Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre (Version January 2025)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

STUDY TITLE: DEVELOPMENT OF NK CELL- AND T CELL- ENGAGING BI- AND MULTI-SPECIFIC BIOLOGICS TO REDIRECT IMMUNE RESPONSES TOWASRDS PLASMA CELLS AND MYELOMA CELLS.

Study Number: NKT vs MM

Inclusion Criteria

1. Age ≥ 18 years
2. Able to give informed consent
3. Diagnosed with or suspected of having multiple myeloma, or is a healthy volunteer
4. Able and willing to donate research specimens

Exclusion Criteria

1. Another active major non-plasma cell malignancy (but permitting non-metastatic skin tumors), previously treated with chemotherapy within the past 2 years
2. Known HIV or HTLV infection
3. Known symptomatic Covid-19 infection in the past 2 weeks
4. Any serious medical condition or psychiatric illness that would prevent the subject from signing the informed consent form.
5. Declined to participate.
6. Unable to speak or understand English to a level necessary for reading and understanding the consent form and instructions

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

SKY92 GENE EXPRESSION ANALYSIS FOR PATIENTS WITH MULTIPLE MYELOMA

Protocol Short Name: SKY92

Eligibility Criteria

1. >18 years of age
2. Signed an informed consent – paper or electronically
3. Patients with either:
   a) A confirmed diagnosis of Multiple Myeloma, newly diagnosed
   b) A confirmed diagnosis of Smoldering Myeloma, newly diagnosed
   c) Disease relapse
4. Planned to have a BM sample collected or already provided a BM sample for SKY92 clinical gene expression profiling

Contact: Dr. Keith Stewart/ Harjot Vohra- **Open Enrollment**

NON-INTERVENTIONAL, INVESTIGATOR-INITIATED STUDY EVALUATING CLINICAL UTILITY OF CLONOTYPIC MASS SPECTROMETRY-BASED ASSAY (EASYM) FOR DISEASE RESPONSE ASSESSMENT IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM).
Protocol Number: EASYM

Inclusion Criteria

1. Must be able to understand and voluntarily sign an informed consent form (ICF).
2. Must be ≥ 18 years of age at the time of signing the ICF.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Newly diagnosed with MM (diagnosed as per recent IMWG 2014 criteria) with measurable M-protein or light chains.
5. Requiring systemic treatment.
6. Availability of baseline serum samples (either at diagnosis or up to 4 cycles of induction therapy) for baseline M protein sequencing.
7. Baseline M-protein >2g/L or involved serum free light chain of > 2000mg/l
8. Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

Exclusion Criteria

1. Non-secretory myeloma.
2. Light chain myeloma with involved serum free light chain of < 2000mg/L with no measurable M protein at diagnosis.
3. Smoldering myeloma.
4. POEMS or AL amyloid.

Contact: Dr. Suzanne Trudel /Harjot Vohra – **Open Enrollment**

AN INTEGRATED APPROACH TO CHARACTERIZE HIGH-RISK DISEASE IN MYELOMA AT PRINCESS MARGARET.
Protocol Number: HiPerMM

Inclusion Criteria

1. Age ≥ 18 years
2. Ability to give informed consent
3. Newly diagnosed with active multiple myeloma
4. Eligible for autologous stem-cell transplantation (ASCT)
5. Classified as intermediate-high risk (stage III) or high risk (stage IV) risk as per the R2-ISS criteria
6. Able and willing to donate research specimens within the 1st month of induction treatment.

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 questionnaires and follow instructions.

Contact: Dr. Suzanne Trudel /Harjot Vohra – **Open Enrollment**

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

Inclusion Criteria

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

Exclusion Criteria

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

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

AN OPEN-LABEL, 2-ARM, MULTICENTER, RANDOMIZED PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ELRANATAMAB (PF-06863135) + DARATUMUMAB + LENALIDOMIDE VERSUS DARATUMUMAB + LENALIDOMIDE + DEXAMETHASONE IN TRANSPLANT-INELIGIBLE PARTICIPANTS WITH NEWLY-DIAGNOSED MULTIPLE MYELOMA.
Protocol Number: C1071006 (MAGNETISMM-6)

Inclusion Criteria

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

2. Diagnosis of MM as defined according to IMWG criteria, including measurable disease based on IMWG criteria as defined by at least 1 of the following (as assessed by the central laboratory for Part 2):
   - Serum M-protein ≥0.5 g/dL;
   - Urinary M-protein excretion ≥200 mg/24 hours;
   - Involved FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

3. **Part 1 only**: Participant with NDMM or RRMM. NDMM participant must be transplant-ineligible as defined by age ≥65 years or transplant-ineligible as defined by age <65 years with comorbidities impacting the

possibility of transplant.
Participants with RRMM must have received 1-2 prior lines of MM therapy including at least one IMiD and one PI.

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

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

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

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

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

Exclusion Criteria

Medical Conditions:

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

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

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

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

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

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

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

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

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

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

defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions will be taken into consideration.

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

c. HBV:

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

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

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

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

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

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

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

Prior/Concomitant Therapy:

9. Part 1 only:

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

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

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

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

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

14. Hepatic and renal function characterized by the following:

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

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

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

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

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

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

Protocol Number: C1071007 (MAGNETISMM-7)

Inclusion Criteria

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

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

6. MRD positive (≥10-5) at screening by central laboratory NGS test (Adaptive Biotechnologies clonoSEQ® assay).
   - **Must have an archived bone marrow aspirate sample(s) that identifies the dominant malignant (index) clone that is used to track MRD status by central laboratory assessment (Adaptive Biotechnologies clonoSEQ® assay). This sample should preferably be collected before induction treatment (e.g., at diagnosis) or before transplant.** A sample collected after transplant may be accepted with sponsor approval. If a participant has an Adaptive Biotechnologies' clonoSEQ® MRD

assay result from previous testing that identifies the index multiple myeloma clone, and the result is retrievable and useable in this study, an archival sample will not be required.

- **A bone marrow aspirate sample collected during screening is required to determine MRD status.**

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

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

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

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

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

Exclusion Criteria

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

19. Ongoing Grade ≥ 3 peripheral sensory or motor neuropathy.
20. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
21. Live attenuated vaccine within 4 weeks of the first dose.
22. Known or suspected hypersensitivity to the study interventions or any of its excipients.
23. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
24. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
25. Previous MM maintenance treatment.
26. Prior treatment with BCMA targeted therapy.
27. Previous administration with an investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
28. Serum pregnancy test (for females of childbearing potential) positive at screening.

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

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

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

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

Non-Interventional

Inclusion criteria:

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

Exclusion criteria:

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

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

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

Non-Interventional

Inclusion criteria:

1. Age ≥ 60
2. Completed chemotherapy and/or radiation therapy and are being followed at University Health Network.
3. Patient must be in remission after completing chemotherapy or radiation
4. Peripheral blood counts must have returned to normal as defined by:
    a. Platelets $\geq 100 \times 10^9$/L
    b. PMN $\geq 1 \times 10^9$/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$<1.0 \times 10^9$/L) (The identification and definition of appropriate myelosuppressive chemotherapy and radiation regimens will be at the discretion of the treating physician and will vary among disease sites).
8. Patients must have the ability to understand the requirements of the study and provide written informed consent, which includes authorization for release of protected health information
9. Patient must be willing to provide a peripheral blood sample.

Exclusion criteria:

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

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

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

Non-Interventional

Inclusion criteria:

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

Exclusion criteria:

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

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

EVOLUTION OF CLONAL HEMATOPOIETIC (CHIP) MUTATIONS DURING TRANSPLANT IN MULTIPLE MYELOMA (M4-CHIP)
Protocol Number: M4-CHIP

Inclusion Criteria

1. Meeting inclusion criteria for the M4 study
2. Consented to samples being used for future research in the M4 study
3. Patients with samples collected from at least 3 of 4 study timepoints: (1) pre-transplant, (2) 100 days post-ASCT, (3) 1-year post-maintenance, and (3) 2-years post-maintenance.

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

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

Non-Interventional

Inclusion criteria:

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

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

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

SECOND LINE THERAPY

A PHASE 1, FIRST-IN-HUMAN, OPEN-LABEL, DOSE ESCALATION STUDY OF JNJ-87562761 IN RELAPSED/REFRACTORY MULTIPLE MYELOMA.
Protocol Number: 87562761MMY1001 (GPRC5D in RRMM)

Inclusion Criteria

1. Be ≥ 18 years of age (the legal age of majority in the jurisdiction in which the study is taking place, whichever is greater) at the time of informed consent.

2. Disease Characteristics

Relapsed, refractory multiple myeloma with measurable disease defined as:

- Serum monoclonal paraprotein (M-protein)level >0.5 g/dL; **or**
- Urine M-protein level >200 mg/24 hours; **or**

Light chain multiple myeloma: serum immunoglobulin free light chain (FLC) >10 mg/dL and abnormal serum immunoglobulin kappa-lambda FLC ratio

3. Prior Therapy Requirements

Must have had prior therapy including proteasome inhibitors, immunomodulatory agent and anti-CD38 therapy.

4. Have an ECOG performance status of 0 to 1.

5. **Renal Function**

Have an eGFR of >30 mL/min/1.73m^2 computed with the online calculator on the CKD-EPI website (http://ckdepi.org/equations/gfr-calculator/) use of the CKD-EPIcr result.

