul-**Open Enrollment**

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

SECOND LINE THERAPY

A PHASE III, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BELANTAMAB MAFODOTIN IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (BPD) VERSUS POMALIDOMIDE PLUS BORTEZOMIB AND DEXAMETHASONE (PVD) IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (DREAMM 8)

***Protocol Number*: 207499**

Inclusion Criteria

1. ≥18 years of age.
2. Have been previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) and must have documented disease progression during or after their most recent therapy.
3. Measurable hematologic disease at Screening as defined by at least one of the following:
   - Urine M-protein excretion ≥200 mg/24 h, or
   - Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
   - Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65) only if patient has no measurable urine or serum M spike.
4. Have undergone autologous stem cell transplant (SCT) or are considered transplant ineligible. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
   - Autologous SCT was >100 days prior to the first dose of study medication
   - No active bacterial, viral, or fungal infection(s) present
5. Adequate organ system functions as defined by the laboratory assessments listed below:
   - Absolute neutrophil count ≥ 1.5 x 109/L (without growth factor support for the past 14 days, excluding erythropoietin)
   - Platelet count ≥ 75 x 109/L
   - Hemoglobin ≥ 8 g/dL

- Total bilirubin ≤1.5 × ULN; (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
- ALT ≤ 2.5 x ULN
- eGFR ≥ 30 mL/ min/1.73 m2 (As calculated by Modified Diet in Renal Disease (MDRD) formula)
- Urine Dipstick: Negative/trace (if □1+ only eligible if confirmed □500 mg/g (56 mg/mmol) by albumin/creatinine ratio (spot urine from first void)

Exclusion Criteria

1. Active plasma cell leukemia at the time of screening. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, and skin changes).
2. Participants after prior allogeneic SCT.
    - NOTE: Participants who have undergone syngeneic transplant will be allowed only if no history of or no currently active graft versus host disease (GvHD).
3. Systemic anti-myeloma therapy (including chemotherapy and systemic steroids) or use of an investigational drug within 14 days or five half-lives (whichever is shorter) preceding the first dose of study drug; Prior treatment with a monoclonal antibody drug within 30 days of receiving the first dose of study drugs.
4. Plasmapheresis within 7 days prior to the first dose of study drug.
5. Received prior treatment with or intolerant to pomalidomide.
6. Received prior BCMA targeted therapy.
7. Intolerant to bortezomib or refractory to bortezomib (i.e., participant experienced progressive disease during treatment, or within 60 days of completing treatment, with a bortezomib-containing regimen of 1.3 mg/m2 twice weekly).
8. Evidence of cardiovascular risk, such as
    - ECG significant abnormality, 2nd degree (Mobitz Type II) or 3rd degree (Atrioventricular block);
    - Class III and Class IV heart failure; bypass grafting;
    - History of myocardial infarction, acute coronary syndromes, coronary angioplasty or stenting or bypass grafting within 3 months of screening
    - Uncontrolled hypertension
9.Any major surgery within the last 4 weeks.
10. Note: Participants intolerant or refractory to bortezomib at 1.3 mg/m2 dose twice weekly dosing schedule are not eligible.
11.Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice.
12.Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.
    - NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
13.Presence of active renal conditions (e.g. infection, severe renal impairment requiring dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible,
14. Current corneal disease except for mild punctate keratopathy.
15. 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 to the study procedures.
16. Pregnant or lactating female.

Contact: Dr. Suzanne Trudel /Trisha Ramnanan – **Enrollment temporarily on hold**

DESENSITIZATION OF IMMUNOMODULATING AGENT-RELATED HYPERSENSITIVITY REACTIONS AS A MEANS TO PROVIDE THERAPEUTIC OPTIONS IN THE MANAGEMENT OF PLASMA CELL DISORDERS (DEHYPERPCD)

Protocol Number: RV-CL-MM-PI-13170

Inclusion Criteria

1. History of HSR to lenalidomide or pomalidomide within 30 days of signing consent.
2. Registered into the mandatory Lenalidomide or Pomalidomide Pregnancy Prevention (PPP) plan for subjects in clinical trials, and be willing and able to comply with the requirements.
3. Females of reproductive potential must adhere to the scheduled pregnancy testing and the contraceptive techniques as required by the Global Pregnancy Prevention plan for subjects in clinical trials

4. Diagnosed with multiple myeloma or amyloidosis, who had experienced moderately-severe (Grade 3 CTCAE v5.0) cutaneous reactions, with or without being symptomatic (itchy rash) to IMiDs OR complained of angioedema or anaphylaxis reactions (in additional to body rash) attributable to lenalidomide or pomalidomide.
5. Afebrile at least 48 hours prior to proposed desensitization day.
6. For patients with existing body rash, a complete resolution of rash is needed at least 7 days prior to desensitization.
7. Patients with other allergy history may also be included.
8. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).
9. Renal function as follows:
    a. Calculated creatinine clearance ≥ 60ml/min by Cockcroft-Gault formula for lenalidomide OR Serum creatinine ≤ 2.0 mg/dL (≤177 μmol/L) for Pomalidomide. For those patients who had their lenalidomide or pomalidomide dose previously adjusted, due to renal impairment, and do not meet the stated renal eligibility criteria, could be considered eligible upon discussion with Sponsor Investigator.
    b. Total bilirubin ≤ 1.5 x ULN
    c. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

Exclusion Criteria:

1. Female who is pregnant or suspected of being pregnant or who intends to become pregnant, breast feeding or likely to breast feed during the study duration.
2. Male subjects donating semen / sperm, and male and female subjects donating blood
3. Inability to take oral medications, or are unable to tolerate IMiDs (other than hypersensitivity reactions).
4. Disease progression or resistance to IMiDs.
5. History of Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
6. Patients who are taking IMiDs-based therapy for an indication other than MM and/or systemic amyloidosis
7. The development of erythema nodosum, if characterized by a desquamating rash while taking thalidomide, IMiDs or similar drugs.
8. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.
9. Patients who have completed 3 RDPs and continued to have breakthrough HSR post RDP.
10. Patients who had experienced an IMiDs-related hypersensitivity reaction that is less than Grade 3 (Grade 1 and 2) as per CTCAE v5.0.
11. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent participation
12. Peripheral neuropathy > grade 2.
13. In the opinion of the investigator, clinically significant ECG, CHF, MI within 12 months or uncontrolled angina pectoris.

Contact: Dr. Anca Prica/Daniel Socko– **Open for enrollment**

A PHASE 1B/2 STUDY OF SELINEXOR (KPT-330) IN COMBINATION WITH BACKBONE TREATMENTS FOR RELAPSED/REFRACTORY AND NEWLY DIAGNOSED MULTIPLE MYELOMA
Protocol Number: KCP-330-017

Interventional

Inclusion criteria:

1. Patients must have measurable disease as defined by at least one of the following: a. Serum M-protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA b. Urinary M-protein excretion at least 200 mg/24 hours c. Serum FLC ≥ 100 mg/L, provided that FLC ratio is abnormal d. If SPEP is felt to be unreliable for routine M-protein measurement (e.g., for IgA MM), then quantitative Ig levels by nephelometry or turbidometry are acceptable
2. Any non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #22) that patients had from treatments in previous clinical studies must have resolved to ≤ Grade 2 by Cycle 1 Day 1.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
4. Adequate hepatic function within 28 days prior to C1D1: Total bilirubin < 2x upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3x ULN) and both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5x ULN

