Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre (Version January 2019)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

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/Vinita Dhir -**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/Harminder Paul -**Open Enrollment**

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

Non-Interventional

Inclusion criteria:

1. Patients must have or be suspected of a diagnosis of AL amyloidosis, MM, or related clonal plasma cell disorder (PCD) such as smoldering myeloma or MGUS.
2. Patient must be ≥ 18 years old.

3. Patients are undergoing standard of care blood draw.
4. All patients must have signed and dated an informed consent form.

Healthy Subject Inclusion Criteria

1. 18-60 years old
2. 110 lbs. and above
3. Not pregnant
4. Not known to be anemic

Contact: Dr. Rodger Tiedemann/Harminder Paul-**Open Enrollment**

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

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

Protocol Number: MCRN 007

Inclusion Criteria:

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
a. Have undergone stem cell transplant, or have been considered transplant ineligible;
b. Previously undergone at least 2 prior lines of treatment and must have received lenalidomide and a proteasome inhibitor (in separate regimens or in combination);
c. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for ≥ 1 cycle during a previous MM treatment (i.e., relapsed MM); and/or
d. Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
2. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
a. Transplant was > 100 days prior to study enrolment;
b. No active infection
3. Subjects with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):

☐ Serum M-protein ≥ 5 g/L;

☐ Urine M-protein ≥ 200 mg/24 h;

☐ Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/l and an abnormal serum free light chain ratio (< 0.26 or > 1.65).

4.The following laboratory results must be met within 10 days of first study drug administration:

☐ Absolute neutrophil count (ANC) > 1.0 x 109/L. Growth factors cannot be given within 10 days of study drug administration;

☐ Serum ALT ≤ 2.5 x upper limit of normal (ULN);

☐ eGFR (MDRD) ≥ 40 mL/min a (Appendix 2);

☐ Platelet count > 75 x 109/L. Platelet transfusions to help subjects meet eligibility criteria are not allowed within 10 days before study enrollment;

☐ Hemoglobin ≥ 8.0 g/dL;

☐ Total bilirubin ≤ 1.5 x ULN, unless known to have Gilbert's disease. If Gilberts, isolated bilirubin > 1.5 and <3 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;

☐ Albumin/creatinine ratios (spot urine) <500mg/g (56 mg/mmol);

☐ Albumin ≥ 2.0 g/dL (20 g/L).

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Exclusion criteria:

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

Contact: Dr. Suzanne Trudel/Cindy Rajah– **Open Enrollment**

A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects with Relapsed or Refractory Multiple Myeloma and Subjects with Relapsed or Refractory Acute Myeloid Leukemia*

Protocol Number: AMG 176 20150161

Inclusion Criteria:

Adult subjects must satisfy the following criteria to be enrolled in the study:

1. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Subjects must have a documented diagnosis of MM and measurable disease at enrollment. Measurable disease per the IMWG response criteria (assessed within 28 days prior to enrollment), as indicated by one or more of the following:

a. Serum M-protein ≥ 0.5 g/dL
b. Urine M-protein ≥ 200 mg/24 hours
c. Subjects who do not meet 1 of the 2 prior criteria: serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal sFLC ratio (< 0.26 or > 1.65)

2. All subjects must have Pathologically documented, definitively diagnosed, multiple myeloma relapsed or refractory disease after at least 2 lines of therapy including a proteasome inhibitor and an immunomodulatory agent. The investigator must be of the opinion that no other treatment option will result in a durable response.

3. Subjects must have the following hematological values without transfusion or growth factor support
   a. Absolute neutrophil count ≥ 1.0 X 109/L
   b. Platelet count ≥50X 109/L (in patients where < 50% of bone marrow nucleated cells were plasma cells) or ≥ 30 X 109/L (in patients where ≥50% of bone marrow nucleated cells were plasma cells)
   c. Subjects should not have received platelet transfusions for at least 1 week prior to screening
   d. Hemoglobin > 8 g/dL
   e. Subjects may receive RBC transfusions or receive supportive care with erythropoietin or darbepoetin

4. Subjects must have the following lab values

- Hepatic function, as follows; TBA < 5 X ULN,
- AST and ALT < 3 X ULN,
- Total bilirubin < 1.5 X ULN (except subjects with Gilbert's syndrome)
- Left ventricular ejection fraction (LVEF) > 50% 2-D (ECHO) is the preferred method of evaluation.
- Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/minute

Exclusion criteria:

1. Previously received an allogeneic stem cell transplant within 6 months OR having received immunosuppressive therapy within the last three months OR having signs or symptoms of acute or chronic graft-versus-host disease
2. Autologous stem cell transplant less than 90 days prior to study day 1
3. Multiple myeloma with IgM subtype
4. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
5. Existing plasma cell leukemia or rapidly proliferating extra-medullary disease
6. Waldenstrom's macroglobulinemia
7. Amyloidosis
8. Glucocorticoid therapy (prednisone > 30 mg/day or equivalent) within 7 days prior to starting treatment. Topical or inhaled corticosteroids are permitted.
9. Enrollment in other investigational procedures while participating in this study
10. History of other malignancy except: • Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
    • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    • Adequately treated cervical carcinoma in situ without evidence of disease
    • Adequately treated breast ductal carcinoma in situ without evidence of disease
    • Prostatic intraepithelial neoplasia without evidence of prostate cancer
    • Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
11. Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II)
12. History of arterial thrombosis in the past 6 months
13. Active infection requiring intravenous anti-infective treatments within 1 week of study enrollment (day 1)
14. Known or suspected HIV infection or subjects who are HIV seropositive
15. Known active chronic hepatitis B or C virus (HBV/HCV) infection
16. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to (CTCAE) version 4.0 grade 1, with the exception of grade 2 peripheral neuropathy
17. Treatment with medications known to cause QTc interval prolongation within 7 days of study day 1
18. Anti-tumor therapy (chemotherapy within 14 days, antibody therapy, molecular targeted therapy, or investigational agent within 21 days) of study Cycle 1 Day 1.
19. Prior systemic radiation therapy must have been completed at least 28 days before study drug administration. Prior focal radiotherapy completed at 14 days before study drug administration.
20. Major surgery within 28 days of study Day 1
21. Men and women of reproductive potential who are unwilling to practice an acceptable method of effective birth control

22. Use of any medications (except anti-tumor medications), including herbal medicines (eg, St. John's wort), vitamins, or supplements consumed by the subject within the 30 days prior to receiving the dose of study drug
23. Use of known strong inhibitors of cytochrome P450 (CYP) 3A4/P-gp within the 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days
24. Use of known CYP1A2, CYP2D6, CYP2C9 sensitive substrates with a narrow therapeutic window within 3 half-lives of the drug or its major active metabolite, whichever is longer, following the last dose of the drug to receiving the first dose of AMG 176
25. Use of known cytochrome P450 (CYP) 3A4 sensitive substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer
26. Use of known organic anion polypeptide transporters (OATP) OATP1B1 and/or OATP1B3 or Breast Cancer Resistance Protein (BCRP) substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer.

Contact: Dr. Suzanne Trudel/Cindy Rajah– **Open Enrollment**

***Please note that site is only accepting Multiple Myeloma patients and not AML patients.**

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

Protocol Number: CelMod CC-92480-MM-001

Inclusion Criteria:

Adult subjects must satisfy the following criteria to be enrolled in the study:

1. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Subjects must have a documented diagnosis of MM and measurable disease at enrollment. Measurable disease is defined as:
   a. M-protein quantities ≥ 0.5 g/dL by sPEP or
   b. ≥ 200 mg/24-hour urine collection by uPEP or
   c. Serum FLC levels > 100 mg/L (milligrams/liter) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in subjects without detectable serum or urine M-protein or
   d. for subjects with immunoglobulin class A (IgA), myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 0.50 g/dL.
3. All subjects must:
   a. have documented disease progression on or within 60 days from the last dose of their last myeloma therapy and,
   b. have failed treatment with, are intolerant to or are not otherwise candidates for available therapies that are known to confer clinical benefit to subjects with RRMM.

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

7. Subjects must have the following laboratory values:
   - Absolute neutrophil count (ANC) ≥ 1.25 x 109/L without growth factor support for ≥ 7 days (≥ 14 days for pegfilgrastim).
   - Hemoglobin (Hgb) ≥ 8 g/dL.
   - Platelets (plt) ≥ 75 x 109/L without transfusion for ≥ 7 days (≥ 50 x 109/L for subjects with > 50% plasma cells in bone marrow).
   - Corrected serum calcium ≤ 13.5 mg/dL (≤ 3.4 mmol/L).
   - 24-hr creatinine clearance (CrCl) ≥ 45 mL/min.
   - AST/SGOT and ALT/SGPT ≤ 3.0 x upper limit of normal (ULN).
   - Serum bilirubin ≤ 1.5 x ULN.
   - Uric acid ≤ 7.5 mg/dL (446 μmol/L).
   - PT/INR < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN, (for subjects not receiving therapeutic anticoagulation).

Note: Subjects receiving therapy for a thromboembolic event that occurred >3 months prior to enrollment are eligible as long as they are on a stable regimen of anticoagulation with warfarin, low-molecular weight heparin or other approved therapeutic anticoagulation regimen.