6. **Hepatic Function**

- AST
- ALT
- Total bilirubin
- For bilirubin in cases of known congenital nonhemolytic hyperbilirubinemias such as Gilbert's Syndrome:
- Isolated total bilirubin ≥1.5 x ULN with conjugated [direct] bilirubin ≤1.5 x ULN

7. **Hematologic Values**

Participants should have

- Hemoglobin ≥8 g/dL (≥5 mmol/L)(without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted)
- Absolute neutrophil count ≥1×10^9/L (without use of granulocyte colony stimulating factor (G-CSF)within 7 days prior to the date
- Platelets ≥50×109/L (without transfusion support in the 7 days prior to the laboratory test)

8. **Sex and Contraceptive/Barrier Requirements**

While on study treatment and for 6 months after the last dose of study treatment, a participant must:

- Not breastfeed or pregnant
- Not donate gametes (i.e., eggs or sperm)or freeze for future use for the purposes of assisted reproduction
- Wear an external condom.
- If of childbearing potential,
  - have a negative highly sensitive (e.g., β-hCG) pregnancy test at screening and within 24 hours before the first dose of study treatment, and agree to further pregnancy tests,
  - Practice at least one highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used.
- If a participant's partner is of childbearing potential,
  - The partner must practice a highly effective method of contraception unless the participant is vasectomized.

9. **Informed Consent**

Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

10. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

Exclusion Criteria

30. Active plasma cell leukemia (>2×109/L plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or immunoglobulin light chain amyloidosis.
31. Non-hematologic Treatment toxicity from prior anticancer therapy that has not resolved to baseline level or to ≤Grade 1 (except alopecia, tissue post-RT fibrosis, or Grade <3 peripheral neuropathy). Participants must have resolution of AEs related to prior GPRC5D therapies (if applicable).
32. Known loss of expression of GPRC5D antigen.
33. Known allergies, hypersensitivity, or intolerance to excipients of JNJ-87562761 (refer to the IB).
34. Pulmonary compromise requiring supplemental oxygen used to maintain adequate oxygenation.
35. Had major surgery or had significant traumatic injury within 2 weeks. Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.
36. Evidence of serious, uncontrolled, ongoing viral, bacterial, or systemic fungal infection requiring antiviral, antibacterial, or antifungal treatment.
37. Active disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment. Note: Exception for participants with vitiligo, type 1 diabetes, and prior autoimmune thyroiditis that are currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.

38. Current disabling psychiatric conditions, active substance abuse (e.g., alcohol or drug abuse), severe dementia, or altered mental status.
39. **Cardiovascular Dysfunction**
    Any of the following within 6 months prior to first dose of study treatment: severe or unstable angina, myocardial infarction, major thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident), clinically significant ventricular arrhythmias or heart failure New York Heart Association functional classification Class III to IV. Uncomplicated deep vein thrombosis is not considered exclusionary
40. **Disease Characteristics**
    Stem cell transplantation:
    a) Allogenic stem cell transplant within 6 months. Participants who received an allogenic transplant must be off all immunosuppressive medications for ≥42 days without signs of graft-versus-host disease.
    b) Received an autologous stem cell transplant ≤12 weeks.
41. **Prior Malignancies**
    Can have a prior or concurrent second malignancy (other than the disease under study) whose natural history or treatment is unlikely to interfere with any study endpoints of safety or the efficacy of the study treatment(s) on Allowed Recent Second or Prior Malignancies for details).
42. **Brian and Central nervous System Metastases**
    Central nervous system involvement or clinical signs of meningeal involvement of multiple myeloma. If either is suspected, whole brain MRI and lumbar cytology are required during screening.
43. **HIV Status**
    Human immunodeficiency virus-positive participants are not eligible if they meet any of the following:

a) Detectable viral load (ie, ≥50 copies/mL) at screening
b) CD4+ count ≤300 cells/mm3 at screening
c) Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of screening.
d) Not receiving highly active antiretroviral therapy (HAART). Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

NOTE: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

44. **Viral Hepatitis Assessments**
    Active hepatitis of infectious origin.
    a) Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen [HBsAg]. Participants with resolved infection (i.e., participants who are HBsAg negative with positive antibodies to total hepatitis B core antigen [anti- HBc]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR.
    b) Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV) antibody.
    c) Other clinically active liver disease of infectious origin.
45. **Prior/Concomitant Therapy**
    Prior antitumor therapy as follows, in the specified time frame prior to the first dose of study treatment:
    a) Targeted therapy, epigenetic therapy, monoclonal antibody treatment, or treatment with an investigational drug or an invasive investigational medical device within 21 days or at least 5 half-lives, whichever is less.
    b) Gene-modified adoptive cell therapy (e.g., CAR-modified T cells, CAR-modified natural killer cells, iNK cells) within 3 months.
    c) Treatment with anti-CD38 directed therapies within 3 months.
    d) Prior exposure to GPRC5D targeting agents, if not within 3 months, may be allowed after discussion with the sponsor.
    e) Conventional chemotherapy within 21 days.
    f) Proteasome inhibitor therapy within 14 days.
    g) Immunomodulatory agent therapy within 7 days.
    h) Radiotherapy within 14 days. However, if palliative focal radiation was used, the participant is eligible irrespective of the end date of radiotherapy.
46. A cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study treatment.
47. Receiving any disallowed therapies as noted in Section 6.9 Concomitant Therapy before the planned first dose of study treatment.
48. Has received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study treatment.
49. **Other Exclusions**

Any condition for which, in the opinion of the investigator or sponsor, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators must ensure that all study inclusion /exclusion criteria have been met at screening and prior to the first dose of study treatment. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records)after screening but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study.

Contact: Dr. Suzanne Trudel /Trisha Ramnanan – **Open Enrollment**

A PHASE 1 RANDOMIZED, OPEN-LABEL PHARMACOKINETIC COMPARABILITY STUDY COMPARING PRE- AND POST-CHANGE TECLISTAMAB IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Protocol Number: 64007957MMY1008 - MajesTEC10

Inclusion Criteria

1. ≥18 years of age.
2. Diagnosis of multiple myeloma as defined by the criteria
   A. Multiple myeloma diagnosis according to IMWG criteria
   B. Measurable disease at screening as defined by any of the following:
      1.Serum M-protein level ≥0.5 g/dL (central laboratory); or
      2.Urine M-protein level ≥200 mg/24 hours (central laboratory); or
      3.Serum immunoglobulin free light chain ≥10 mg/dL (central laboratory) and abnormal serum immunoglobulin kappa lambda free light chain ratio
3. Relapsed or refractory disease as defined below:
   A. Relapsed disease is defined as an initial response to previous treatment, followed by confirmed progressive disease by IMWG criteria >60 days after cessation of treatment.
   B. Refractory disease is defined as failure to achieve a response or confirmed progressive disease by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.
4. Received 1 to 3 prior lines of antimyeloma therapy, including a minimum of 2 consecutive cycles each of a PI, lenalidomide, and an anti-CD38 monoclonal antibody (or minimum of 6 doses if anti-CD38 monoclonal antibody was only part of a maintenance regimen) in any prior line
5. Progressive disease or failure to achieve a response to last line of therapy based on IMWG criteria.
6. Have an ECOG performance status score of 0 to 2
7. Have clinical laboratory values meeting the following criteria:
   - **Hemoglobin** ≥8 g/dL;
   - **Platelets** ≥75×10^9/L in participants in whom <50% of bone marrow nucleated cells are plasma cells or ≥50×10^9/L in participants in whom ≥50% of bone marrow nucleated cells are plasma cells
   - **ANC** ≥1.0×10^9 /L
   - **AST** and **ALT** ≤2.5×ULN
   - **eGFR** ≥30 mL/min based on Modified Diet in Renal Disease Formula calculation or creatine clearance measured by a 24-hour urine collection
   - **Total bilirubin** ≤2×ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case if total bilirubin is >2×ULN, then direct bilirubin ≤1.5×ULN is required)
   - **Serum calcium corrected for albumin** ≤3.5 mmol/L or free ionized calcium ≤1.6 mmol/L
8. Follow pregnancy prevention and precautionary measures.