5. Adequate renal function within 28 days prior to C1D1. Estimated creatinine clearance (CrCl) calculated using the formula of Cockroft and Gault (1976): • ≥ 20 mL/min for SVd, SDd, and SKd arms • ≥ 30 mL/min for SNd arm • ≥ 45 mL/min for SPd, SPVd, and SPEd arms
6. Adequate hematopoietic function within 28 days prior to C1D1: total white blood cell (WBC) count ≥ 1,500/mm3, ANC ≥ 1,000/mm3, hemoglobin (Hb) ≥ 8.0 g/dL, and platelet count ≥ 150,000/mm3
7. SPd (Arm 1) Only: Relapsed and or refractory MM with:
   a. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for ≥ 1 cycle during a previous MM regimen (i.e., relapsed MM)
   b. ≤ 25% response (i.e., patients never achieved ≥ MR) or PD during or within 60 days from the end of the most recent MM regimen (i.e., refractory MM)
   c. Previously undergone ≥ 2 cycles of lenalidomide and a PI (in separate therapeutic regimens [not for maintenance] or in combination)
   d. In the expansion arm at RP2D, patients must not be pomalidomide refractory
8. SVd (Arm 2) Relapsed or refractory MM with:
   a. Documented evidence of relapse after ≥ 1 previous line of therapy
   b. Not refractory to bortezomib in their most recent line of therapy

Exclusion criteria:

1. Smoldering MM
2. MM that does not express M-protein or FLC (i.e., non-secretory MM is excluded), and quantitative immunoglobulin levels cannot be used instead
3. Documented active systemic amyloid light chain amyloidosis
4. Active plasma cell leukemia
5. Red blood cell (RBC) and platelet transfusions and blood growth factors within 14 days of C1D1
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to C1D1, and radio-immunotherapy within 6 weeks prior to C1D1. Prior radiation is permitted
7. Treatment with an investigational anti-cancer therapy within 3 weeks prior to C1D1
8. Prior autologous stem cell transplantation < 1 month, or allogeneic stem cell transplantation < 3 months prior to C1D1
9. Active graft versus host disease after allogeneic stem cell transplantation
10. Life expectancy < 3 months
11. Major surgery within 4 weeks prior to C1D1
12. Active, unstable cardiovascular function: a.Symptomatic ischemia, or b.Uncontrolled clinically significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or c.Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3, or d.Myocardial infarction (MI) within 3 months prior to C1D1, or e.Ejection fraction (EF) < 50% at Screening
13. Uncontrolled active hypertension
14. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to first dose
15. Known active hepatitis A, B, or C
16. Known human immunodeficiency virus (HIV) infection or HIV seropositivity
17. Any active gastrointestinal dysfunction that prevents the patient from swallowing tablets, or interferes with absorption of study treatment
18. Prior exposure to a SINE compound, including Selinexor

Contact: Dr. Christine Chen/Rebecca Noronha – **Open for Enrollment only for arm SPd (**Selinexor + Pom + Dex)

THIRD LINE THERAPY

AN OPEN-LABEL, MULTICENTER, NON-RANDOMIZED PHASE 2 STUDY OF ELRANATAMAB (PF-06863135) MONOTHERAPY IN PARTICIPANTS WITH MULTIPLE MYELOMA WHO ARE REFRACTORY TO AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY DRUG AND ONE ANTI-CD38 ANTIBODY

Protocol Number: C1071003

Inclusion Criteria

1. Male or female participants age ≥18 years. A female participant is eligible to participate if she is not pregnant or breastfeeding.
2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Prior diagnosis of MM as defined according to IMWG criteria.
4. Measurable disease based on IMWG criteria 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)
5. Refractory to all three; IMiD,
6. Refractory to at least one PI.
7. Refractory to at least one anti-CD38 antibody.
8. Relapsed or refractory to last anti-MM regimen.
9. Cohort A: Has not received prior BCMA-directed therapy.
Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.
10. ECOG performance status ≤2.
11. LVEF ≥40% as determined by a MUGA scan or ECHO.
12. Adequate 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
13. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min
14. 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).
15. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.
16. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

1. Participants are excluded from the study if any of the following criteria apply:
    a. Smoldering MM.
    b. Active plasma cell leukemia.
    c. Amyloidosis.
    d. POEMS syndrome
    e. Stem cell transplant within 12 weeks prior to enrollment or active GVHD.
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 (e.g., unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);
    b. Clinically significant cardiac arrhythmias (e.g., uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
    c. 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);
    d. Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).
3. Ongoing Grade ≥2 peripheral sensory or motor neuropathy.
4. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).
5. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
6. Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.
7. 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.
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.

9. Previous treatment with an anti-BCMA bispecific antibody.
10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or five (5) half-lives preceding the first dose of study intervention used in this study (whichever is longer).
11. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
12. Known or suspected hypersensitivity to the study intervention or any of its excipients.
13. Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.

Contact: Dr. Suzanne Trudel /Olga Levina – **Enrollment temporarily on hold**

STUDY TITLE: A PHASE 1/2 DOSE ESCALATION AND COHORT EXPANSION STUDY OF SAFETY AND EFFICACY OF ANTI-BCMA ALLOGENEIC CRISPR-CAS9–ENGINEERED T-CELLS (CTX120) IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CRSP-ONC-002

Inclusion Criteria:

1.Age ≥18 years.
2.Able to understand and comply with protocol-required study procedures and voluntarily sign a written informed consent document.
3.Diagnosis of multiple myeloma with relapsed or refractory disease, as defined by IMWG response criteria, and at least 1 of the following:

- Have had at least 2 prior lines of therapy, including an IMiD (e.g., lenalidomide, pomalidomide), PI (e.g., bortezomib, carfilzomib), and a CD38-directed monoclonal antibody (e.g., daratumumab; if approved and available in country/region).
- MM that is 'double-refractory' to IMiD and PI combination, defined as progression on or within 60 days of treatment with these agents.
- MM relapsed within 12 months after autologous stem cell transplant.

4.Measurable disease, including at least 1 of the following criteria:

- Serum monoclonal protein (M-protein) ≥0.5 g/dL.
- Urine M-protein ≥200 mg/24 hours.
- Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal.

5.Eastern Cooperative Oncology Group performance status 0 or 1.
6.Meets criteria to undergo LD chemotherapy and CAR T cell infusion.
7.Adequate organ function:

- Renal: Estimated glomerular filtration rate >50 ml/min/1.73 m2.
- Liver: Aspartate transaminase or alanine transaminase <3 x upper limit of normal (ULN); total bilirubin <2 x ULN.
- Cardiac: Hemodynamically stable and left ventricular ejection fraction ≥45% by echocardiogram.
- Pulmonary: Oxygen saturation level on room air >91% per pulse oximetry.

8.Female subjects of childbearing potential (postmenarcheal with an intact uterus and at least 1 ovary, who are less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from enrollment through at least 12 months after CTX120 infusion.
9.Male subjects must agree to use effective contraception from enrollment through at least 12 months after CTX120 infusion.

Exclusion criteria:

1.Prior allogeneic SCT.
2.Less than 60 days from autologous SCT at time of screening and with unresolved serious complications.
3.Plasma cell leukemia (>2.0 × 109/L circulating plasma cells by standard differential), or nonsecretory MM, or Waldenstrom's Macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis with end organ involvement and damage.
4.Prior treatment with any of the following therapies:
a. Any gene therapy or genetically modified cell therapy, including CAR T cells or natural killer cells.
b. Prior treatment with BCMA-directed therapy, including BCMA-directed antibody, bispecific T-cell engager, or antibody-drug conjugate.
c. Radiation therapy within 14 days of enrollment. Palliative radiation therapy for symptom management is permitted.
5.Known contraindication to cyclophosphamide, Fludarabine, or any of the excipients of CTX120 product.
6.Evidence of direct central nervous system (CNS) involvement by multiple myeloma.