Exclusion criteria:

27. Subject has non- or oligosecretory multiple myeloma

28. Subject has plasma cell leukemia or active leptomeningeal myelomatosis.
29. Subject has documented, systemic light chain amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes (POEMS) Syndrome.
30. Subject has immunoglobulin class M (IgM) myeloma
31. Subject has a history of allogeneic bone marrow transplantation
32. Subject is undergoing dialysis.
33. Subjects with peripheral neuropathy ≥ Grade 2.
34. Subjects with gastrointestinal disease that may significantly alter the absorption of CC-92480
35. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - LVEF < 45% as determined by ECHO or MUGA scan at Screening.
    - Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiographic (ECG) finding at Screening.
    - A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval >480 milliseconds (ms) using Frederica's QT correction formula; a history of or current risk factors for Torsades de Pointe (eg. heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval.
    - Congestive heart failure (New York Heart Association Class III or IV).
    - Myocardial infarction ≤6 months prior to starting CC-92480.
    - Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris.
36. Concurrent administration of strong CYP3A modulators. Examples of these drugs include (but are not limited to):
    - CYP3A inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
    - CYP3A inducers: carbamazepine, phenytoin, and rifampin.

    If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
37. Subject had prior systemic myeloma treatment (approved or investigational) ≤ 5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
38. Subject had major surgery ≤ 2 weeks prior to starting CC-92480. Note: Subjects must have recovered from any clinically significant effects of recent surgery.
39. HIV
40. Known active chronic hepatitis B or C virus (HBV/HCV) infection
41. A history of concurrent second cancer requiring ongoing systemic treatment
42. Subjects has a history of prior malignancy other than MM, unless the subject has been free of disease for ≥3 years except for the following noninvasive malignancies treated with curative intent:
    - Basal or squamous cell carcinoma of the skin.
    - Carcinoma in situ of the cervix or breast.
    - Stage 1 bladder cancer.
    - Incidental histological findings of localized prostate cancer such as tumor stage 1a or 1b (T1a or T1b) using the Tumor/Node/Metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent.
43. Subject has a history of anaphylaxis to thalidomide, lenalidomide, pomalidomide or dexamethasone
44. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480 or dexamethasone
45. Subject has undergone either of the following within 14 days of initiating CC-92480:
    - Plasmapheresis.
    - Radiation therapy other than local therapy for symptomatic relief of MM associated bone lesions.
46. Subject has received immunosuppressive medication within 14 days prior to the first dose of CC-92480. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection).
    - Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent.
    - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
47. Subject is unable or unwilling to undergo protocol required venous thromboembolism (VTE) prophylaxis. Thromboembolism prophylaxis consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study beginning 48 hours prior to Cycle 1, Day 1 until 48 hours after last CC-92480 administration.

Contact: Dr. Suzanne Trudel/Susi Snitzler– **Open Enrollment**

AN OPEN-LABEL, MULTICENTER, PHASE I TRIAL EVALUATING THE SAFETY AND PHARMACOKINETICS OF ESCALATING DOSES OF BFCR4350A IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA
Protocol Number: GO39775

Key Inclusion Criteria:

1. Patients must have R/R MM for which no established therapy for MM is appropriate and available or be intolerant to those established therapies
2. Agreement to provide bone marrow biopsy and aspirate samples as per protocol
3. Adverse events from prior anti-cancer therapy resolved to Grade ≤ 1, with the following exceptions:
    a. Any grade alopecia, peripheral sensory or motor neuropathy must have resolved to Grade ≤ 2
4. Measurable disease defined as at least one of the following:
    a. Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)
    b. Urine M-protein ≥ 200 mg/24 hr.
    c. Serum free light chain (SFLC) assay: Involved SFLCs ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (< 0.26 or > 1.65)
5. Laboratory values:
    a. Hepatic function: AST and ALT ≤ 3 × ULN; Total bilirubin ≤ 1.5 × ULN; patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
    b. Hematologic function: Platelet count ≥ 75,000/mm3 without transfusion within 14 days prior to first dose of BFCR4350A, ANC ≥ 1000/mm3, Total hemoglobin ≥ 8 g/dL
    c. Creatinine ≤ 2.0 mL/dL and creatinine clearance (CrCl) ≥ 30 mL/min (either calculated or per 24-hr urine collection)
    d. Serum calcium (corrected for albumin) level at or below the ULN
6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of BFCR4350A and tocilizumab (if applicable)
7. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm

Key Exclusion Criteria:

1. Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 4 weeks before first BFCR4350A infusion
2. Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA4, anti−PD-1, and anti−PD-L1 therapeutic antibodies, within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first BFCR4350A infusion
3. Treatment-related, immune-mediated adverse events associated with prior immunotherapeutic agents as follows:
    a. Grade ≥ 3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy
    b. Grade 1−2 adverse events that did not resolve to baseline after treatment discontinuation
4. Treatment with radiotherapy, any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first BFCR4350A infusion
5. Autologous stem cell transplantation (SCT) within 100 days prior to first BFCR4350A infusion
6. Prior allogeneic SCT
7. Primary or secondary plasma cell leukemia as defined by an absolute plasma cell count exceeding 2000/μL or 20% of the peripheral blood white cells
8. Prior solid organ transplantation
9. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
10. Patients with history of confirmed progressive multifocal leukoencephalopathy
11. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)