Exclusion Criteria

50. Received any bispecific antibody and/or CAR-T cell therapy
51. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study drug or its excipients
52. Received the following prior anti-myeloma therapy, within the specified time frame prior to randomization:
    a. Targeted therapy, epigenetic therapy, or treatment with an investigational drug or an invasive investigational medical device within 21 days or ≥5 half-lives, whichever is less
    b. Investigational vaccine within 4 weeks
    c. Monoclonal antibody therapy within 21 days

d. Cytotoxic therapy within 21 days
e. Proteasome Inhibitor therapy within 14 days
f. Immunomodulatory Drugs (IMiDs) agent therapy within 14 days
g. Radiotherapy within 14 days or focal radiation within 7 days
h. Gene-modified adoptive cell therapy (e.g. chimeric antigen receptor modified T cells, NK cells) within 3 months
i. Plasmapheresis within 28 days

53. Received a maximum cumulative dose of corticosteroids of ≥140 mg of prednisone or equivalent within 14 days prior to randomization
54. Regarding stem cell transplant:
    a. An allogeneic stem cell transplant within 6 months before randomization. Participants who received an allogeneic transplant must be off all immunosuppressive medications for ≥42 days without signs of graft-versus-host disease before randomization.
    b. An autologous stem cell transplant within 12 weeks prior to randomization.
55. Received a live, attenuated vaccine within 4 weeks before the first dose of study drug. Non-live or non-replicating vaccines authorized for emergency use (e.g. COVID-19) by local health authorities are allowed.
56. CNS involvement or clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain MRI and lumbar cytology may be required.
57. Plasma cell leukemia, smoldering multiple myeloma, Waldenström's macroglobulinemia, POEMS syndrome, or primary amyloid light chain amyloidosis.
58. Any of the following:
    a. Any ongoing myelodysplastic syndrome or B cell malignancy (other than multiple myeloma).
    b. Any history of malignancy, other than multiple myeloma, which is considered at high risk of recurrence requiring systemic therapy
    c. Any active malignancy (i.e. progressing or requiring treatment change in the last 24 months) other than multiple myeloma. The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:
        1. Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low-grade, <3 cm, no CIS)
        2. Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone
        3. Non-invasive cervical cancer
        4. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer (anti-hormonal therapy is permitted)
        5. Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (RP/RT/focal treatment)
        6. Other malignancy that is considered cured with minimal risk of recurrence in consultation with the Sponsor.
59. Stroke, transient ischemic attack, or seizure within 6 months prior to randomization.
60. Presence of the following cardiac conditions
    a. New York Heart Association stage III or IV congestive heart failure
    b. Myocardial infarction, unstable angina, or coronary artery bypass graft ≤6 months prior to randomization
    c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
    d. Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities
61. Participant is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.
62. Participant plans to father a child while enrolled in this study or within 3 months after the last dose of study treatment
63. Participant had major surgery or had significant traumatic injury within 2 weeks prior to randomization, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to be treated in the study.
64. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:
    a. Acute diffuse infiltrative pulmonary disease
    b. Evidence of active systemic viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy
    c. History of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroid disease that is currently euthyroid based on clinical symptoms and laboratory testing
    d. Disabling psychiatric conditions (e.g. alcohol or drug abuse), severe dementia, or altered mental status
    e. History of noncompliance with recommended medical treatments
    f. Any other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
65. Seropositive for hepatitis B: defined by a positive test for HBsAg. Participants with resolved infection (i.e. participants who are HBsAg negative with antibodies to total anti-HBc with or without the presence of anti-HBs) must be screened using RT-PCR measurement of HBV-DNA levels. Participants with a known history of HBV infection must be screened using RT-PCR

measurement of HBV-DNA levels irrespective of serological results. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV-DNA by RT-PCR.

66. Active hepatitis C infection as measured by positive HCV-RNA testing. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing. If a participant with history of chronic hepatitis C infection (defined as both HCV antibody and HCV-RNA positive) completed antiviral therapy and has undetectable HCV-RNA 12 weeks following the completion of therapy, the participant is eligible for the study
67. Human immunodeficiency virus-positive with 1 or more of the following:
    a. History of AIDS-defining conditions
    b. CD4 count <350 cells/mm3
    c. Detectable viral load during screening or within 6 months prior to screening
    d. Not receiving highly active antiretroviral therapy
    e. Had a change in antiretroviral therapy within 6 months of the start of screening
    f. Receiving antiretroviral therapy that may interfere with study treatment as assessed after discussion with the Sponsor.

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

A PHASE 3 RANDOMIZED STUDY COMPARING TALQUETAMAB IN COMBINATION WITH POMALIDOMIDE (TAL-P), TALQUETAMAB IN COMBINATION WITH TECLISTAMAB (TAL-TEC), AND INVESTIGATOR'S CHOICE OF EITHER ELOTUZUMAB, POMALIDOMIDE, AND DEXAMETHASONE (EPD) OR POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE (PVD) IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MYELOMA WHO HAVE RECEIVED 1 TO 4 PRIOR LINES OF THERAPY INCLUDING AN ANTI-CD38 ANTIBODY AND LENALIDOMIDE

Protocol Number: 64407564MMY3009 (MonumenTAL-6)

Inclusion Criteria

1. ≥18 years of age.
2. Documented multiple myeloma as defined by the criteria below:
    a. Multiple myeloma diagnosis according to the IMWG diagnostic criteria
    b. Measurable disease at screening as assessed by central laboratory, defined by any of the following:
        i. Serum M-protein level ≥0.5 g/dL (central laboratory); or
        ii. Urine M-protein level ≥200 mg/24 hours (central laboratory); or
        iii. Light chain multiple myeloma without measurable M-protein in the serum or the urine: serum Ig FLC ≥10 mg/dL (central laboratory) and abnormal serum Ig kappa lambda FLC ratio (central laboratory).

3. Relapsed or refractory disease as defined below:
    a. Relapsed disease is defined as an initial response to prior treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.
    b. Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.

4. Documented evidence of PD or failure to achieve a minimal response to the last line of therapy based on investigator's determination of response by IMWG criteria on or after their last regimen.

5. Have an ECOG performance status score of 0, 1, or 2 at screening and immediately prior to the start of administration of study treatment.

6. A POCBP must have a negative highly sensitive serum pregnancy test within 10 to 14 days prior to C1D1 and a further negative serum or urine pregnancy test within 24 hours prior to the start of study treatment, and must agree to further urine or serum pregnancy tests during the study and within 6 months after receiving the last dose of study treatment.

7. Received 1 to 4 prior lines of antimyeloma therapy including a minimum of 2 consecutive cycles of an anti-CD38 mAb at the dosing schedule (or minimum of 6doses if anti-CD38 mAb was only part of a maintenance regimen) in any prior line and 2 consecutive cycles of lenalidomide in any prior line.

8. Have clinical laboratory values meeting the following criteria during the Screening Phase and within 72 hours of the first dose of study treatment. If 1 or more criteria are not met 72 hours prior to dosing, one repeat of laboratory testing is permitted.

- **Hemoglobin:** ≥8 g/dL (≥5 mmol/L; without transfusion support or erythropoietin use within 7 days before the laboratory test).
- **Platelets:** $\geq 75\times10^9$/L in participants in whom <50% of bone marrow nucleated cells are PCs and $\geq 50\times10^9$/L in participants in whom ≥50% of bone marrow nucleated cells are PCs (without transfusion support or thrombopoietin receptor agonist within 7 days before the laboratory test).
- **Absolute Neutrophil Count (ANC):** $\geq 1\times10^9$/L (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF before the laboratory test).
- **Aspartate aminotransferase (AST) and alanine aminotransferase (ALT):** ≤2.5×ULN
- **eGFR:** ≥30 mL/min based on Modified Diet in Renal Disease 4-variable formula calculation or creatinine clearance measured by a 24-hour urine collection.
- **Total bilirubin:** ≤2×ULN; except in participants with congenital bilirubinemia, such as congenital nonhemolytic hyperbilirubinemia (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)

9. HIV-positive participants are eligible if they meet all of the following:
   a. No detectable viral load (i.e., <50 copies/mL) at screening
   b. CD4+ count >300 cells/mm3 at screening
   c. No AIDS-defining opportunistic infection within 6 months of screening
   d. Receiving HAART. Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

Exclusion Criteria

68. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study drug or its excipients (refer to the talquetamab IB, teclistamab IB, and appropriate prescribing information). Additional exclusion criteria pertaining to specific study drugs include:
    a. GPRCD5-directed therapy or pomalidomide.
    b. A participant is not eligible to receive PVd in Arm C if any of the following are applicable:
        i. Does not meet criteria for bortezomib retreatment (failure to achieve at least PR to prior bortezomib treatment, or progression by IMWG criteria on therapy or within 6 months after cessation of prior bortezomib treatment)
        ii. Intolerance, defined as prior therapy discontinued due to any AE related to bortezomib
        iii. Grade 1 peripheral neuropathy with pain or Grade ≥2 peripheral neuropathy as defined by NCI-CTCAE Version 5.0
        iv. Received a strong CYP3A4 inducer within 5 half-lives prior to randomization.
    c. A participant is not eligible to receive EPd (Arm C) if they have received prior elotuzumab therapy.
    d. Received prior teclistamab therapy.
    e. Participants with history of multiple myeloma that is refractory to any T-cell-redirected therapy per IMWG diagnostic criteria.
69. Stroke, transient ischemic attack, or seizure within 6 months prior to signing ICF.
70. Presence of the following cardiac conditions:
    a. NYHA Class III or IV congestive heart failure.
    b. Myocardial infarction or coronary artery bypass graft ≤6 months prior to randomization.
    c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration.
    d. History of severe non-ischemic cardiomyopathy.

71. Major surgery or had significant traumatic injury within 2 weeks prior to the start of administration of study treatment, or will not have fully recovered from surgery, or has major surgery planned during the time the participant is expected to be treated in the study or within 2 weeks after administration of the last dose of study treatment.

72. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:
    a. Acute diffuse infiltrative pulmonary disease.
    b. Evidence of active systemic viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy.
    c. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment. EXCEPTION: Participants with vitiligo, controlled type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.
    d. Disabling psychiatric conditions (e.g., alcohol or drug abuse), severe dementia, or altered mental status.
    e. Any other issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
    f. History of noncompliance with recommended medical treatments.
73. Prior or concurrent exposure to any of the following, in the specified time frame prior to randomization:
    a. T-cell redirection therapy (e.g., antibody therapy or BiTEs) within 3 months.
    b. Gene-modified adoptive cell therapy (e.g., CAR-T cells, NK cells) within 3 months.
    c. Targeted therapy, epigenetic therapy, mAb therapy, cytotoxic therapy, or treatment with an investigational drug or an invasive investigational medical device within 21 days or ≥5 half-lives, whichever is less.
    d. Investigational vaccine other than SARS-CoV-2 vaccine approved or authorized for emergency use within 4 weeks.
    e. Live, attenuated vaccine within 4 weeks. Non-live and non-replicating vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed.
    f. PI therapy within 14 days.
    g. IMiD agent therapy within 14 days.
    h. Focal radiation within 7 days.
74. Received either of the following:
    a. An allogeneic stem cell transplantation within 6 months before the first dose of study treatment. Participants who received an allogeneic transplant must be off all immunosuppressive medications during the 6 weeks before the start of study treatment administration without signs of graft-versus-host disease.
    b. An autologous stem cell transplantation within 12 weeks before the start of study treatment administration.
75. A maximum cumulative dose of corticosteroids of ≥140 mg of prednisone or equivalent within 14-day period before the first dose of study drug (does not include pretreatment medications).
76. Any of the following:
    a. Hepatitis B infection (i.e., HbsAg or HBV-DNA positive): In the event the infection status is unclear, quantitative viral levels are necessary to determine the infection status.
    b. Active hepatitis C infection as measured by positive HCV-RNA testing. Participants with a history of HCV antibody positivity must undergo HCV-RNA testing. If a participant with history of chronic hepatitis C infection (defined as both HCV antibody and HCV-RNA positive) completed antiviral therapy and has undetectable HCV-RNA for at least 12 weeks following the completion of therapy, the participant is eligible for the study.
77. Known active CNS involvement or exhibits clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain MRI and lumbar cytology are required.
78. PC leukemia at the time of screening, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), or primary amyloid light chain amyloidosis.
79. Any of the following:

    a. Ongoing myelodysplastic syndrome or B cell malignancy (other than multiple myeloma).
    b. Any history of malignancy, other than multiple myeloma, which is considered at high risk of recurrence requiring systemic therapy.

    c. Any active malignancy (i.e., progressing or requiring treatment change in the last 24 months) other than multiple myeloma. The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:
        i. Non-muscle invasive bladder cancer (solitary Ta-PUN-LMP or low grade, <3 cm, no CIS)

ii. Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone
iii. Non-invasive cervical cancer
iv. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history oflocalized breast cancer (antihormonal therapy is permitted)
v. Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (RP/RT/focal treatment)
vi. Other malignancy that is considered cured with minimal risk of recurrence in consultation with the sponsor's medical monitor.

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

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

Protocol Number: R5458-ONC-2245

Inclusion Criteria

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

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

Exclusion Criteria

1. Diagnosis of plasma cell leukemia, amyloidosis (including myeloma associated amyloidosis), Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or POEMS syndrome.
2. Prior treatment with elotuzumab and/or pomalidomide
3. Participants with known MM brain lesions or meningeal involvement

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

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

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

Inclusion Criteria

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

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

Exclusion Criteria

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

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

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

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

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

Protocol Number: CA057-003

Inclusion Criteria

1. MM with relapsed or refractory disease and must:
    i. Have documented disease progression by the International Myeloma Working Group (IMWG) Uniform Response Criteria during or after their last myeloma therapy
    ii. Be refractory to, intolerant to, or not a candidate for available, established therapies known to provide clinical benefit in MM.
2. Have measurable disease including at least 1 of the following criteria:
    i. M-protein quantities ≥ 1.0 g/dL by serum protein electrophoresis (sPEP)
    ii. M-protein quantities ≥ 200 mg/24 hour urine collection by urine protein electrophoresis (uPEP)
    iii. Serum free light chain (sFLC) levels > 100 mg/L of the involved light chain and an abnormal kappa/lambda (κ/λ) ratio in participants without measurable serum or urine M-protein
    iv. Immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 1 g/dL
3. Participant consents to serial bone marrow aspirations (BMAs) and/or biopsies (BMBs) during screening and study treatment, and may consent to BMA and/or BMB at the end of treatment
4. ECOG Performance Status of 0 or 1
5. ≥18 years of age
6. Females of childbearing potential (FCBP) must agree and adhere to all testing and contraception requirements in the mezigdomide (CC-92480) Global Pregnancy Prevention Plan (PPP).

7. Female of Child Bearing Potential participants and all male participants must follow study pregnancy prevention contraception requirements and Pregnancy Prevention Program. Varies depending on study treatment.
8. Male participant must agree to refrain from donating sperm or semen while on study treatment, during dose interruptions, and for up to 4 months after last dose of study treatment (duration dependent on study drug).
9. Female of Child Bearing Potential participants must agree to refrain from donating eggs or breastfeeding while on study treatment and up to 7 months after last dose of study treatment (duration dependent on study drug)
10. Must agree to refrain from donating blood while on study treatment, during dose interruptions, and for ≥ 28 days following last dose of study treatment.

Exclusion Criteria

1. Current or history of central nervous system involvement of MM
2. Plasma cell leukemia; Waldenstrom's macroglobulinemia; polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome; or clinically significant light-chain amyloidosis.
3. Cannot tolerate oral medications and/or has gastrointestinal disease that may significantly alter the absorption of oral study treatments
4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   i. Left ventricular ejection fraction (LVEF) < 45% as determined by echocardiography (ECHO) or multi-gated acquisition (MUGA) scan at screening
   ii. Complete left bundle branch, bifascicular block, or other clinically significant abnormal electrocardiographic finding at screening
   iii. A prolongation of QT interval on screening electrocardiogram (ECG) as defined by corrected QT interval (QTc) > 480 ms using Fridericia's QT correction formula; a history of or current risk factors for Torsades de Pointe (eg, heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval
   iv. Congestive heart failure (New York Heart Association Class III or IV)
   v. Myocardial infarction or stroke ≤ 6 months prior to starting study treatments
   vi. Unstable angina or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris
   vii. Uncontrolled hypertension
5. HIV positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if:
   i. They have received antiretroviral therapy (ART) for at least 4 weeks prior to starting study treatment as clinically indicated while enrolled on study.
   ii. They continue taking ART as clinically indicated and while enrolled on study.
   iii. CD4 counts and viral load are monitored per standard of care by a local health care provider.
6. History of hepatitis B or C virus or has virologic or serological evidence of hepatitis A, B, or C virus infection. Participants who had hepatitis C virus (HCV) but have received an antiviral treatment and show no detectable HCV viral ribonucleic acid (RNA) for 6 months are eligible.
7. History of concurrent second cancer requiring ongoing systemic treatment.
8. Prior malignancy other than MM, except if the participant has been free of disease for ≥ 3 years or the participant had 1 of the following non-invasive malignancies treated with curative intent without known recurrence:
   i. Basal or squamous cell carcinoma of the skin
   ii. Carcinoma in situ of the cervix or breast
   iii. Stage 1 bladder cancer
   iv. Incidental histological findings of localized prostate cancer such as tumor Stage 1a or 1b (T1a or T1b) using the tumor, nodes, and metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent
9. Participant has active, uncontrolled, or suspected infection.
10. SARS-CoV-2 infection within 7 days for asymptomatic or mild symptomatic infections or 14 days for severe/critical illness prior to Cycle 1 Day 1 (C1D1). Acute symptoms must have resolved. A longer duration may be needed based on the investigator's clinical judgement. Acute symptoms must have resolved and, based on investigator assessment in consultation with the Clinical Trial Physician or Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.
11. Medical condition including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study.
12. History of retinal vein occlusion (RVO)
13. For trametinib-containing arms, participant with known risk factors for gastrointestinal perforation including history of diverticulitis and metastases to gastrointestinal tract. Note: Concomitant use of medicinal products with a recognized risk of gastrointestinal perforation is not exclusionary but should be avoided, if possible per protocol.
14. History of interstitial lung disease (ILD) or pneumonitis, or the participant has active dyspnea or other condition that may put the participant at increased risk of development of ILD or pneumonitis.