7.History or presence of clinically relevant CNS pathology such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, or another condition that in the opinion of the investigator may increase CAR T cell–related toxicities.
8.Unstable angina, clinically significant arrhythmia, or myocardial infarction within 6 months of enrollment.
9.Presence of bacterial, viral, or fungal infection that is uncontrolled or requires IV anti-infective.
10.Positive for presence of human immunodeficiency virus type 1 or 2, or active hepatitis B virus or hepatitis C virus infection. Subjects with prior history of hepatitis B or C infection who have documented undetectable viral load (by quantitative polymerase chain reaction or nucleic acid testing) are permitted.
11.Previous or concurrent malignancy, except basal cell or squamous cell skin carcinoma, adequately resected and in situ carcinoma of cervix, or a previous malignancy that was completely resected and has been in remission for ≥5 years.
12.Received live vaccine within 28 days of enrollment.
13.Use of systemic anti-tumor therapy or investigational agent within 14 days prior to enrollment. Use of physiological doses of steroids (e.g., ≤10 mg/day prednisone or equivalent) will be permitted for subjects previously on steroids if clinically indicated.
14.Primary immunodeficiency disorder or active autoimmune disease requiring steroids and/or other immunosuppressive therapy.
15.Diagnosis of significant psychiatric disorder or other medical condition that, in the opinion of the investigator, could impede the subject's ability to participate in the study.
16.Women who are pregnant or breastfeeding.

Contact: Dr. Christine Chen/ Daniel Socko– **Enrollment temporarily on hold**

A PHASE 1/2 MULTI-CENTER, OPEN LABEL, DOSE ESCALATION STUDY TO DETERMINE THE RECOMMENDED PHASE 2 DOSE, SAFETY AND EFFICACY OF THE ANTIBODY DRUG CONJUGATE GSK2857916 IN COMBINATION WITH POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (MM)

Protocol Number: MCRN 007

Inclusion Criteria:

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
a. Have undergone stem cell transplant, or have been considered transplant ineligible
b. Previously undergone at least 2 prior lines of treatment and must have received lenalidomide and a proteasome inhibitor (in separate regimens or in combination);
c. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for ≥ 1 cycle during a previous MM treatment (i.e., relapsed MM); and/or
d. Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
2. Subjects 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 study enrolment
b. No active infection
3. Subjects with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):
- Serum M-protein ≥ 5 g/L;
- Urine M-protein ≥ 200 mg/24 h;
- 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).

4. The following laboratory results must be met within 10 days of first study drug administration:
- Absolute neutrophil count (ANC) > 1.0 x 109/L. Growth factors cannot be given within 10 days of study drug administration;
- Serum ALT ≤ 2.5 x upper limit of normal (ULN);
- eGFR (MDRD) ≥ 40 mL/min a (Appendix 2);
- Platelet count > 75 x 109/L. Platelet transfusions to help subjects meet eligibility criteria are not allowed within 10 days before study enrollment;
- Hemoglobin ≥ 8.0 g/dL;
- Total bilirubin ≤ 1.5 x ULN, unless known to have Gilbert's disease. If Gilberts, isolated bilirubin > 1.5 and <3 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;
- Albumin/creatinine ratios (spot urine) <500mg/g (56 mg/mmol);
- Albumin ≥ 2.0 g/dL (20 g/L).

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Exclusion criteria:

1 Prior pomalidomide use.
2. Serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures
3. Pregnant or lactating females.
4. Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness. The subject must not be receiving active therapy, other than hormonal therapy for this disease and the disease must be considered medically stable for at least 2 years.
5. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect subject's safety). Subjects with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in inclusion criteria (i.e. albumin/creatinine spot urine < 500 mg/g (56 mg/mmol).
6. Evidence of cardiovascular risk including any of the following:
a. QTc interval ≥ 470 msecs. Note that the QT interval should be corrected for heart rate by Fridericia's formula (QTcF).
b. Evidence of current clinically significant uncontrolled arrhythmias; including clinically significant ECG abnormalities; including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of screening.
d. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 3).
e. Uncontrolled hypertension.
7. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb) at screening or within 3 months prior to first dose of study treatment.
8. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment. Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Note: Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
9. 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.
10. Current corneal epithelial disease except for mild punctate keratopathy (mild punctate keratopathy is allowed).
11. Known active infection requiring antibiotic, anti-viral or anti-fungal treatment.
12. Evidence of active mucosal or internal bleeding.
13. Hypersensitivity to thalidomide, lenalidomide (such as Steven Johnson Syndrome) or intolerance to dexamethasone. Hypersensitivity, such as rash, that can be medically managed is allowable.
14. Peripheral neuropathy ≥ Grade 2 despite supportive therapy.
15. Radiotherapy (with the exception of local, palliative radiotherapy for management of pain) or systemic therapy (standard or biologic anticancer agent) within 14 days of initiation of study drug treatment.
16. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drug.
17. Any major surgery within the last 4 weeks.
18. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or any of the components of the study treatment.

Contact: Dr. Suzanne Trudel/Daniel Socko– **Enrollment temporarily on hold**

A PHASE 1 MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS AND PRELIMINARY EFFICACY OF CC-92480 IN COMBINATION WITH DEXAMETHASONE IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol Number: CelMod CC-92480-MM-001

Inclusion Criteria:

Adult subjects must satisfy the following criteria to be enrolled in the study:
1. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Subjects must have a documented diagnosis of MM and measurable disease at enrollment. Measurable disease is defined as:
    a. M-protein quantities ≥ 0.5 g/dL by sPEP or
    b. ≥ 200 mg/24-hour urine collection by uPEP or

c. Serum FLC levels > 100 mg/L (milligrams/liter) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in subjects without detectable serum or urine M-protein or

d. 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.

3. All subjects must:

a. have documented disease progression on or within 60 days from the last dose of their last myeloma therapy and,

b. have failed treatment with, are intolerant to or are not otherwise candidates for available therapies that are known to confer clinical benefit to subjects with RRMM.

Note: Prior lines of therapy must include (at a minimum) a proteasome inhibitor and a CM-agent administered individually (in any order) or together.

7. Subjects must have the following laboratory values:

- Absolute neutrophil count (ANC) ≥ 1.25 x 109/L without growth factor support for ≥ 7 days (≥ 14 days for pegfilgrastim).
- Hemoglobin (Hgb) ≥ 8 g/dL.
- Platelets (plt) ≥ 75 x 109/L without transfusion for ≥ 7 days (≥ 50 x 109/L for subjects with > 50% plasma cells in bone marrow).
- Corrected serum calcium ≤ 13.5 mg/dL (≤ 3.4 mmol/L).
- 24-hr creatinine clearance (CrCl) ≥ 45 mL/min.
- AST/SGOT and ALT/SGPT ≤ 3.0 x upper limit of normal (ULN).
- Serum bilirubin ≤ 1.5 x ULN.
- Uric acid ≤ 7.5 mg/dL (446 μmol/L).
- PT/INR < 1.5 x ULN and 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.

Exclusion criteria:

1. Subject has non- or oligosecretory multiple myeloma
2. Subject has plasma cell leukemia or active leptomeningeal myelomatosis.
3. Subject has documented systemic light chain amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes (POEMS) Syndrome.
4. Subject has immunoglobulin class M (IgM) myeloma
5. Subject has a history of allogeneic bone marrow transplantation
6. Subject is undergoing dialysis.
7. Subjects with peripheral neuropathy ≥ Grade 2.
8. Subjects with gastrointestinal disease that may significantly alter the absorption of CC-92480
9. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - LVEF < 45% as determined by ECHO or MUGA scan at Screening.
    - Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiographic (ECG) finding at Screening.
    - A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval >480 milliseconds (ms) using Frederica'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 ≤6 months prior to starting CC-92480.
    - Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris.
10. Concurrent administration of strong CYP3A modulators. Examples of these drugs include (but are not limited to):
    - CYP3A inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
    - CYP3A inducers: carbamazepine, phenytoin, and rifampin.