12. History of other malignancy that could affect compliance with the protocol or interpretation of results. - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
    a. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to first BFCR4350A infusion.
13. Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
    a. Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.
    b. Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed.
14. Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
15. Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
16. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics within 4 weeks prior to first BFCR4350A infusion
17. Known or suspected chronic active EBV infection.
18. Recent major surgery within 4 weeks prior to first BFCR4350A infusion
19. Positive serologic or PCR test results for acute or chronic HBV infection: Patients whose HBV infection status cannot be determined by serologic test results
20. Acute or chronic HCV infection
21. Known history of HIV seropositivity
22. Administration of a live, attenuated vaccine within 4 weeks before first BFCR4350A infusion or anticipation that such a live attenuated vaccine will be required during the study.
23. Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of corticosteroid treatment ≤ 10 mg/day prednisone or equivalent within 2 weeks prior to first dose of BFCR4350A
    a. Patients who received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval of the Medical Monitor
    b. The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
24. History of illicit drug or alcohol abuse within 12 months prior to screening,

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

A PHASE 1B STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF OPROZOMIB IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: 20160104

Inclusion Criteria:

1. Subject must have a pathologically documented, definitively diagnosed, multiple myeloma relapse, or refractory progressive disease after at least 2 lines of therapy for multiple myeloma. Prior therapeutic treatment or regimens must include a proteasome inhibitor and lenalidomide
2. Measurable disease (assessed within 28 days prior to day 1), as indicated by one or more of the following:
    - Serum M-protein ≥ 0.5 g/dL
    - Urine M-protein ≥ 200 mg/24 hours
    - In subjects without detectable serum or urine M-protein: serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal sFLC ratio
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
4. Hematological function, as follows, without transfusion support:
    - Absolute neutrophil count ≥ 1.0 X 109/L
    - Platelet count ≥ 75 X 109/L (in patients with < 50% of bone marrow nucleated cells were plasma cells) or ≥ 50 X 109/L (in patients with ≥ 50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support
    - Hemoglobin > 8 g/dL (> 80 g/L) Use of erythropoietic stimulating factors and

red blood cell (RBC) transfusions per institutional guidelines is allowed, however most recent RBC transfusion must not be within 7 days prior to obtaining screening hemoglobin

5. Coagulation function as follows: PT/INR and PTT < 1.5 x Institutional Upper Limit of Normal (ULN)
6. Renal function as follows: estimated glomerular filtration rate based on Modification of Diet in Renal Disease calculation (MDRD) > 30 mL/min/1.73 m^2
7. Hepatic function, as follows: AST and ALT < 3 x ULN, Total bilirubin < 1.5 x ULN (except subjects with Gilbert's syndrome)

Exclusion Criteria:

1. Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study(s)
2. Previously received an allogeneic stem cell transplant and the occurrence of one or more of the following:
   - received the transplant within 6 months prior to study day 1
   - received immunosuppressive therapy within the last 3 months prior to study day
   - having signs or symptoms of acute or chronic graft-versus-host disease
3. Autologous stem cell transplant < 90 days prior to study day 1
4. Multiple myeloma with IgM subtype
5. POEM syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
6. Plasma cell leukemia (> 2.0 X109/L circulating plasma cells by standard differential)
7. Waldenstrom's macroglobulinemia, Amyloidosis
8. Requirement for plasmapheresis during the screening period
9. Dexamethasone at cumulative doses of greater than 160 mg or equivalent within 21 days prior to study day 1 is not allowed. Use of topical or inhaled steroids is Acceptable
10. History of other malignancy
11. Current use of therapeutic doses of anticoagulation unless agreed upon by the investigator and the Amgen Medical Monitor. Please note: thromboprophylaxis is recommended with pomalidomide treatment
12. History of clinically significant GI hemorrhage (Grade ≥ 2) in the 6 months prior to study day 1, unless agreed upon by the investigator and the Amgen Medical monitor
13. Known positive results for Human Immunodeficiency Virus (HIV)
14. Prior systemic radiation therapy must have been completed at least 28 days before study day 1.
15. Prior focal radiotherapy completed at least 14 days before study day 1
16. Prior use of pomalidomide if subjects required pomalidomide dose reduction or pomalidomide discontinuation due to toxicity

Contact: Dr. Donna Reece/Cindy Rajah – **Open for Enrollment**

PHASE 1 / 2 TRIAL OF IDASANUTLIN IN COMBINATION WITH IXAZOMIB AND DEXAMETHASONE IN PATIENTS WITH 17P DELETED, RELAPSED MULTIPLE MYELOMA (MC1582/MMRC-061)

Protocol Number: MC1582/MMRC-061

Inclusion Criteria:

1. Diagnosis of MM with deletion 17p (del17p) or monosomy 17 by FISH who have received at least one line of therapy.
2. The following laboratory values obtained ≤14 days prior to registration.
   a. Calculated creatinine clearance ≥30 mL/min
   b. AST (SGOT) and ALT (SGPT) ≤3.0 x upper limit of normal (ULN)
   c. Total bilirubin ≤1.5 × the upper limit of the normal range (ULN)
   d. Absolute neutrophil count (ANC) ≥1500/mm3
   e. Platelet count ≥75,000/mm3
   f. Hemoglobin ≥8.0 g/dL

   NOTE: White blood count and platelet count criteria must be met without any transfusion or growth factor support.
3. Patients with measurable disease defined as at least one of the following:
   i. Serum monoclonal protein ≥1.0 g/dL by protein electrophoresis
   b. >200 mg of monoclonal protein in the urine on 24-hour electrophoresis
   c. Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
4. ECOG performance status 0, 1 or 2

Exclusion Criteria:

1. Other malignancy requiring active therapy.
   EXCEPTIONS: Non-melanoma skin cancer, DCIS or carcinoma-in-situ of the cervix.
   NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer
2. Other concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational.
   NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.
3. Patient has >Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.
4. All CYP2C8 inhibitors, inducers, and substrates should be discontinued ≥7 days prior to registration. Systemic treatment with CYP2C8 inhibitors (anastrozole, montelukast, quercetin, trimethoprim, gemfibrozil, rosiglitazone, pioglitazone), inducers (carbamazepine, phenytoin, rifabutin, rifampin), or substrates (amiodarone, repaglinide, rosiglitazone, sorafenib, torsemide) should be discontinued ≥7 days prior to registration.
5. Systemic treatment with strong inhibitors of CYP3A4 (clarithromycin, telithromycin, itraconazole, Voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A4 inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, Gingko biloba, St. John's wort) are not allowed ≤14 days before registration.
6. Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within the past 6 months. Note: Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
7. QTc >470 milliseconds (msec) on a 12-lead ECG obtained during the Screening period.
8. Known human immunodeficiency virus (HIV) positive.
9. Known hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection
10. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or idasanutlin including difficulty swallowing
11. Diarrhea >Grade 1, based on the NCI CTCAE grading, or currently taking antidiarrheals
12. Need for ongoing therapeutic anticoagulation.
13. Patients that have previously been treated with ixazomib, or who participated in a blinded study with ixazomib (whether treated with ixazomib or not).

Contact: Dr. Suzanne Trudel/Rebecca Noronha- **Enrollment on hold by Sponsor**

A PHASE II OPEN LABEL, MULTICENTER, TRIAL OF JNJ-42756493 IN COMBINATION WITH DEXAMETHASONE FOR THE TREATMENT OF FGFR3 WILD-TYPE OR MUTATION POSITIVE RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: PM-MM003

Inclusion Criteria:

1. A diagnosis of MM and documentation of at least 1 prior line of therapy including proteasome and immunomodulatory agents (in separate regimens or in combination).
2. Documented lab results confirming FGFR3 expression and mutational status determined by a clinical grade, next generation sequencing platform (e.g. Michigan Center for Translational Pathology, Foundation Medicine, Inc.) approved by the Sponsor-Investigator, the results of which must be obtained prior to registration.
3. Patients with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):
   a. Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
   b. Urine M-protein ≥ 200 mg/24 h
   c. Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
4. The following laboratory results must be met within 7 days of first study drug administration:
   a. Absolute neutrophil count (ANC) ≥ 1,000 cells/dL (1.0 x 109/L). Growth factors cannot be given within 7 days of study drug administration.
   b. Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN).
   c. Creatinine clearance ≥ 40 mL/min either directly measured via 24-hour urine collection or calculated using Cockroft-Gault.
   d. Platelet count ≥ 50,000 cells/dL (50 x 109/L). Platelet transfusions to help patients meet eligibility criteria are not allowed within 7 days before study enrollment.
   e. Hemoglobin ≥ 8.0 g/dL.
   f. Total bilirubin ≤ 1.5 x ULN, unless known to have Gilbert's disease.
   g. Albumin ≥ 2.0 g/dL (20 g/L).

h. Electrolytes: Magnesium within 0.85 to 1.25 x institutional ULN; Sodium≥130 mEq/L; and potassium within institutional normal limits (correction with supplementation and re-testing is permitted).

Exclusion Criteria:

1. Patients in whom FGFR3 expression or mutational status cannot be determined.
2. Chemotherapy, limited palliative radiotherapy or other anti-myeloma therapy within 14 days prior to the first dose of study drug. In addition, any treatment-related toxicity should have recovered < Grade 1 unless deemed to be irreversible (an example of an irreversible toxicity would include steroid induced cataracts or peripheral neuropathy).
3. Patients who are receiving any other investigational agent.
4. Patients with known CNS involvement, plasma cell leukemia or amyloidosis.
5. Use of an investigational drug within 21 days or five-half-lives, whichever is shorter but not less than 14 days, preceding the first dose of study drug.
6. History of allogeneic stem cell transplant.
7. Autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug.