15. Pregnant, nursing, or breastfeeding, or who intend to become pregnant during participation in the study
16. Inability to comply with restrictions and prohibited treatments as listed in protocol.
17. For Part 1: Participant received prior therapy with CC-92480. For Part 2: Participant received prior therapy with CC-92480, tazemetostat, BMS-986158, or trametinib.
18. Previously received allogeneic stem-cell transplant at any time or received autologous stem-cell transplant within 12 weeks of initiating study treatment.
19. Received any of the following within 14 days prior to initiating study treatment:
    i. Plasmapheresis
    ii. Major surgery (as defined by the investigator)
    iii. Radiation therapy other than local therapy for myeloma associated bone lesions
    iv. Use of any systemic anti-myeloma drug therapy
20. Used any investigational agents within 28 days or 5 half-lives (whichever is shorter) prior to study treatment.
21. Received immunosuppressive medication within 14 days prior to initiating study treatment. The following are exceptions to this criterion:
    i. Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection)
    ii. Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent
    iii. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
22. COVID-19 vaccine within 14 days prior to C1D1. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to C1D1.
23. Live/attenuated vaccine, including live vaccines for COVID-19, within 30 days prior to study treatment
24. Concurrent administration of strong CYP3A modulators including within 14 days prior to initiating study treatment
25. Concurrent administration of proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole; etc.) including within 14 days prior to study treatment.
26. Unable or unwilling to undergo protocol-required thromboembolism prophylaxis
27. Evidence of organ dysfunction or any clinically significant deviation from normal by physical examination or in vital signs, by ECG, or by clinical laboratory determinations beyond what is consistent with the target population and in addition to the specific criteria above and below

28. Participant has any of the following laboratory values (determined by local lab); qualifying laboratory value must occur at most recent measurement prior to cohort assignment and must be no more than 14 days prior to cohort assignment:
    i. **Absolute neutrophil count (ANC)** < 1.0 x 10^9/L (< 1000/µL) without growth factor support within 7 days prior to screening complete blood count (CBC) (14 days if pegfilgrastim is used)
    ii. **Platelets** < 75 x 10^9/L (< 75,000/µL) and no platelet transfusions within the 7-day period leading up to the screening CBC
    iii. **Hemoglobin** < 8 g/dL (< 4.9 mmol/L) and no RBC transfusions are allowed within the 72-hour period leading up to the screening CBC
    iv. **Potassium** outside normal limits and cannot be corrected with supplements
    v. **Corrected serum calcium** > 13.5 mg/dL (> 3.4 mmol/L)
    vi. **Serum AST/serum glutamic oxaloacetic transaminase (SGOT**) and **ALT/serum glutamic pyruvic transaminase (SGPT)** > 3x ULN
    vii. **Serum bilirubin** > 1.5x ULN; > 3.0 mg/dL is allowed for participants with documented Gilbert's Syndrome
    viii. **Estimated glomerular filtration rate (eGFR)** < 45 mL/min/1.73 m^2 calculated using the Modified Diet in Renal Disease (MDRD) formula (see Appendix 7)
    ix. **International normalized ratio (INR)** ≥ 1.5x ULN and **partial thromboplastin time (PTT)** ≥ 1.5x ULN (only for participants who are not on anticoagulants). Note: Participants receiving therapy for a thromboembolic event that occurred > 3 months prior to enrollment are eligible as long as they are on a stable regimen of anticoagulation with warfarin, low-molecular weight heparin, or another approved therapeutic anticoagulation regimen
29. History of severe allergic or anaphylactic reactions or hypersensitivity to a CRBN-modulating agent, BETi, EZH2i, MEKi, or any of their excipients
30. Current or recent (within 3 months of study intervention administration) gastrointestinal disease that could impact upon the absorption of study intervention
31. Any gastrointestinal surgery that could impact upon the absorption of study intervention

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

THIRD LINE THERAPY

None

FOURTH LINE OF THERAPY

OUTPATIENT-BASED TECLISTAMAB STEP-UP DOSING IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: PROCESS DEVELOPMENT IN ACADEMIC AND COMMUNITY CENTRES, AND EVALUATING IMPACT ON CAREGIVER BURDEN

Protocol Number: Outpatient TEC/64007957MMY4009

Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Eligible for teclistamab treatment as per Health Canada approved indication:
   a. Age 18 and greater
   b. Relapsed or refractory multiple myeloma
   c. Received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody
   d. Demonstrated disease progression on the last therapy
2. For Cohorts 1 and 2, participants must agree to receive treatment at PM. For Cohort 3, participants must agree to receive treatment at Stronach Regional Cancer Centre.
3. Must sign an ICF (or their legally acceptable representative must sign) indicating that the participant understands the purpose of, and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the patient's disease.
4. Have one or more caregivers meeting criteria as per Appendix 7.
5. Have clinical laboratory values meeting the following criteria during the Screening Phase:

Hematology	
Hemoglobin	≥80g/L; prior RBC transfusion allowed but not within 7 days before the laboratory test; recombinant human erythropoietin use is permitted
Platelets	≥50×10^9/L; prior platelet transfusion allowed but not within 7 days before the laboratory test
Absolute neutrophil count	≥1.0×10^9/L (growth factor support is permitted)
Chemistry	
AST and ALT	≤3×ULN
eGFR	≥40 mL/min based on calculated creatinine clearance
Total bilirubin	≤2.0×ULN
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal	

6. Rockwood Clinical Frailty Scale – threshold score ≤ 5 (Appendix 6)
7. A woman of childbearing potential must have a negative highly-sensitive serum pregnancy test at screening and must agree to:
   a. Practicing true abstinence; or
   b. Have a sole partner who is vasectomized; or
   c. Practicing ≥1 highly-effective, user-independent method of contraception (see Appendix 14).

NOTE: Participant must agree to continue the above throughout the study, thereafter to continue with product monograph guidelines with ongoing teclistamab off-study.

8. A woman must agree not to donate eggs (ova, oocytes) or freeze for future use, for the purposes of assisted reproduction during the study. Upon study end, female participants must agree to continue with product monograph guidelines with ongoing teclistamab off study.
9. A man must wear a condom (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study, and thereafter to continue with product

monograph guidelines. If a female partner is of childbearing potential, she must also be practicing a highly effective method of contraception.

NOTE: If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/suppository), but his female partner is not required to use contraception.

10. A male participant must agree not to donate sperm for the purpose of reproduction during the study, and thereafter to follow product monograph guidelines with ongoing teclistamab off-study.

Exclusion Criteria

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

1. Contraindications or life-threatening allergies, hypersensitivity, or intolerance to any study drug or its excipients (refer to the teclistamab Product Monograph and appropriate package inserts)
2. Prior or concurrent exposure to any of the following:
    a. Teclistamab or any anti-BCMA therapy
    b. Other myeloma therapy (standard of care or investigational) including corticosteroids, within 3 days of first step-up dose of teclistamab
3. Toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy
4. High risk disease features including:
    a. CNS involvement with myeloma
    b. Extramedullary disease (≥1 soft tissue plasmacytoma not associated with bone)
    c. Circulating plasma cells (plasma cell leukemia)
    d. Rapidly progressive disease, as per investigator assessment
5. Concurrent disorders, including:
    e. Light chain amyloidosis
    f. Second malignancy requiring active therapy, exceptions including prostate cancer receiving androgen deprivation therapy or adequately treated breast cancer carcinoma on anti-hormonal agents and considered to have a very low risk of recurrence
    g. Underlying neurologic dysfunction (history of seizure, CVA or TIA, intracranial hemorrhage, dementia or other cognitive impairment)
    h. Hepatitis B infection (HBV-DNA positive). Patients with HepBsAg or HepBcAb positive are allowed on study, only if on antiviral prophylaxis and HBV-DNA viral load is undetectable. Refer to Appendix 15.
    i. Active infection requiring anti-infective therapy (prophylactic antibiotics are allowed). CMV IgG positivity allowed, but must be CMV PCR negative.
    j. Underlying coagulopathy that may increase the risk of bleeding in the setting of cytopenia.
6. Presence of the following cardiac conditions:
    a. New York Heart Association stage III or IV congestive heart failure
    b. Myocardial infarction or coronary artery bypass graft ≤6 months prior to randomization
    c. History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration
    d. History of severe non-ischemic cardiomyopathy
7. Major surgery within 2 weeks prior to the start of administration of study treatment (kyphoplasty or vertebroplasty are not considered major surgery).
8. Concurrent medical or psychiatric condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study, such as:
    a. Uncontrolled diabetes
    b. Acute diffuse infiltrative pulmonary disease
    c. Evidence of active systemic viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy
    d. History of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing
    e. Disabling psychiatric conditions (e.g., alcohol or drug abuse), severe dementia, or altered mental status
    f. Other comorbidities felt by treating physician to require hospitalization for teclistamab step-up dosing, such as poorly controlled pain despite use of narcotics, multiple concurrent comorbidities (diabetes, advanced age, cardiac disease)

g. Any other issue that would impair the ability of the participant to receive or tolerate planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

h. History of non-compliance with recommended medical treatments

Lifestyle Considerations

1. Carry a "Patient Card" with important safety information for patients receiving treatment with teclistamab for the duration of study participation.
2. Agree not to donate blood during therapy, during dose interruptions, and for ≥ 28 days after the last dose of study treatment.
3. Be willing to remain in close proximity (within 1 hour) to the hospital (PM for Cohorts 1 and 2; Southlake for Cohort 3) starting after Step-up Dose 1 of teclistamab until completion of Cycle 1 Day 27, as described in Appendix 7
4. Be willing to be hospitalized for administration of teclistamab following specified AEs as described in Appendix 7.
5. Agree to have a caregiver in the home and to accompany outside of the home until completion of study (Cycle 1 Day 27), as described in Appendix 7.