    If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
11. Subject had prior systemic myeloma treatment (approved or investigational) ≤ 5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
12. Subject had major surgery ≤ 2 weeks prior to starting CC-92480. Note: Subjects must have recovered from any clinically significant effects of recent surgery.
13. HIV

14. Known active chronic hepatitis B or C virus (HBV/HCV) infection
15. A history of concurrent second cancer requiring ongoing systemic treatment
16. Subjects has a history of prior malignancy other than MM, unless the subject has been free of disease for ≥3 years except for the following noninvasive malignancies treated with curative intent:
    - Basal or squamous cell carcinoma of the skin.
    - Carcinoma in situ of the cervix or breast.
    - Stage 1 bladder cancer.
    - Incidental histological findings of localized prostate cancer such as tumor stage 1a or 1b (T1a or T1b) using the Tumor/Node/Metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent.
17. Subject has a history of anaphylaxis to thalidomide, lenalidomide, pomalidomide or dexamethasone
18. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480 or dexamethasone
19. Subject has undergone either of the following within 14 days of initiating CC-92480:
    - Plasmapheresis.
    - Radiation therapy other than local therapy for symptomatic relief of MM associated bone lesions.
20. Subject has received immunosuppressive medication within 14 days prior to the first dose of CC-92480. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical or local corticosteroid injections (eg, 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 (eg, computed tomography [CT] scan premedication).
21. Subject is unable or unwilling to undergo protocol required venous thromboembolism (VTE) prophylaxis. Thromboembolism prophylaxis consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study beginning 48 hours prior to Cycle 1, Day 1 until 48 hours after last CC-92480 administration.

Contact: Dr. Suzanne Trudel/Olga Levina– **Open for enrollment ONLY Part 2**

FOURTH LINE OF THERAPY

AN OPEN-LABEL, 3-ARM, MULTICENTER, RANDOMIZED PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ELRANATAMAB (PF-06863135) MONOTHERAPY AND ELRANATAMAB+ DARATUMUMAB VERSUS DARATUMUMAB + POMALIDOMIDE + DEXAMETHASONE IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST 2 PRIOR LINES OF THERAPY INCLUDING LENALIDOMIDE AND A PROTEASOME INHIBITOR

Protocol Number: C1071005

Inclusion Criteria

1. ≥18 years of age.
    a. Male participants and female participants of childbearing potential must agree to use methods of contraception.
2. Prior diagnosis of MM as defined according to IMWG criteria.
3. Prior anti-MM therapy:
    a. **Part 1: At least 3 prior lines of anti-MM therapy** including treatment with lenalidomide and a PI.
    b. Part 2: At least 2 prior lines of anti-MM therapy including treatment with lenalidomide and a PI.
4. Measurable disease based on IMWG criteria 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).
5. Eastern Cooperative Oncology Group (ECOG) performance status grade of ≤1.
6. LVEF ≥40% as determined by a MUGA scan or ECHO.
7. Adequate hepatic function characterized by the following:

a. **Total bilirubin** ≤1.5 x ULN;
b. **AST** ≤2.5 x ULN and **ALT** ≤2.5 x ULN.

8. Estimated **creatinine clearance** ≥30 mL/min (according to the Cockcroft Gault formula, by 24-hour urine collection for creatinine clearance, or per the local institutional standard method).
9. 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 28 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 28 days prior to planned start of dosing); and
   c. **Hemoglobin** ≥8 g/dL (transfusion support is permitted if completed at least 28 days prior to planned start of dosing).
10. **Corrected serum calcium** ≤14 mg/dL (≤3.5 mmol/L), or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).
11. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.

Exclusion Criteria

Medical Conditions:
1. Smoldering MM.
2. Plasma cell leukemia.
3. Systemic amyloid light chain amyloidosis.
4. POEMS Syndrome
5. Stem cell transplant within 12 weeks prior to enrollment, or active GVHD.
6. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrolment:
   a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);
   a. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
   b. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism);
   c. Prolonged QT syndrome (or QTcF >470 msec at screening).
7. Ongoing Grade 2 or higher peripheral sensory or motor neuropathy.
8. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
9. Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrolment.
   a. COVID-19/SARS-CoV2: While SARS-CoV2 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-CoV2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV2, he/she is excluded.
10. Any other active malignancy within 3 years prior to enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
11. Participants with known or suspected hypersensitivity to the study interventions or any of their excipients.
12. Other surgical (including major surgery within 14 days prior to enrolment), 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.

Prior/Concomitant Therapy:
13. Previous treatment with a BCMA-directed therapy.
14. Anti-CD38-directed therapy within 6 months preceding the first dose of treatment in this study.
15. **Part 2 only**: Refractory to prior anti-CD38-directed therapy (disease progression while on or within 60 days of the last dose of any anti-CD38-directed therapy, regardless of response).
16. **Part 2 only**: Previous pomalidomide therapy.
17. Concurrent or anticipated use of a non-topical medication known to be a strong CYP1A2 inhibitor within 7 days prior to first dose of study intervention and throughout study duration.
18. Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.

Prior/Concurrent Clinical Study Experience:
19. Administration with an investigational product (e.g. drug or vaccine) concurrent with study intervention or 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). A participant may be eligible if they are in the follow-up phase of an investigational study if they meet the criteria for

time elapsed from previous administration of investigational product. Cases must be discussed with sponsor's medical monitor to judge eligibility.

Diagnostic Assessments:
20. 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).

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

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 (eg, 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 (eg, 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 (eg, intra-articular injection), or steroids as premedication for hypersensitivity reactions (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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 (eg, 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. Subject has any condition that confounds the ability to interpret data from the study.
23. Inadequate pulmonary function as defined as oxygen saturation (SpO2) < 92 % on room air.
24. Subject weight is ≤ 40 kg at screening

Contact: Dr. Donna Reece /Daniel Socko – **Open 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**

A PHASE 1B STUDY OF SUBCUTANEOUS DARATUMUMAB REGIMENS IN COMBINATION WITH BISPECIFIC T CELL REDIRECTION ANTIBODIES FOR THE TREATMENT OF SUBJECTS WITH MULTIPLE MYELOMA.

Protocol Number: 64407564MMY1002

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:
    - Received at least 3 prior lines of therapy (see definition below) including a PI (≥2 cycles or 2 months of treatment) and an IMiD (≥2 cycles or 2 months of treatment) in any order during the treatment (except for subjects who discontinued either of these treatments due to a severe allergic reaction within the first 2 cycles/months).
    - Undergone at least 1 complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the line of therapy
    - Disease that is double refractory to a PI and an IMiD. For subjects who have received more than 1 type of PI, the disease must be refractory to the most recent one. Similarly, for those who have received more than 1 type of IMiD, the disease must be refractory to the most recent one.
4. Measurable disease at screening as defined by any of the following:
    - Serum monoclonal protein (M-protein) level □1.0 g/dL (in non-IgG myeloma, an M-protein level 0.5 g/dL);
    - or Urine M-protein level □200 mg/24 hours;
    - or Light chain multiple myeloma: Serum Ig free light chain (FLC) 10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.
5. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 at screening and C1D1.
6 Clinical laboratory values:
    - **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)

Exclusion Criteria

20. Treatment in the prior 3 months with an anti-CD38 therapy (e.g., daratumumab), or discontinuation of a prior anti-CD38 therapy at any time due to an adverse event related to the anti-CD38 therapy.
21. Prior antitumor therapy as follows, before the first dose of study drug:

- Targeted therapy, epigenetic therapy, or treatment with an investigational drug or an invasive medical device within 21 days or at least 5 half-lives, whichever is less.
- Monoclonal antibody treatment within 21 days (anti-CD38 treatment cannot be used within the prior 3 months.
- 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

22. A cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drugs.
23. Live, attenuated vaccine within 4 weeks prior to the first dose of study drug unless approved by sponsor.
24. 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).
25. 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
    - An immunosuppressive drug (e.g., cyclosporine, tacrolimus) within 28 days before the first dose of study drug.
26. 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.
27. 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.
28. Known to be seropositive for human immunodeficiency virus.
29. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]).
30. 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
31. Either of the following:
    - Chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1 second (FEV1) <50% of predicted normal.
    - Moderate or severe persistent asthma within the past 2 years or uncontrolled asthma of any classification.
32. Pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 100 days after the last dose of study drug.
33. 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 /Daniel Socko – **Open Enrollment**

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 3 prior lines of therapy for MM, or in the presence of high-risk cytogenetics (del[17p], t[4;14], t[14;16] or gain[1q]) should have had at least 2 prior lines of therapy. Induction therapy followed by autologous transplantation and maintenance therapy represents one line of therapy; lines of therapy are defined per International Myeloma Workshop Consensus Panel. For each line of therapy, the patient should have received at least one complete treatment cycle.
3. The patients should have received treatment with at least one proteasome inhibitor, one IMiD and daratumumab.

Note: Patients should be either relapsed or refractory to daratumumab or can't tolerate the treatment of daratumumab.

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 ≥ 0.5 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. Patients should meet the following:
a. Complete blood count (CBC) results (without transfusion and growth factor support) within 7 days of testing: ANC ≥ 1.0 × 109/L, platelet count ≥ 75 × 109/L (If the proportion of plasma cells in the bone marrow is > 50%, patients with platelet ≥ 50 × 109/L will be eligible), Hb ≥ 7.0 g/dL
Note: Platelet count ≥ 50 × 109/L will be eligible for leukapheresis after medical monitor's approval
b. Blood biochemistry: 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)
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:
a. Previous anti-BCMA therapy (antibody drug conjugate or bi-specific T cell engager) without response to treatment (≥PR); b. Previous anti-BCMA CAR-T therapy (with or without response to the treatment)
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. Patients have received stem cell transplantation less than 12 weeks before leukapheresis
7. Patients have received any anti-cancer treatment 2 weeks before leukapheresis or 3 weeks before 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. *Note: Any treatment encroaching into the 14- or 21-day washout period listed under items 8 and 9 may be allowable if discussed with and approved by the study medical monitor.*
8. Patients have received ≥ 20 mg prednisone daily or other equivalent dose of steroids within 14 days before leukapheresis or lymphodepletion
9. Patients have received major surgery 1 weeks prior to leukapheresis or 3 weeks prior to lymphodepletion (excluding cataract and other local anesthesia)
10. 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- **Open for enrollment**

A PHASE 1/2 OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF AMG 701 MONOTHERAPY, OR IN COMBINATION WITH POMALIDOMIDE, WITH AND WITHOUT DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (PARADIGMM-1B)

Protocol Number: 20170122 (AMG 701)

Inclusion Criteria:

1. Multiple myeloma meeting the following criteria:
• Pathologically-documented diagnosis of multiple myeloma that is relapsed or is refractory (see Section 12.13) as defined by the following:
- Relapsed after ≥ 3 lines of prior therapy that must include a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and a CD38-directed antibody in combination in the same line or separate lines of treatment OR refractory to PI, IMiD and CD38-directed antibody
- Note: Subjects enrolled in dose-confirmation Group C must be relapsed/refractory or intolerant to GSK2857916 (belantamab mafodotin)

• Measurable disease, defined by 1 or more of the following at time of screening (Note: extramedullary disease in the absence of medullary disease will be allowed in Group B of dose-confirmation):
- a serum M protein ≥ 0.5 g/dL measured by serum protein electrophoresis (SPEP)
- urinary M protein excretion ≥ 200 mg/24 hours
- involved sFLC measurement > 10 mg/dL, provided that the sFLC ratio is abnormal as per IMWG response criteria

2. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
3. Life expectancy of at least 3 months as per investigator`s judgment at time of screening
4. Hematological function without transfusion support as follows:
- absolute neutrophil count (ANC) ≥ 1.0 x 109/L (without growth factor support)
- platelet count ≥ 50 x 109/L (without transfusions within 7 days from screening assessment)
- hemoglobin ≥ 8.0 g/dL (transfusions permitted no later than 48 hours before screening)

5. Renal function as follows:
• calculated or measured creatinine clearance ≥ 30 mL/min using:
- the Cockcroft-Gault equation OR
- via 24-hour urine collection with plasma and urine creatinine concentrations

6. Hepatic function as follows:
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN)
- total bilirubin (TBIL) < 1.5 x ULN (unless considered due to Gilbert's syndrome)

Additional Inclusion Criteria for AMG701 combination therapy with pomalidomide and dexamethasone:

7. Subjects must have received ≥ 2 lines of prior therapy that must include a proteasome inhibitor (PI), lenalidomide, and where approved and available a CD38-directed antibody. These therapies may be in the same line or separate lines of treatment.
8. Subjects must have responded to at least 1 prior line with at least a PR
9. Subjects that have previously received pomalidomide must not have been removed from therapy due to toxicity attributable to pomalidomide and must be at least 6 months from their last dose of pomalidomide
10. Subjects must not have known intolerance to doses of dexamethasone up to 40 mg weekly (20 mg weekly if > 75 years).

Exclusion criteria:

1. Known extramedullary relapse in the absence of any measurable medullary involvement (exception: inclusion of these subjects will be allowed in Group B of dose-confirmation- and dose-expansion)
2. Known central nervous system involvement by multiple myeloma
3. Previously received an allogeneic stem cell transplant and the occurrence of 1 or more of the following:

- received the transplant within 6 months prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- any active acute graft versus host disease (GvHD) requiring systemic therapy within the last 4 weeks prior to start of study treatment
- any systemic therapy against GvHD within 4 weeks prior to start of investigational product treatment

4. Autologous stem cell transplantation less than 90 days prior to study day 1
5. **Recent** history of primary plasma cell leukemia **(within last 6 months prior to enrollment)** or evidence of primary or secondary plasma cell leukemia at the time of screening
6. Waldenstrom's Macroglobulinemia
7. Prior amyloidosis (patients with multiple myeloma with asymptomatic deposition of amyloid plaques found on biopsy would be eligible if all other criteria are met)
8. Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids (unless the dose is ≤ 10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus within 2 weeks before study day 1
9. Last anticancer treatment (chemotherapy, IMiD, PI, molecular targeted therapy) < 2 weeks prior to study day 1
10. Last treatment with a therapeutic antibody less than 4 weeks prior to study day 1
11. Radiation therapy to multiple anatomic sites within 28 days prior to study day 1. Focal radiotherapy within 14 days prior to study day 1.
12. Major surgery defined as surgery requiring general anesthesia with endotracheal intubation within 28 days prior to study day 1, unless discussed with and eligibility approved by Amgen medical monitor
13. Prior treatment with any drug or construct that targets BCMA on tumor cells (e.g., other bispecific antibody constructs, antibody drug conjugates, or CAR-T cells), other than group C where prior treatment with GSK2857916 (belantamab mafodotin) is required.
14. Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study. Other investigational procedures while participating in this study are excluded.