Contact: Dr. Suzanne Trudel/Cindy Rajah-**Open for enrollment**

A PHASE 3 RANDOMIZED, CONTROLLED, OPEN-LABEL STUDY OF SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE (SVD) VERSUS BORTEZOMIB AND DEXAMETHASONE (VD) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Protocol number: KCP-330-023 (BOSTON)

Key Inclusion Criteria

1. Documented evidence of progressive MM (based on the Investigator's determination according to the modified IMWG response criteria) on or after their most recent regimen.
2. Prior treatment with bortezomib or other PI is allowed. Must have had at least a 6-month PI-treatment-free interval prior to C1D1 of study treatment.
3. Resolution of any clinically significant non-hematological toxicities (if any) from previous treatments to ≤ Grade 1 by C1D1.
4. Adequate hepatic function within 28 days prior to C1D1:
    a. Total bilirubin < 1.5 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 × ULN), and
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) normal to < 2 × ULN.
5. Adequate renal function within 28 days prior to C1D1 (estimated creatinine clearance [CrCl] of ≥ 20 mL/min
6. Adequate hematopoietic function within 7 days prior to C1D1: total white blood cell (WBC) count ≥ 1500/mm3, absolute neutrophil count ≥ 1000/mm3, hemoglobin ≥ 8.5 g/dL and platelet count ≥ 75,000/mm3 (patients for whom < 50% of bone marrow nucleated cells are plasma cells) or ≥ 50,000/mm3 (patients for whom ≥ 50% of bone marrow nucleated cells are plasma cells).
    a. Patients receiving hematopoietic growth factor support must have a 2-week interval between growth factor support and the Screening assessments, but they may receive growth factor support during the study.
    b. Patients must have at least a 2-week interval from the last red blood cell (RBC) transfusion and 1-week interval prior to the Screening

Key Exclusion Criteria:

1. Has received Selinexor or another XPO1 inhibitor previously.
2. Prior malignancy that required treatment, or has shown evidence of recurrence
3. Has any concurrent medical condition or disease (e.g., uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, active, unstable cardiovascular function).
4. Active plasma cell leukemia, systemic light chain amyloidosis, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, MM involving the central nervous system or Spinal cord compression.
5. Greater than Grade 2 neuropathy or ≥ Grade 2 neuropathy with pain at baseline, regardless of whether or not the patient is currently receiving medication.
6. Intolerance, hypersensitivity, or contraindication to glucocorticoids.
7. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to C1D1.
8. Prior autologous stem cell transplantation < 1 month or allogeneic stem cell transplantation < 4 months prior to C1D1.
9. Active graft versus host disease (after allogeneic stem cell transplantation) at C1D1.

10. BSA < 1.4 m2 at baseline.
11. Life expectancy of < 4 months.

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

AN OPEN LABEL CONTINUATION STUDY OF THE ORAL AKT INHIBITOR GSK2110183 IN SUBJECTS WITH HEMATOLOGIC OR SOLID TUMOR MALIGNANCY.

PROTOCOL Number: PKB115131 (Rollover)

Inclusion Criteria:

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. **Is currently participating in a GSK2110183 study (monotherapy or in combination with an approved anti-cancer agent) sponsored by GSK or by another research organization working on behalf of GSK.**
2. Currently benefitting from continued treatment and have an acceptable safety profile with GSK2110183 as determined by the investigator following previous treatment with GSK2110183 either as monotherapy or as part of a combination treatment regimen.
3. Continued ability to swallow and retain orally administered study treatment(s) and does not have any clinically significant GI abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
4. Has adequate organ function:
    - Absolute neutrophil count (ANC) ≥1.0 x 109/L
    - Hemoglobin ≥8.0 g/dL
    - Platelets ≥50 x 109/L
    - PT/INR and PTT ≤1.5x ULN
    - Total bilirubin ≤1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
    - AST and ALT ≤3xULN. If liver involvement is present and ALT and AST levels are>3xUNL and<5xULN, enrollment into PKB115131 can occur as long as there is no concurrent bilirubin or INR elevation
    - Serum creatinine OR Calculated creatinine clearance ≤ ULN≥30 mL/min
    - Ejection Fraction (LVEF) ≥ 50% by TTE or MUGA

Exclusion criteria:

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Permanent discontinuation of GSK2110183 in the parent study due to toxicity or disease progression.
2. Concomitant use of any type of anti-cancer treatment other than studied in the parent protocol.
3. Local access to commercially available GSK2110183.
4. Current use of a prohibitive medication(s) as listed in Section 7.2 of the protocol
5. Current use of anticoagulants is only allowed if PTT/INR values fulfill entry criteria.
6. Any unresolved toxicity > Grade 2, except for alopecia, (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.0) from parent study treatment at the time of transition to this study.
7. History of HIV infection.
8. Peripheral neuropathy Gr>1
9. History of hepatitis B or C infection (subjects with evidence of cleared hepatitis B are permitted).
10. Evidence of severe or uncontrolled systemic diseases (e.g., unstable, or uncompensated respiratory, hepatic, renal, metabolic or cardiac disease).
11. QTcF interval > 500 msecs at the time of transition to this study.
12. Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
13. Evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association [NYHA, 1994] functional classification system at the time of transition to this study.
14. Symptomatic or untreated leptomeningeal, CNS or brain metastases or spinal cord compression at the time of transition to this study.