Caregivers of multiple myeloma subjects treated with outpatient-based teclistamab (Part 2):

Inclusion Criteria

Each potential caregiver participant must satisfy all of the following criteria to be enrolled in Part 2 of the study:

1. Agree to be a caregiver for a participant with multiple myeloma enrolled in this study protocol to receive outpatient teclistamab (any of Cohorts 1, 2, 3)
2. Age 18 and greater
3. English-speaking
4. Must sign an ICF
5. Attend mandatory orientation, equipment training, and provide transportation by car to and from PM until two days after completion of first three doses (at minimum 8 days to encompass step up dosing), and twice weekly to Day 27
6. Accompany the participant through the night and during the day, with no more than 2hour gaps during the day during which the patient is alone, to end of study (Day 27 or completion of 6 total doses [2 step up doses + 4 full doses], whichever is later). More than one caregiver may participate to fill the required hours of accompaniment.
7. Agree to help administer home medications, buy groceries, prepare food and otherwise support the participant
8. Agree and capable of monitoring the participants vital signs, apply the ICE score, record findings, and report to the study team (by phone or in person)

Exclusion Criteria

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

1. Not sufficiently comfortable or understanding of the use of vital sign equipment, applying the ICE score, or other caregiver requirements, as per Investigator discretion
2. Unable to complete caregiver follow-up assessments at 30 and 90 days after last treatment subject dose.
   Individuals who do not meet the criteria for participation in this study (screen failures) will not be rescreened and will be replaced to meet planned sample size. Screen failures for conditions under which the repeat of any screening procedures, is allowed.

Contact: Dr. Christine Chen/Trina Wang – **Open Enrollment**

A PHASE 1B/2 DOSE-ESCALATION AND COHORT-EXPANSION STUDY TO DETERMINE THE SAFETY AND EFFICACY OF BGB-11417 AS MONOTHERAPY, IN COMBINATION WITH DEXAMETHASONE, DEXAMETHASONE/CARFILZOMIB, DEXAMETHASONE/DARATUMUMAB, AND DEXAMETHASONE/POMALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND T(11;14)
Protocol Number: BGB-11417-105

Inclusion Criteria

1. ≥ 18 years old
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
3. A confirmed diagnosis of multiple myeloma (must have an M-component in serum and/or urine)
4. Measurable disease defined as:
    a. M-spike ≥ 500 mg/dL, or
    b. Urine protein M-spike of ≥ 200 mg/day, or
    c. Serum free light chains ≥ 10 mg/dL, and an abnormal κ:λ ratio
5. Participant has documented relapsed or progressive MM on or after any regimen or who are refractory to the most recent line of therapy.
    Note:
    - Relapsed MM is defined as previously treated MM that progresses and requires initiation of salvage therapy but does not meet the criteria for refractory MM.
    - Refractory MM is defined as disease that is nonresponsive (failure to achieve minimal response or development of progressive disease) while on primary or salvage therapy or progresses within 60 days of last therapy.
        a. Patients in Part 1 should have relapsed or progressive disease and have had≥ 3 prior lines of therapy including a proteasome inhibitor, IMiD agent, and an anti-CD38 monoclonal antibody.
        b. Patients in Part 2 (Cohorts 1 and 2):
        i. Patients should have relapsed or progressive disease and have had ≥ 3 prior lines of therapy including a proteasome inhibitor, an IMiD, and an anti-CD38 monoclonal antibody.
        c. Part 2 (Cohorts 3, 4, and 5):
        i. Patients should have relapsed or progressive disease and have had ≥ 1 prior line of therapy.
        ii. Patients must have been exposed to a combination therapy containing an anti-CD38 monoclonal antibody.
        iii. Prior treatment with carfilzomib is allowed, but the patient must not be considered carfilzomib refractory by the investigator and not have received carfilzomib within the past 6 months.
6. Positivity for t(11;14) by a validated fluorescence in situ hybridization (FISH) assay in a predefined central laboratory:
    a. A fresh bone marrow aspirate sample must be collected at screening and sent to central laboratory for t(11;14) FISH testing.
    b. Enrollment requires centrally confirmed t(11;14) results.
7. Either > 100 days after autologous stem cell transplant or ≥ 6 months after allogeneic transplant and without active graft-versus-host disease (ie, requiring treatment)
8. At least 2 months should have elapsed after previous chimeric antigen receptor T-cell therapy
9. Adequate organ function defined as:
    a. Hemoglobin ≥ 8.0 g/dL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
    b. Platelet count ≥ 75,000/μL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
    c. Absolute neutrophil count (ANC) ≥ 1000/mm^3 [ANC = (% of segmented neutrophils + % of segmented bands) x total WBC count] within 7 days before first dose of study treatment
    NOTE: The screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim (or other pegylated myeloid growth factors) and at least 7 days following the most recent administration of filgrastim or other myeloid growth factors
    d. ALT and AST ≤ 3 x upper limit of normal (ULN) and total bilirubin ≤ 2.0 x ULN
    e. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 45 mL/min/1.73 m^2 calculated by the MDRD-6 formula. Web-based calculator available at:
    https://qxmd.com/calculate/calculator_141/mdrd-egfr-6-variable

10. Women of childbearing potential must have a negative serum pregnancy test ≤ 7 days before the first dose of study drug(s). In addition, they must use a highly effective method of birth control initiated before the first dose of study drug(s), for the duration of the study treatment period, and for 90 days after the last dose of sonrotoclax, dexamethasone, daratumumab, or pomalidomide, or 180 days after the last dose of carfilzomib, whichever is longer. See Appendix 10 for highly effective methods of birth control and the definition of childbearing
11. Nonsterile men must use a highly effective method of birth control along with barrier contraception for the duration of the study treatment period and for ≥ 90 days after the last dose of study drug. During this same period, they must not donate sperm. Sterile men must use barrier contraception. In addition, partners of these men who could become pregnant should also utilize a highly effective method of birth control. See Appendix 10 for highly effective methods of birth control and the definition of sterile.
12. Life expectancy ≥ 6 months
13. Able to comply with the requirements of the study
14. Ongoing toxicities from prior anticancer therapies should have resolved or decreased to ≤ Grade 1 in severity (except for alopecia)

Exclusion Criteria

1. Participant has any of the following conditions:
    a. Non secretory MM (Serum free light chains < 10 mg/dL)
    b. Solitary plasmacytoma
    c. Active plasma cell leukemia (5% of peripheral white blood cells)
    d. Waldenström macroglobulinemia
    e. Amyloidosis
    f. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome
2. Chronic respiratory disease that requires continuous oxygen and/or respiratory failure requiring assisted ventilation
3. Significant cardiovascular disease, including but not limited to:
    a. Myocardial infarction ≤ 6 months before screening
    b. Ejection fraction ≤ 50%
    c. Unstable angina ≤ 3 months before screening
    d. New York Heart Association Class III or IV congestive heart failure (see Appendix 5)
    e. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
    f. Heart rate-corrected QT interval > 480 milliseconds based on Fridericia's formula
    g. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    h. Uncontrolled hypertension at screening, defined as systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg by ≥ 2 consecutive measurements
4. Prior therapy with BGB-11417 or other agents inhibiting Bcl-2 activity (eg, venetoclax)
5. Known infection with human immunodeficiency virus (HIV).
6. Serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if HBV DNA is undetectable (limitation of sensitivity < 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (limitation of sensitivity < 15 IU/mL).
7. Major surgery within 4 weeks prior to enrollment.
    Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, or meninges), the surgery is considered major.
8. Acute infections requiring antimicrobial therapy (antibiotic, antifungal, or antiviral) that have not been resolved for > 14 days prior to Cycle 1 Day 1.
9. Need for chronic corticosteroid therapy (> 10 mg prednisone or equivalent daily).
10. Any other medical condition that, in the opinion of the investigator, would adversely affect the participant's participation in the study or will render the administration of study drug(s) hazardous or obscure the interpretation of safety or efficacy results.
11. Psychiatric or cognitive dysfunction precluding active participation with the study protocol.
12. Radiation therapy that could affect bone marrow (eg, encompassing ≥ 5% of total bone marrow).
13. Use of the following substances prior to the first dose of study drug(s):
    a. ≤ 30 days prior to the first dose of study drug(s)
    − Any biologic and/or anti-CD38-based therapy
    b. ≤ 14 days prior to the first dose of study drug(s)

− Systemic chemotherapy or therapeutic radiation therapy (palliative radiation therapy for bone lesions is acceptable)
c. ≤ 7 days prior to the first dose of study drug(s)
− Corticosteroid given with antineoplastic intent
− Dexamethasone for any indication
− BTK inhibitor, tyrosine kinase inhibitor, or other targeted small molecule (with 5 half-lives ≥ 7 days) given with antineoplastic intent

14. A history of other active malignancies, including myelodysplastic syndrome, within the past 2 years prior to study entry, with the following exceptions
    a. Adequately treated in situ carcinoma
    b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    c. Prostate cancer ≤ Gleason Grade 6 and with stable prostate-specific antigen levels off treatment
    d. Previous malignancy, > 2 years with no evidence of disease, confined and surgically resected (or treated with other modalities) with curative intent, and unlikely to impact survival during the duration of the study
15. If patient had prior allogeneic stem cell transplant, there is evidence of ongoing graft-versus host disease.
16. Pregnant or lactating women.
17. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedure, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
18. Receiving any treatment with a moderate or strong CYP3A4 inhibitor (≤ 7 days or 5 half-lives) or moderate or strong CYP3A4 inducer (≤ 14 days or 5 half-lives) before first dose of sonrotoclax. See Appendix 6 for guidance on CYP3A inhibitors and inducers.
    Note: For patients in the pomalidomide cohort, a mandatory washout period of 7 days must be completed for patients on strong CYP1A2 inhibitors prior to Cycle 1 Day 1.
19. History of hypersensitivity to excipient(s) of sonrotoclax, dexamethasone, carfilzomib, daratumumab, or pomalidomide.
20. Vaccination with a live vaccine ≤ 35 days before first dose of study drug(s).