15. Treatment with medications known to cause QTc interval prolongation within the washout periods described in Section 12.9. unless approved by the Amgen medical monitor
16. Unresolved toxicities from prior anticancer therapy, defined as not having resolved to CTCAE version 4.0 grade 1 or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia or toxicities from prior anticancer therapy that are considered irreversible (defined as having been present and stable for > 4 weeks) which may be allowed if they are not otherwise described in the exclusion criteria and there is agreement to allow by both the investigator and Amgen medical monitor.
17. Clinically-not controlled chronic or ongoing bacterial, fungal, viral or other infectious disease requiring treatment at the time of study day 1 or within the 14 days before study day 1
18. Active hepatitis B and C based on the following results:
    • Positive for hepatitis B surface antigen (HepBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)
    • Negative HepBsAg and positive for hepatitis B core antibody: Negative hepatitis B virus DNA by polymerase chain reaction (PCR) result is necessary.
    • Positive Hepatitis C virus antibody (HepCAb): Negative hepatitis C virus RNA by PCR result is necessary.
19. Positive results for human immunodeficiency virus (HIV)
20. Baseline ECG QTc > 470 msec (applying Fridericia's correction), defined as the average of individual baseline ECGs
21. History of malignancy other than multiple myeloma within the past 3 years with the following exceptions:

    - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
    - Adequately-treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately-treated cervical carcinoma in situ without evidence of disease
    - Breast ductal carcinoma in situ with full surgical resection (i.e., negative margins) and without evidence of disease
    - Prostate cancer with a Gleason score < 7 with undetectable prostate specific antigen (PSA) over 12 months
    - Treated medullary or papillary thyroid cancer
    - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
    - Similar neoplastic conditions with an expectation of > 95% five-year disease-free survival
    - See Exclusion Criterion 5 for exclusion of subjects with plasma cell leukemia
22. Known hypersensitivity to immunoglobulins or to any components of the study drug
23. Current or known history of autoimmune diseases requiring systemic treatment in past 5 years, excluding autoimmune thyroid disease, for which treatment should be completed 6 months prior to enrollment.
24. Males and females of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study through 75 days (females) and 135 days (males) after receiving the last dose of study drug. Refer to Section 12.5 for additional contraceptive information.
25. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 75 days after receiving the last dose of study drug
26. Females with a positive pregnancy test
27. Females planning to become pregnant while on study through 75 days after receiving the last dose of study drug
28. Males who are unwilling to abstain from sperm donation while on study through 135 days after receiving the last dose of study drug
29. Subjects likely to not be available to complete all protocol-required study visits or procedures including BM aspirates/biopsies, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

Additional Exclusion Criteria for AMG701 combination therapy with pomalidomide and dexamethasone:

31. History of serious hypersensitivity associated with thalidomide, pomalidomide, or lenalidomide (> grade 3)
32. Multiple myeloma with IgM subtype
33. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
34. Contraindication to pomalidomide or dexamethasone
35. Glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent dose of other corticosteroids
36. Treatment with systemic immune modulators including, but not limited to, non-topical systemic corticosteroids (unless the dose is ≤ 10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus within 2 weeks before study day 1 or 4 weeks before study day 1 for Phase 1 dose-confirmation
37. Female subjects of childbearing potential with a positive pregnancy test assessed within 14 days prior to first dose of study drugs and/or a positive urine pregnancy test within 24 hours prior to first dose. In addition, females of childbearing potential unwilling to undergo pregnancy testing weekly during the first 4 weeks of pomalidomide use followed by pregnancy testing every 4 weeks in females with regular menses or every 2 weeks in females with irregular menstrual cycles.
38. Male subjects with a female partner of childbearing potential and female subjects of childbearing potential who are unwilling to use 2 methods of contraception (1 of which must be highly effective during the study and for an additional 75 days (females)

and 135 days (males) after receiving the last dose of AMG 701, or 28 days after the last dose pomalidomide (males and females) or dexamethasone (females), whichever occurs later. Refer to Section 12.5 for additional contraceptive information.
39. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 75 days after receiving the last dose of AMG 701, or 28 days after the last dose pomalidomide or dexamethasone, whichever occurs later
40. Females planning to become pregnant while on study through 75 days after receiving the last dose of AMG 701 or 28 days after the last dose pomalidomide or dexamethasone, whichever occurs later
41. Male subjects with a pregnant partner who are unwilling to practice abstinence or use a latex or synthetic condom (even if they have had a vasectomy with medical confirmation of surgical success) during treatment (including during dose interruptions) and for an additional 135 days after the last dose of AMG 701, or 28 days after the last dose pomalidomide, whichever occurs later.
42. Males who are unwilling to abstain from sperm donation while on study through 135 days after receiving the last dose of AMG 701 or 28 days after the last dose pomalidomide, whichever occurs later

Contact: Dr. Suzanne Trudel/Daniel Socko – **Open for Enrollment ONLY Phase 1b Monotherapy**

A PHASE 1, MULTICENTER, OPEN-LABEL, DOSE FINDING STUDY OF CC-99712, A BCMA ANTIBODYDRUG CONJUGATE, IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol Number: CC-99712-MM-001

Inclusion Criteria:

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
a. Have disease that is nonresponsive while on their last antimyeloma therapy
b. Previously undergone at least 3 prior lines of treatment and must have received an immunomodulatory agent and a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody (in separate regimens or in combination);
2. Subjects with measurable disease defined as at least one of the following:
- Serum M-protein ≥ 0.5 g/dL by sPEP;
- Urine M-protein ≥ 200 mg/24 h;
- Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/l and an abnormal serum free light chain ratio
- a serum IgA level ≥ 0.50 g/dL.

3. Subject consents to serial bone marrow aspirations and/or biopsies

4. Subject has adequate organ system functions defined as:
- Absolute neutrophil count (ANC) > 1.0 x 109/L (Without Growth factor support for the past 14 days, excluding erythropoietin)
- Serum creatinine clearance ≥ 60 mL/min
- Platelet count > 75 x 109/L.
- Hemoglobin ≥ 8.0 g/dL;
- Total bilirubin ≤ 1.5 x ULN.
- Potassium within normal limits or correctable with supplements
- ALT and AST ≤2.5 X upper limit of normal (ULN);
- International normalized ratio (INR) < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Exclusion criteria:

1. In Part A only, subject has received prior investigational therapy directed at BCMA including, but not limited to, antibody-drug conjugates (BCMA-ADC), bispecific T cell-engaging antibodies or molecules, or BCMA-directed T cell therapy (e.g., BCMA chimeric antigen receptor [CAR] T cells).
2. Subject has symptomatic central nervous system involvement of MM.
3. Subject has nonsecretory MM, plasma cell leukemia, Waldenstrom's Macroglobulinemia, POEMS syndrome
4. Subjects with a history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months
5. Subject had a prior autologous stem cell transplant ≤ 3 months prior
6. Subject had a prior allogeneic stem cell transplant ≤ 6 months prior to starting CC-99712.
7. Subject had a prior chimeric antigen receptor T (CAR T) cell product ≤ 4 weeks prior to starting CC-99712.