NOTE: Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs (EIAEDs). Continued stability of brain metastases must be confirmed with imaging.

Contact: Dr. Christine Chen/Diana Arones– **Open for enrollment**

AMYLOIDOSIS TRIALS:

Inclusion Criteria:

1. Male or female patients 18 years or older.
2. Biopsy-proven diagnosis of AL amyloidosis according to the following standard criteria:
    a. Histochemical diagnosis of amyloidosis, as based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence
    b. If clinical and laboratory parameters insufficient to establish AL amyloidosis or in cases of doubt, amyloid typing may be necessary
3. Measurable disease as defined by serum differential free light chain concentration (dFLC, difference between amyloid forming [involved] and nonamyloid forming [uninvolved] free light chain [FLC]) ≥ 50 mg/L).
4. Objective, measurable major (cardiac or renal) organ amyloid involvement as defined as follows (amyloid involvement of at least 1 required):
    a. Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram greater than 12 mm in the absence of a history of hypertension or valvular heart disease, or in the presence of unexplained low voltage (< 0.5 mV) on the electrocardiogram
    b. Renal involvement is defined as proteinuria (predominantly albumin) > 0.5 g/day in a 24- hour urine collection

    Note: Amyloid involvement of other organ systems is allowed, but not required.
5. Must be relapsed or refractory after 1 or 2 prior therapies.
    For this protocol, relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy.
    a. Patient may not be refractory to proteasome inhibitor therapy
    b. Given that the physician may select from an offered list of regimens to treat a specific patient, the patient may be refractory to an agent/s listed within the list of offered treatment choices
    c. Must have recovered (ie, ≤ Grade 1 toxicity or patient's baseline status) from the reversible effects of prior therapy
    d. If a patient has received a transplant as his/her first-line therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant
6. Patient must meet criteria for 1 of the following AL Amyloidosis Risk Stages (as defined by NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds):
    a. Stage 1: both NT-proBNP and troponin T under threshold
    b. Stage 2: either NT-proBNP or troponin T [but not both] over threshold;
    c. Stage 3: both NT-proBNP and troponin T over threshold (but NT-proBNP < 8000 pg/mL)
7. ECOG Performance Status ≤ 2
8. Clinical laboratory values:
    a. Absolute neutrophil count ≥ 1000/μL
    b. Platelet count ≥ 75,000/μL
    c. Total bilirubin ≤ 1.5 X ULN
    d. Alkaline phosphatase ≤ 5 X ULN,
    e. ALT or AST ≤3 X ULN
    f. Calculated creatinine clearance ≥ 30 mL/min
9. Female patients who:
    a. If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study treatment, AND
    b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
    c. Agree to completely abstain from heterosexual intercourse

    Male patients, even if surgically sterilized (ie, status post vasectomy), who:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, AND
    b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
    c. Agree to completely abstain from heterosexual intercourse

10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion Criteria:

1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis.
2. Female patients who are lactating, breastfeeding, or pregnant.
3. Medically documented cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure (Section 15.6), myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically important autonomic disease.
4. Clinically overt multiple myeloma, including monoclonal BM plasma cells ≥10% to ≥ 30%, and at least 1 of the following:
    a. Bone lesions
    b. Hypercalcemia, defined as a calcium of > 11 g/dL
5. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements or GI procedure that could interfere with the oral absorption or tolerance of treatment.
6. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational or which would be considered as a treatment of AL amyloidosis. However, patients may be on chronic steroids (maximum dose 20 mg/day prednisone or equivalent [Section 15.7]) if they are being given for disorders other than amyloidosis (eg, adrenal insufficiency, rheumatoid arthritis, etc.).
7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
8. Ongoing or active infection, known HIV positive, known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection.
9. Psychiatric illness/social situations that would limit compliance with study requirements.
10. Known allergy to boron, MLN9708, any of the study treatments, their analogues, or excipients.
11. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, Voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.

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

A RANDOMIZED PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DARATUMUMAB IN COMBINATION WITH CYCLOPHOSPHAMIDE, BORTEZOMIB AND DEXAMETHASONE (CYBORD) COMPARED WITH CYBORD ALONE IN NEWLY DIAGNOSED SYSTEMIC AL AMYLOIDOSIS

Protocol Number: C1602154767414AMY3001

Inclusion Criteria:

1. 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) or older.
2. Histopathological diagnosis of amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent material in Congo red-stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance

    Considerations for specific populations where other types of amyloidosis may be encountered:
    - For male subjects 70 years of age or older who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry typing of AL amyloid in a tissue biopsy is recommended to rule out other types of amyloidosis such as age-related amyloidosis or hereditary amyloidosis (ATTR mutation)
3. Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following:
    - serum M-protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation (IFE) performed at a central laboratory),
    - serum free light chain ≥5.0 mg/dL with an abnormal kappa: lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥5 mg/ dL.

