

Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre
(Version October 2018)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

CLINICAL-GRADE MOLECULAR PROFILING OF PATIENTS WITH MULTIPLE MYELOMA AND RELATED PLASMA CELL MALIGNANCIES

Protocol Number MMRF-002 (Non-Interventional)

Inclusion Criteria:

1. Patients must have a diagnosis of multiple myeloma or related plasma cells malignancies
2. Patients are undergoing standard of care bone marrow aspirates.
3. Patients (male or female) from any race or ethnicity must be 18 years of age at the time of registration
4. Procedure-specific signed informed consent form (ICF) prior to initiation of any study-related procedures.

Exclusion Criteria:

1. It is the enrolling study physician's discretion to decide if a patient is not fit enough to undergo tissue biopsy.
2. Patients who are incarcerated are not eligible to participate.
3. Women who are pregnant.
4. Patients who have had another malignancy within the last five (5) years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)

Contact: Dr. Suzanne Trudel/Harminder Paul– **Open 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/Vinita Dhir -**Open Enrollment**

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

Non-Interventional

Inclusion criteria:

1. Age \geq 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 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) $\geq 1.25 \times 10^9/L$ without growth factor support for ≥ 7 days (≥ 14 days for pegfilgrastim).
- Hemoglobin (Hgb) ≥ 8 g/dL.
- Platelets (plt) $\geq 75 \times 10^9/L$ without transfusion for ≥ 7 days ($\geq 50 \times 10^9/L$ 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 $\mu\text{mol/L}$).
- PT/INR < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN, (for subjects not receiving therapeutic anticoagulation).

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

Exclusion criteria:

1. Subject has non- or oligosecretory multiple myeloma
2. Subject has plasma cell leukemia or active leptomeningeal myelomatosis.
3. Subject has documented, systemic light chain amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes (POEMS) Syndrome.
4. Subject has immunoglobulin class M (IgM) myeloma
5. Subject has a history of allogeneic bone marrow transplantation
6. Subject is undergoing dialysis.
7. Subjects with peripheral neuropathy \geq Grade 2.
8. Subjects with gastrointestinal disease that may significantly alter the absorption of CC-92480
9. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:
 - LVEF $< 45\%$ as determined by ECHO or MUGA scan at Screening.
 - Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiographic (ECG) finding at Screening.
 - A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval >480 milliseconds (ms) using Frederica's QT correction formula; a history of or current risk factors for Torsades de Pointe (eg. heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval.
 - Congestive heart failure (New York Heart Association Class III or IV).
 - Myocardial infarction ≤ 6 months prior to starting CC-92480.
 - Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris.
10. Concurrent administration of strong CYP3A modulators. Examples of these drugs include (but are not limited to):
 - CYP3A inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
 - CYP3A inducers: carbamazepine, phenytoin, and rifampin.If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
11. Subject had prior systemic myeloma treatment (approved or investigational) ≤ 5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
12. Subject had major surgery ≤ 2 weeks prior to starting CC-92480. Note: Subjects must have recovered from any clinically significant effects of recent surgery.
13. HIV
14. Known active chronic hepatitis B or C virus (HBV/HCV) infection
15. A history of concurrent second cancer requiring ongoing systemic treatment
16. Subjects has a history of prior malignancy other than MM, unless the subject has been free of disease for ≥ 3 years except for the following noninvasive malignancies treated with curative intent:
 - Basal or squamous cell carcinoma of the skin.
 - Carcinoma in situ of the cervix or breast.

- Stage 1 bladder cancer.
 - Incidental histological findings of localized prostate cancer such as tumor stage 1a or 1b (T1a or T1b) using the Tumor/Node/Metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent.
17. Subject has a history of anaphylaxis to thalidomide, lenalidomide, pomalidomide or dexamethasone
 18. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480 or dexamethasone
 19. Subject has undergone either of the following within 14 days of initiating CC-92480:
 - Plasmapheresis.
 - Radiation therapy other than local therapy for symptomatic relief of MM associated bone lesions.
 20. Subject has received immunosuppressive medication within 14 days prior to the first dose of CC-92480. The following are exceptions to this criterion:
 - Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection).
 - Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent.
 - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
 21. Subject is unable or unwilling to undergo protocol required venous thromboembolism (VTE) prophylaxis. Thromboembolism prophylaxis consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study beginning 48 hours prior to Cycle 1, Day 1 until 48 hours after last CC-92480 administration.