8. Subject had a prior systemic cancer-directed treatments 2 weeks prior to starting CC-99712
9. Subject has known human immunodeficiency virus (HIV) infection or Hepatitis B or C infection.
10. . Subject has a history of concurrent second cancers or history of Cirrhosis.
11. Subject has a history of clinically significant corneal disease requiring therapy or ongoing active corneal disease. 17. Subject has active peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

Contact: Dr. Suzanne Trudel/Daniel Socko- **Open for enrollment**

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: GO39775

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– **Open for enrollment**

CHRONIC LYMPHOCYTIC LEUKEMIA TRIALS:

A PHASE 1B, MULTI-CENTER, OPEN-LABEL STUDY TO DETERMINE THE SAFETY, PHARMACOKINETICS, AND PRELIMINARY EFFICACY OF CC-99282 IN COMBINATION WITH OBINUTUZUMAB IN SUBJECTS WITH RELAPSED OR REFRACTORY CHRONIC LYMHOPCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Protocol Number: CC-99282-CLL-001

Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have a documented diagnosis of CLL/SLL requiring treatment (IW CLL Guidelines for the Diagnosis and Treatment of CLL. In addition:

a. Presence of clinically measurable disease determined by at least one of the factors listed:

- nodal lesion that measures ≥ 1.5 cm in longest dimension (LD) and ≥ 1.0 cm in longest perpendicular dimension (LPD), or
- spleen that measures ≥ 14 cm in longest vertical dimension (LVD) with a minimum of 2 cm enlargement, or
- liver that measures ≥ 20 cm in LVD with a minimum of 2 cm enlargement, or
- peripheral blood B lymphocyte count > 5000/uL

5. Subject must meet the criteria for relapsed and/or refractory disease according to the IW CLL Guidelines to > 2 prior lines of therapy.
6. All eligible subjects must be relapsed after or be refractory to ≥ 2 prior lines of therapy, one of which must have included an inhibitor of B-cell receptor signaling (approved BTKi or PI3Ki) or Venetoclax. Prior therapy with regimen containing Obinutuzumab is permitted.
7. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
8. Subjects who meet the following laboratory parameters:

a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3 or ≥ 1000 cells/mm3 if secondary to bone marrow involvement by disease.
b. Platelet count ≥100,000 cells/mm3 (100 x 109/L) or ≥ 50,000 cells/mm3 (50 x 109/L) if secondary to bone marrow involvement by disease.
c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) < 3.0 x upper limit of normal (ULN).
d. Serum bilirubin < 1.5 x ULN unless due to Gilbert's syndrome.
e. Estimated serum creatinine clearance of ≥ 60 mL/min using the Cockcroft-Gault equation or directly determined from the 24-hour urine collection method.

9. Agree to scheduled pregnancy testing and Pregnancy Risk Management Plan during the course of the study, and 28 days after the end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.

A female of childbearing potential (FCBP) is a female who:

1) has achieved menarche at some point,
2) has not undergone a hysterectomy or bilateral oophorectomy, or
3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months) and must:
a. Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy.
b. Screening pregnancy test (urine or serum) will be done at Day -14, Day -1, pre-Cycle 1
Day 1, and a second confirmatory test (serum) will be done within 24 hours of Cycle 1 Day 1. In addition, pregnancy test must be done 24 hours prior to Cycle 1 Day 15 prior to administration of CC-99282. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
c. 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 without interruption as defined in the PPP and provided to the subject at the time of informed consent, 28 days prior to starting CC-99282, during the study therapy (including during dose interruptions), and for 28 days after discontinuation of study therapy or 18 months after last dose of Obinutuzumab, whichever is the last.
d. Avoid conceiving for 28 days after the last dose of CC-99282.
e. Agree to abstain from breast feeding while on CC-99282 and for 28 days after its discontinuation.
f. Agree to refrain from donating ova while on CC-99282 for 30 days after its discontinuation.
Male subjects must:
Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom (a latex condom is recommended) (Appendix D) during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 3 months following investigational product discontinuation, or longer if required for each compound and/or by local regulations, even if he has undergone a successful vasectomy.
Males must agree to refrain from donating semen or sperm while on CC-99282 and for 90 days after its discontinuation.

Exclusion criteria:

The presence of any of the following will exclude a subject from enrollment:
1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Prior allogeneic stem cell transplant (SCT)/bone marrow transplant within 12 months of signing the ICF. Subjects who received allogeneic SCT ≥ 12 months before signing the ICF may be eligible provided there is no ongoing graft-versus-host disease (GVHD) and no ongoing immune suppression therapy.
5. Ongoing or active infection requiring parenteral antibiotics.
6. Uncontrolled intercurrent illness including, but not limited to:
a. Chronic symptomatic congestive heart failure (Class III or IV of the New York Heart Association Classification for Heart Disease).
b. Active central nervous system involvement as documented by spinal fluid cytology or imaging.
c. Uncontrolled/active autoimmune hemolytic anemia or thrombocytopenia.
d. Other concurrent severe and/or uncontrolled concomitant medical conditions that could cause unacceptable safety risks or compromise compliance with protocol.
7. Subject has received prior systemic anti-cancer treatment (approved or investigational) ≤ 5 half-lives or 4 weeks prior to starting CC-99282, whichever is shorter.
8. Subject has received prior CAR-T or other T-cell targeting treatment (approved or investigational) ≤ 4 weeks prior to starting CC-99282.
9. Subject has received prior therapy with CRBN-modulating drug (e.g., lenalidomide, Avadomide/CC-122, pomalidomide) ≤ 4 weeks prior to starting CC-99282.
10. History of second malignancies with life expectancy of ≤ 2 years or requirement of therapy that would confound study results. Such cases should be discussed with medical monitor. This does not include the following:
a. Basal cell carcinoma of the skin.
b. Squamous cell carcinoma of the skin.
c. Carcinoma in situ of the cervix.
d. Carcinoma in situ of the breast.
e. Carcinoma in situ of the bladder.
f. Incidental histologic finding of prostate cancer (Tumor, Node, Metastasis [TNM] stage of T1a or T1b).
11. Known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV), or hepatitis B or C virus (HBV, HCV). Hepatitis B screening is mandatory for all patients (HBsAg and anti-HBc). Patients with active hepatitis B

disease should not be treated with Obinutuzumab. Patients should be referred to a specialist if they are carriers before treatment starts (see Gazyva PI or Gazyvaro SmPC). Subjects who are positive for anti-HBc and/or anti-HBs but negative for HBsAg and HBV DNA may be treated after consultation with a hepatologist. This does not include false positive result for patients receiving intravenous immunoglobulin (IVIG).
12. Peripheral neuropathy ≥ Grade 2.
13. Subject is on chronic systemic immunosuppressive therapy or corticosteroids (e.g., prednisone or equivalent not to exceed 10 mg per day within the last 14 days) or subjects with clinically significant GVHD.
a. Stable use of inhaled corticosteroids is allowed.
b. The use of topical steroids for ongoing skin or ocular GVHD is permitted.
14. History of hypersensitivity to lenalidomide, pomalidomide, thalidomide.
15. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
a. LVEF < 45% as determined by MUGA scan or ECHO.
b. Complete left bundle branch, or bifascicular, block.
c. Congenital long QT syndrome.
d. Persistent or uncontrolled ventricular arrhythmias or atrial fibrillation.
e. QTcF > 470 msecs on Screening ECG (mean of triplicate recordings).
f. Unstable angina pectoris or myocardial infarction ≤ 6 months prior to starting CC-99282.
16. Persistent diarrhea or malabsorption ≥ NCI CTCAE Grade 2, despite medical management.
17. Active disease transformation (i.e., Richter's Syndrome); subjects with Richter's Syndrome that has resolved > 2 years from signing the ICF are eligible.
18. Known acute or chronic pancreatitis.
19. Pregnant or lactating females.
20. Hypersensitivity to Obinutuzumab or to any of the excipients.
21. Concurrent administration of strong CYP3A4/5 modulators.