    Note: Measurable disease by urine Bence-Jones proteinuria is not sufficient for study
4. One or more organs impacted by AL amyloidosis according to consensus guidelines (NCCN guidelines version 1.2016).
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2
6. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:
    a. Absolute neutrophil count ≥1.0 × 109/L;

b. Hemoglobin level ≥8.0 g/dL (≥5 mmol/L); red blood cell transfusion allowed until 7 days before randomization
c. Platelet count ≥50 × 109/L; Platelet transfusions are acceptable without restriction during the Screening period
d. Alanine aminotransferase level (ALT) ≤2.5 times the ULN
e. Aspartate aminotransferase (AST) ≤2.5 times the ULN
f. Total bilirubin level ≤1.5 × ULN except for subjects with Gilbert syndrome, in which case direct bilirubin ≤2 × ULN
g. Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m2. Please note the eGFR is measured by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

7. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse (if this is the preferred and usual lifestyle of the subject) or to use 2 methods of reliable birth control simultaneously.
8. During the study, and for 1 year after stopping cyclophosphamide or 3 months after receiving the last dose of daratumumab, whichever is longer, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.
9. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control; eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during and up to 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. All men must also not donate sperm during the study and for 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer.
10. A woman of childbearing potential must have a negative serum or urine pregnancy test (serum preferred) result within 14 days prior to randomization.
11. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

Exclusion Criteria:

1. Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38, with the exception of 160 mg dexamethasone (or equivalent corticosteroid) maximum exposure prior to randomization
2. Previous or current diagnosis of symptomatic multiple myeloma, including the presence of lytic bone disease, plasmacytomas, ≥60% plasma cells in the bone marrow, or hypercalcemia
3. Evidence of significant cardiovascular conditions as specified below:
   a. NT-ProBNP >8500 ng/L
   b. New York Heart Association (NYHA) classification IIIB or IV heart failure
   c. Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy
   d. Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass grafting within 6 months
   e. For subjects with congestive heart failure, cardiovascular-related hospitalizations within 4 weeks prior to randomization
   f. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but not placed (Subjects who do have a pacemaker/ICD are allowed on study)
   g. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >500 msec. Subjects who have a pacemaker may be included regardless of calculated QTc interval.
   h. Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion
4. Planned stem cell transplant during the first 6 cycles of protocol therapy are excluded. Stem cell collection during the first 6 cycles of protocol therapy is permitted
5. History of malignancy (other than AL amyloidosis) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
6. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
7. Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).
8. Know to be seropositive for human immunodeficiency virus (HIV).
9. Any of the following:

a. Known to be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

b. Known to be seropositive for hepatitis C (except in the setting of a sustained virology response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

10. Grade 2 sensory or Grade 1 painful peripheral neuropathy.
11. Known hypersensitivity or contraindication to any of the study drugs including bortezomib, boron, mannitol, or cyclophosphamide or any of its metabolites.
12. Concurrent medical condition or disease (eg, active systemic infection) 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.
13. Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.
14. Known allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to IB), or known sensitivity to mammalian-derived products.
15. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
16. Woman who is pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 year after discontinuation of cyclophosphamide or 3 months following discontinuation of daratumumab, whichever is longer
17. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1 Day 1.
18. Major surgery within 2 weeks before Cycle 1 Day 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study treatment administration. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.
19. Subjects who are taking CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of study treatment.

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

An Open-Label, Rollover Protocol for Patients Previously Enrolled in Millennium-Sponsored Ixazomib Studies

Protocol Number: Millenium Rollover C16027

Inclusion Criteria:

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care. **Patients should consent and enter the study within a maximum of 8 weeks of their last dose of ixazomib in the parent study or as agreed by the Millennium clinician/designee.**
2. Previously treated with ixazomib (excluding comparator or placebo patients not on current treatment with ixazomib) in a Millennium-sponsored study. Patients will be eligible to enter the rollover study when:
   a) The parent study is closed or planned to be closed; and
   b) The patient is on ixazomib monotherapy or on a drug combination with another medication, established while in his/her parent study; and
   c) In the opinion of the investigator and confirmed by the Millennium medical monitor, the patient may continue to benefit from treatment with ixazomib (eg, response to therapy or stable disease without evidence of disease progression).
3. Agree to continue to practice contraceptive methods as outlined in the parent study.

Exclusion criteria:

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. The patient meets any of the criteria for treatment discontinuation in the parent study.
2. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the eligibility period.

Contact: Dr. Vishal Kukreti/Olga Levina– **rollover ONLY from parent study C16007**