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

Contact: Dr. Christine Chen / Olga Levina – **Open for Enrollment except for DARA ARM, which is on Hold**

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

Protocol Number: K36MMSET-001

Inclusion Criteria

1. Voluntarily provide informed consent prior to initiation of study specific activities
2. ≥18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) score ≤ 1
4. Patients must have a confirmed diagnosis of RRMM (as per IMWG).
   - Patients must have received at least 3 prior lines of therapy as defined by IMWG, including a PI, an IMiD, and an anti-CD38 antibody
   - Patients must have exhausted available therapeutic options that are expected to provide a meaningful clinical benefit, either through disease relapse, treatment refractory disease, intolerance, or refusal of the therapy
   - *For expansion cohorts in Part B only:* Have t(4;14) confirmed by standard of care fluorescence in situ hybridization (FISH) testing or GOF mutation in MMSET confirmed by local sequencing test.
5. Measurable disease, including at least 1 of the following criteria:
   - Serum M protein (detected by serum protein electrophoresis [SPEP]) ≥ 0.50 g/dL
     − For patients with immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA ≥ 0.50 g/dL (IgA will similarly be used for response)

- Urine M protein (detected by urine protein electrophoresis [UPEP]) ≥ 200 mg/24 h
- Serum free light chain (sFLC) involved light chain ≥ 10 mg/dL (100 mg/L) provided sFLC ratio is abnormal
- ≥ 1 extramedullary lesion on imaging, including ≥ 1 lesion that is ≥ 1 cm in size and able to be followed by imaging assessments (Dose Escalation Only)
- Bone marrow plasma cells ≥ 10% (Dose Escalation Only)

6. Recovery to Grade ≤ 1 for any nonhematologic toxicities due to prior therapy, excluding alopecia or Grade 2 neuropathy
7. Ability and willingness to adhere to study visit schedule and protocol requirements

Exclusion Criteria

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

iii. History of or current plasma cell leukemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, and skin changes) syndrome, solitary bone lesion or bone lesions as the only evidence for plasma cell dyscrasia, myelodysplastic syndrome, or a myeloproliferative neoplasm or light chain amyloidosis.

iv. Active central nervous system (CNS) disease: patients with previously treated stable CNS disease are eligible

v. Inadequate bone marrow function defined by:
- Absolute neutrophil count (ANC) < 1000 cells/mm3
- Platelets (PLT) < 75,000 cells/mm3
- Hemoglobin < 8 g/dL (may be transfused provided no evidence of active bleeding)

vi. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)

vii. Total bilirubin > 1.5 × ULN, > 2 × ULN for patients with documented Gilbert's syndrome

viii. Prothrombin time (PT) or partial thromboplastin time (PTT) international normalized ratio (INR) > 1.5 × ULN, OR INR > 1.5 × ULN or within target range if on prophylactic anticoagulation

ix. Creatinine clearance < 50 mL/min by Cockcroft-Gault formula

x. Active, ongoing, or uncontrolled systemic viral, bacterial, or fungal infection. Prophylactic medications, antimicrobials or antiretroviral therapies are permitted provided the agents are not prohibited
- HIV-positive patients with CD4+ T-cell counts < 350 cells/μL or not on a stable antiretroviral regimen for > 4 weeks with a viral load > 400 copies/mL prior to enrollment may not be enrolled
- Hepatitis C virus (HCV)-positive patients who have not completed curative antiviral treatment and have a quantifiable viral load may not be enrolled
- Hepatitis B surface antigen (HBs-AG)-positive and hepatitis B core antigen (anti-HBc)-positive patients may be enrolled following a discussion with the Medical Monitor to discuss anti-hepatitis B virus (HBV) prophylaxis. Patients with chronic HBV infection should complete an anti-HBV therapy regimen with follow-up assessment for response and tolerability prior to initiating study medication

xi. Use of prohibited medications, including acid reducing agents and strong inhibitors or inducers of CYP3A4, within 14 days or 5 half-lives prior to starting KTX-1001

xii. Uncontrolled thromboembolic events or recent severe hemorrhage that, in the opinion of the Investigator or Medical Monitor would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

xiii. Any history of pulmonary embolism or deep vein thrombosis (DVT) within 1 month of enrollment. Therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) is allowed for history of DVT if > 3 months from time of enrollment.

xiv. Active, unstable cardiovascular function; presence of any of the following:
1) Symptomatic ischemia
2) Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on antiarrhythmics are excluded; patients with first degree atrioventricular or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded)
3) Congestive heart failure or New York Heart Association Class ≥ 3
4) Myocardial infarction within 3 months prior to C1D1
5) Uncontrolled hypertension
6) QTc > 470 ms

xv. Active malignancy not related to myeloma that has required therapy in the last 2 years prior to enrollment or is not in complete remission. Exceptions to these criteria include successfully treated nonmetastatic basal cell or squamous cell

skin carcinoma, or prostate cancer that does not require therapy. Other similar malignant conditions may be discussed with and permitted by the Medical Monitor

xvi. Malabsorption syndrome or other condition affecting oral absorption

xvii. Men and women of reproductive potential who are unwilling to practice acceptable methods of effective birth control while on study through 6 months (women) or 3 months (men) after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (refraining from heterosexual intercourse; men, women); vasectomy; tubal ligation; or a condom with spermicide (men) in combination with barrier methods, hormonal birth control or intrauterine device (women)

- Pregnancy, or females planning on becoming pregnant while on study or through 6 months after last study drug administration; or females who are lactating/breast feeding or who plan to breastfeed while on study through 6 months after last study drug administration
- Male patients must refrain from sperm donation, or attempt to conceive from study drug administration until 3 months after last dose of study drug

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

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

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

Inclusion Criteria

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

- Platelets ≥25,000/mm^3 (SSA), and ≥30,000/mm^3 (SSB) (transfusion support is permitted if completed at least 7 days prior to planned start of dosing)
- Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing)

14. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L).
15. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤ 1.

Exclusion Criteria

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

9. Participants with active HBV, HCV, SARS-CoV-2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.
   a. COVID-19/SARS-CoV-2: While SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, he/she is excluded.
10. 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.
11. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
12. Known or suspected hypersensitivity to the study interventions or any of its excipients.
13. Primary refractory MM defined as participants who have never achieved at least a MR with any treatment during the disease course.
14. Participants who are unable to tolerate lenalidomide or discontinued prior lenalidomide due to treatment-related toxicity (SSB).
15. Previous treatment with an anti-BCMA bispecific antibody.
16. Prior treatment with anti-BCMA CAR-T and/or ADC therapy is permitted; however, the participant cannot be refractory to this therapy if it was administered as the last line prior to study enrollment (SSA).
17. Participant is currently using (within 7 days before the first administration of study intervention) drugs that are known strong inhibitors or strong inducers of cytochrome P450 3A4 (CYP3A4) (SSA).
18. Live attenuated vaccine within 4 weeks of the first dose of study intervention.
19. Previous administration with an investigational drug within 30 days or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).
20. Intolerance to or participants who have had a severe (Grade ≥3) allergic or anaphylactic reaction to antibodies or therapeutic proteins.

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

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

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**

Inclusion Criteria:

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

a. Serum M-protein ≥ **1.0 g/dL**
b. Urine M-protein ≥ **200 mg/24 hrs**
c. Serum free light chain (FLC): involved **FLC level ≥ 10 mg/dL (100 mg/L)** provided serum FLC ratio is abnormal.

6. Estimated life expectancy > 12 weeks
7. ECOG performance score 0-1
8. Subjects should meet the following without intensive supportive therapy:

a. Complete blood count (CBC) results:

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

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

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

b. Blood biochemistry:

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

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

Exclusion criteria:

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

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

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

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

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

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

8. Subjects who have received any of the following:

- Autologous stem cell transplantation within one year.

- Allogeneic stem cell transplantation within two years.

9. Subjects who have received radiation in which the field covers > 5% of the bone marrow 30 days before leukapheresis or 14 days before lymphodepletion. Subjects who have received any anticancer treatment other than radiation 14 days before leukapheresis or lymphodepletion. If the field of radiation covers ≤ 5% of the bone marrow, the subjects are eligible to participate in the study regardless of the radiotherapy end date.
10. Patients have received ≥ 20 mg prednisone daily or other equivalent dose of steroids within 14 days before leukapheresis or 72 hours prior to lymphodepletion

Note: Any steroid treatment encroaching into the 14-day washout period may be allowable if discussed with and approved by the study medical monitor.