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

AMYLOIDOSIS TRIALS:

A PHASE 3, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CAEL-101 AND PLASMA CELL DYSCRASIA TREATMENT VERSUS PLACEBO AND PLASMA CELL DYSCRASIA TREATMENT IN PLASMA CELL DYSCRASIA TREATMENT-NAÏVE PATIENTS WITH MAYO STAGE IIIB AL AMYLOIDOSIS
***Protocol Number*: CAEL101-301**

Inclusion Criteria

1. ≥18 years of age.
2. AL amyloidosis stage IIIb based on the 2013 European Modification of the 2004 Standard Mayo Clinic Staging in patients with advanced cardiac involvement
3. Measurable hematologic disease at Screening as defined by at least one of the following:
- dFLC > 4 mg/dL or
- iFLC > 4 mg/dL with abnormal ratio or
- SPEP m-spike > 0.5 g/dL

4. Histopathological diagnosis of amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens AND confirmation of AL derived amyloid deposits by at least one of the following:
- Immunohistochemistry or
- Mass spectrometry or
- Characteristic electron microscopy appearance

5. Cardiac involvement as defined by:

- Documented clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure AND
- At least one of the following:

i. Endomyocardial biopsy demonstrating AL cardiac amyloidosis or
ii. Echocardiogram demonstrating a mean left ventricular wall thickness > 12 mm at diastole in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening or
iii. Cardiac MRI with gadolinium contrast agent diagnostic of cardiac amyloidosis
6. NT-proBNP > 8500 ng/L
7. Planned first-line treatment for plasma cell dyscrasia is CyBorD administered as SoC. Patients will be expected to remain on CyBorD for at least 2 cycles.
8. Adequate bone marrow reserve, hepatic, and renal function as demonstrated by:

- Absolute neutrophil count ≥ 1.0 x 109/L
- Platelet count ≥ 75 x 109/L
- Hemoglobin ≥ 9 g/dL
- Total direct bilirubin ≤ 2 times the upper limit of normal (x ULN) unless due to
- Gilbert's syndrome.
- AST ≤ 3 x ULN
- ALT ≤ 3 x ULN
- ALP ≤ 5 x ULN (except for patients with hepatomegaly and isozymes specific to
- liver, rather than bone)
- eGFR ≥ 15 mL/min

Exclusion Criteria

1.Have any other form of amyloidosis other than AL amyloidosis
2. Received prior therapy for AL amyloidosis or multiple myeloma. A maximum exposure of 160 mg dexamethasone (or equivalent corticosteroid) since diagnosis of AL amyloidosis and prior to randomization is allowed.
3. Meets the IMWG definition of multiple myeloma or POEMS syndrome
4. Have supine systolic blood pressure < 90 mmHg or symptomatic orthostatic hypotension,
defined as a decrease in systolic blood pressure upon standing of > 30 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
5. Taking prednisone or its equivalent > 10 mg/day
6. Taking doxycycline
7. Receiving dialysis
8. Planned stem cell transplant during the first 6 months of protocol therapy.
9. Have had myocardial infarction, uncontrolled angina, severe uncontrolled ventricular
arrhythmias within 6 months prior to screening or percutaneous cardiac intervention with
recent stent or coronary artery bypass grafting within 4 months prior to screening
10. LVEF is < 40% by echocardiogram at Screening per site cardiology interpretation
11. Have severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area < 1.0 cm2) or severe congenital heart disease
12. Have history of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular nodal or sinoatrial nodal dysfunction (Patients who do have a pacemaker or ICD are allowed in the study.)
13. QT corrected by Fridericia's (QTcF) is > 500 msec on Screening ECG as measured and corrected by the core lab. Patients who have a pacemaker may be included regardless of calculated QTc interval.
14. There is evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:

- First degree atrioventricular block
- Second degree atrioventricular block Type 1 (Mobitz Type 1/Wenckebach type)
- Right or left bundle branch block
- Atrial fibrillation with a controlled ventricular rate.

Contact: Dr. Vishal Kukreti /Olga Levina – **Open Enrollment**

A PHASE 3, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CAEL-101 AND PLASMA CELL DYSCRASIA TREATMENT VERSUS PLACEBO AND PLASMA CELL DYSCRASIA TREATMENT IN PLASMA CELL DYSCRASIA TREATMENT-NAÏVE PATIENTS WITH MAYO STAGE IIIA AL AMYLOIDOSIS
***Protocol Number*: CAEL101-302**

Inclusion Criteria

1. ≥18 years of age.
2. AL amyloidosis stage IIIa based on the 2013 European Modification of the 2004 Standard Mayo Clinic Staging in patients with advanced cardiac involvement
3. Measurable hematologic disease at Screening as defined by at least one of the following:
   - dFLC > 4 mg/dL or
   - iFLC > 4 mg/dL with abnormal ratio or
   - SPEP m-spike > 0.5 g/dL

4. Histopathological diagnosis of amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens AND confirmation of AL derived amyloid deposits by at least one of the following:
   - Immunohistochemistry or
   - Mass spectrometry or
   - Characteristic electron microscopy appearance
5. Cardiac involvement as defined by:
   - Documented clinical signs and symptoms supportive of a diagnosis of heart failure in the setting of a confirmed diagnosis of AL amyloidosis in the absence of an alternative explanation for heart failure AND
   - At least one of the following:

i. Endomyocardial biopsy demonstrating AL cardiac amyloidosis or
ii. Echocardiogram demonstrating a mean left ventricular wall thickness > 12 mm at diastole in the absence of other causes (e.g., severe hypertension, aortic stenosis), which would adequately explain the degree of wall thickening or
iii. Cardiac MRI with gadolinium contrast agent diagnostic of cardiac amyloidosis
6. NT-proBNP ≥ 650 and ≤ 8500 ng/L
7. Planned first-line treatment for plasma cell dyscrasia is CyBorD administered as SoC. Patients will be expected to remain on CyBorD for at least 2 cycles.
8. Adequate bone marrow reserve, hepatic, and renal function as demonstrated by:
   - Absolute neutrophil count ≥ 1.0 x 109/L
   - Platelet count ≥ 75 x 109/L
   - Hemoglobin ≥ 9 g/dL
   - Total direct bilirubin ≤ 2 times the upper limit of normal (x ULN) unless due to Gilbert's syndrome.
   - AST ≤ 3 x ULN
   - ALT ≤ 3 x ULN
   - ALP ≤ 5 x ULN (except for patients with hepatomegaly and isozymes specific to
   - liver, rather than bone)
   - eGFR ≥ 15 mL/min

Exclusion Criteria

1.Have any other form of amyloidosis other than AL amyloidosis
2. Received prior therapy for AL amyloidosis or multiple myeloma. A maximum exposure of 160 mg dexamethasone (or equivalent corticosteroid) since diagnosis of AL amyloidosis and prior to randomization is allowed.
3. Meets the IMWG definition of multiple myeloma or POEMS syndrome
4. Have supine systolic blood pressure < 90 mmHg or symptomatic orthostatic hypotension,
defined as a decrease in systolic blood pressure upon standing of > 30 mmHg despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
5. Taking prednisone or its equivalent > 10 mg/day
6. Taking doxycycline
7. Receiving dialysis
8. Planned stem cell transplant during the first 6 months of protocol therapy.

9. Have had myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias within 6 months prior to screening or percutaneous cardiac intervention with recent stent or coronary artery bypass grafting within 4 months prior to screening.
10. LVEF is < 40% by echocardiogram at Screening per site cardiology interpretation
11. Have severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area < 1.0 cm2) or severe congenital heart disease
12. Have history of sustained ventricular tachycardia or aborted ventricular fibrillation or a history of atrioventricular nodal or sinoatrial nodal dysfunction (Patients who do have a pacemaker or ICD are allowed in the study.)
13. QT corrected by Fridericia's (QTcF) is > 500 msec on Screening ECG as measured and corrected by the core lab. Patients who have a pacemaker may be included regardless of calculated QTc interval.
14. There is evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:

- First degree atrioventricular block
- Second degree atrioventricular block Type 1 (Mobitz Type 1/Wenckebach type)
- Right or left bundle branch block
- Atrial fibrillation with a controlled ventricular rate.

Contact: Dr. Vishal Kukreti /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/Harminder Paul -**Open Enrollment**

CONTACTS

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