11. Patients have received major surgery 7 days prior to leukapheresis or 21 days prior to lymphodepletion (excluding cataract and other local anesthesia)
12. Subjects who have significant neurologic disorders such as seizures or dementia or prior brain bleeding (subarachnoid or subdural hematoma within the past 5 years) and unable to safely stop anticoagulation treatment during the screening and treatment phase.
13. *Bridging Therapy:* The subjects shall not receive any bridging therapy within 14 days prior to start of lymphodepletion unless approved by the study medical monitor.

Contact: Dr. Christine Chen/Trina Wang- **Open for Enrollment**

AMYLOIDOSIS TRIALS:

A PHASE 3, RANDOMIZED, MULTICENTER, DOUBLE-BLINDED, PLACEBO-CONTROLLED, EFFICACY ANY SAFETY STUDY OF BIRTAMIMAB PLUS STANDARD OF CARE VS PLACEBO PLUS STANDARD OF CARE IN MAY STAGE IV SUBJECTS WITH LIGHT CHAIN (AL) AMYLOIDOSIS

Protocol Number: NEOD001-301

Inclusion Criteria

1. Aged ≥18 years and legal age of consent according to local regulations
2. Newly diagnosed and AL amyloidosis treatment naïve
3. Bone marrow demonstrating clonal plasma cells
4. Confirmed diagnosis of AL amyloidosis by the following:
   - Histochemical diagnosis of amyloidosis determined by polarizing light microscopy of green birefringent material in Congo red-stained tissue specimens OR characteristic electron microscopy appearance AND
   - Confirmatory immunohistochemistry OR mass spectroscopy of AL amyloidosis
5. If the subject meets any of the following:
   - Is black or of African descent
   - Is over 75 years of age with concurrent monoclonal gammopathy
   - Has a history of familial amyloidosis and has concurrent monoclonal gammopathy AND no tissue is available for typing, and the subject has echocardiographic evidence ofamyloidosis and biopsy-proven amyloidosis with a monoclonal gammopathy, then the subject must have gene sequencing consistent with transthyretin (TTR) wild type (i.e., no TTR mutation present) AND must score 0 in technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (99mTc-DPD; Rapezzi 2011), hydroxymethylenediphosphonate (99mTc-HMDP; Galat 2015), or pyrophosphate (99mTc-PYP; Bokhari 2013) scintigraphy
6. Cardiac involvement as defined by all of the following:
   - Past documented or presently noted 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
   - Either an endomyocardial biopsy demonstrating AL amyloidosis or an echocardiogram demonstrating a mean left ventricular wall thickness at diastole >12 mm in the absence of other causes (e.g., severe hypertension, aortic stenosis),which would adequately explain the degree of wall thickening
7. Confirmed Mayo Stage IV as defined by:

- NT-proBNP ≥1800 pg/mL and
- Troponin-T ≥0.025 ng/mL(mcg/L) or high sensitivity cardiac troponin T ≥40 ng/L and
- dFLC ≥18 mg/dL

8. Planned first-line chemotherapy contains bortezomib administered subcutaneously weekly
9. Adequate bone marrow reserve, hepatic function, and renal function, as demonstrated by:
   - Absolute neutrophil count ≥1.0 × 109/L
   - Platelet count ≥75 × 109/L
   - Hemoglobin ≥9 g/dL
   - Total bilirubin ≤2 × the upper limit of normal (ULN) (***except*** for subjects with Gilbert's syndrome, in which case direct bilirubin ≤2 × ULN)
   - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase ≤3 × ULN
   - Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤3 × ULN
   - Alkaline phosphatase (ALP) ≤5 × ULN (***except*** for subjects with hepatomegaly and isozymes specific to liver, rather than bone)
   - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation
10. Seated systolic blood pressure (BP) 90 to 180 mmHg
11. Distance walked during each Screening 6MWT is >30 meters and <550 meters
12. Women of childbearing potential (WOCBP) must have 2 negative pregnancy tests during Screening, the second within 24 hours prior to the first administration of study drug, and must agree to use highly effective physician-approved contraception, from Screening to 90 days following the last study drug administration
13. Male subjects must be surgically sterile or must agree to use a barrier method, together with the use of highly effective physician-approved contraception by their female partner of childbearing potential, from Screening to 90 days following the last study drug administration
14. Ability to understand and willingness to sign an informed consent form prior to initiation of any study procedures

Exclusion Criteria

1. Non-AL amyloidosis
2. NT-proBNP >8500 pg/mL
3. Meets the International Myeloma Working Group (IMWG) definition of multiple myeloma, except for malignancy biomarker of involved/uninvolved serum free light chain ratio ≥100
4. Subject is eligible for and plans to undergo ASCT or organ transplant during the study
5. Symptomatic orthostatic hypotension that in the medical judgment of the Investigator would interfere with the subject's ability to safely receive treatment or complete study assessments
6. Myocardial infarction, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or ECG evidence of acute ischemia, within 6 months prior to the Month 1-Day 1 Visit
7. Severe valvular stenosis (e.g., aortic or mitral stenosis with a valve area <1.0 cm2) or severe congenital heart disease
8. ECG evidence of acute ischemia or active conduction system abnormalities with the exception of any of the following:
   - First degree AV-block
   - Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type)
   - Right or left bundle branch block
   - Atrial fibrillation with a controlled ventricular rate (uncontrolled [>110 bpm] ventricular rate is not allowed [determined by an average of 3 beats in Lead II or 3 representative beats if Lead II is not representative of the overall ECG])
9. Peripheral neuropathy assessed as National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 with pain, Grade 3, or Grade 4
10. Subject is receiving oral or intravenous antibiotics, antifungals, or antivirals within 1 week of Month 1-Day 1 with the exception of prophylactic oral agents
11. Prior treatment with hematopoietic growth factors, transfusions of blood or blood products within 1 week of Month 1-Day 1
12. Prior radiotherapy within 4 weeks of Month 1-Day 1
13. Major surgery within 4 weeks of Month 1-Day 1 or planned major surgery during the Study
14. Active malignancy with the exception of any of the following:
    - Adequately treated cutaneous basal cell carcinoma, squamous cell carcinoma, or in situ cervical cancer
    - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for 2 years
    - Low-risk prostate cancer with Gleason score <7, prostate-specific antigen <10 ng/mL, and a stage of cancer at most cT2a, cN0, and CM0
    - Any other cancer from which the subject has been disease-free for ≥2 years
15. History of severe allergy to any of the components of birtamimab such as histidine/L histidine hydrochloride monohydrate, trehalose dehydrate, or polysorbate 20 or history of Grade ≥3 infusion-related AEs or hypersensitivity to another monoclonal

antibody, or known hypersensitivity to diphenhydramine (or an equivalent H1 antihistamine) or acetaminophen (or its equivalent, paracetamol)
16. Known, unresolved, or active HIV, hepatitis B, hepatitis C, or SARS-CoV-2 infection
17. Prior treatment with plasma cell-directed chemotherapy, birtamimab, daratumumab, 11-1F4, anti-serum amyloid P antibody, doxycycline for amyloid, or other investigational treatment directed at amyloid
18. Treatment with another investigational agent within 30 days of Month 1-Day 1
19. Women who are pregnant or lactating
20. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the study or which would, in the opinion of the Investigator, unacceptably increase the subject's risk by participating in the study
21. Subject is under legal custodianship
22. History of epilepsy or seizure disorder with the exception of childhood febrile seizures
23. Waldenström's macroglobulinemia and/or immunoglobulin M monoclonal gammopathy

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

CONTACTS

Dr. Donna Reece	416-946-2824
Dr. Christine Chen	416-946-2827
Dr. Suzanne Trudel	416-946-4566
Dr. Vishal Kukreti	416-946-4566
Dr. Anca Prica	416-946-2249
Dr. Sita Bhella	416-946-4501 ext 3194
Dr. Keith Stewart	416-946-4501 ext 3194
Dr. Guido Lancman	416-946-2059
Dr. Chloe Yang	416-946-4501 ext 3194
Giovanni Piza	416-946-4627
Esther Masih Khan	416-946-4501 ext 4576
Mariela Pantoja	416-946-4501 ext 5102
Saima Dean	416-946-4501 ext 2417
Sumeet Kakar	416-946-4501 ext 5755
Harjot Vohra	416-946-4501 ext 2417
Ben Chu	416-946-4501 ext 3423
Jason Bian	416-946-4501 ext 4811
Protus Wadu	416-946-4501 ext 3670
Meseret Worku	416-946-4501 ext 5156
Kaithlan Djayakarsana	416-946-4501 ext 2608
Navjeet Kaur	416-946-4501 ext 2317
Hoda Mohamad	416-946-4501 ext 5241
Kinjal Patel	416-946-4501 ext 2561
Anuradha Saravanan	416-946-4501 ext 5931
Harman Sumal	416-946-4501 ext 5931
Blessing Nwafor	416-946-4501 ext 4811
Skylar Wu	416-946-4501 ext 2561
Olga Levina	416-946-4501 ext 6315
Rebecca Noronha	416-946-4501 ext 4716
Trina Wang	416-946-4501 ext 2680
Naomi Kimbriel	416-946-4501 ext 4365
Trisha Ramnanan	416-946-4501 ext. 5778
Elena Talovikova	416-946-4501 ext 2544