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

A PHASE 2, MULTICENTER STUDY TO DETERMINE THE EFFICACY AND SAFETY OF BB2121 IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA
PROTOCOL NUMBER: BB2121-MM-001

Inclusion Criteria:

1. Documented diagnosis of multiple myeloma
2. Must have received at least 3 prior MM treatment regimens.
3. Must have undergone at least 2 consecutive cycles of treatment for each regimen, unless PD was the best response to the regimen.
4. Must have received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.
5. Must be refractory to the last treatment regimen. Refractory is defined as documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma drug regimen before study entry.
6. Subjects must have measurable disease, including at least one of the criteria below:
 - a. Serum M-protein greater or equal to 1.0 g/dL
 - b. Urine M-protein greater or equal to 200 mg/24 h
 - c. Serum free light chain (FLC) assay: involved FLC level greater or equal to 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal (Clarification by Medical Monitor: Measurable FLC would count for eligibility. However, if patient has disease that is followed by M-protein in serum for response, they need to progress by serum M protein. They cannot progress by FLC alone if the disease has always been followed by serum m protein)

Exclusion Criteria:

1. Subjects with solitary plasmacytomas **or non-secretory myeloma without** other evidence of measurable disease
2. **Inadequate bone marrow function defined by:**
 - **ANC < 1000 cells/mm³** in the absence of growth factor support (Filgrastim within 7 days or pegfilgrastim within 14 days of screening)
 - **Platelet count < 50,000 mm³** in the absence of transfusion support (platelet transfusion within 7 days of screening).
3. Inadequate renal function defined by **CrCl ≤ 45 ml/min** using Cockcroft-Gault equation.
4. International ratio (INR) or partial thromboplastin **time (PTT) > 1.5 × ULN**,
5. Echocardiogram or MUGA with **LVEF < 45%**.
6. Inadequate pulmonary function (oxygen saturation (SaO₂) < 92 % on room air).
7. **Ongoing treatment with chronic immunosuppressants** (e.g., cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled or intranasal corticosteroids are

allowed.

8. Following transmissible disease tests will be done as part of the screening for this study: HIV 1 and 2 antibody/p24 antigen combination, Hepatitis B Surface Antibody (HBsAb), Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (HBcAb), Hepatitis C antibody (HCV antibody), syphilis (by CMIA), HTLV 1 & 2 antibody, HBV DNA and HCV RNA testing. West Nile Virus; CMV, EBV (Dr. Reece's agreement to Bio-Safety Committee)
9. Patients with positive tests for following diseases will be excluded from this study (as per protocol): HIV; hepatitis B virus (HBV); hepatitis C virus.
10. Patient will be verbally screened for the history of travelling in the Zika Virus affected area. If an assay for antibody titer is positive for Zika virus. Patient will be excluded from the study (Dr. Reece's agreement to Bio-Safety Committee)
11. Dr. Reece has agreed to follow the BMT program protocol for patient's eligibility in addition to protocol (patients with West Nile virus and Syphilis will be excluded).
12. Subject requires ongoing treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, or Factor Xa inhibitors).
13. **Washout-page 53:**
 - a. Any prior systemic therapy for MM within 7 days prior to scheduled protocol required leukapheresis.
 - b. Experimental agents within 4 weeks prior to leukapheresis unless no response or PD is documented on the experimental therapy (**Clarification:** If patient's best response to an Investigational Agent (e.g. anti-PDL1) is progressive disease, then 7 days. If not, then 28 days for this experimental agent.
 - c. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis.

Contact: Dr. Donna Reece/Rebecca Noronha- **Open for enrollment (not available for patients outside of the province)**

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

Protocol Number: G039775

Key Inclusion Criteria:

1. Patients must have R/R MM for which no established therapy for MM is appropriate and available or be intolerant to those established therapies
2. Agreement to provide bone marrow biopsy and aspirate samples as per protocol
3. Adverse events from prior anti-cancer therapy resolved to Grade ≤ 1 , with the following exceptions:
 - a. Any grade alopecia, peripheral sensory or motor neuropathy must have resolved to Grade ≤ 2
4. Measurable disease defined as at least one of the following:
 - a. Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)
 - b. Urine M-protein ≥ 200 mg/24 hr.
 - c. Serum free light chain (SFLC) assay: Involved SFLCs ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (< 0.26 or > 1.65)
5. Laboratory values:
 - a. Hepatic function: AST and ALT $\leq 3 \times$ ULN; Total bilirubin $\leq 1.5 \times$ 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 $\geq 75,000/\text{mm}^3$ without transfusion within 14 days prior to first dose of BFCR4350A, ANC $\geq 1000/\text{mm}^3$, 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/ μ L 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 thyroïd 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 $\geq 1.0 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$ (in patients with $< 50\%$ of bone marrow nucleated cells were plasma cells) or $\geq 50 \times 10^9/L$ (in patients with $\geq 50\%$ 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 $< 1.5 \times$ 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 m²
7. Hepatic function, as follows: AST and ALT $< 3 \times$ ULN, Total bilirubin $< 1.5 \times$ 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 1
 - 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 ($> 2.0 \times 10^9/L$ 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 x the upper limit of the normal range (ULN)
 - d. Absolute neutrophil count (ANC) ≥ 1500 /mm³
 - e. Platelet count $\geq 75,000$ /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:

MM Studies Short Version
May 2018

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) $\geq 1,000$ cells/dL ($1.0 \times 10^9/L$). 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 Cockcroft-Gault.
 - d. Platelet count $\geq 50,000$ cells/dL ($50 \times 10^9/L$). 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 \leq Grade 1 by C1D1.
4. Adequate hepatic function within 28 days prior to C1D1:
 - a. Total bilirubin $< 1.5 \times$ upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of $< 3 \times$ ULN), and
 - b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) normal to $< 2 \times$ 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 $\geq 1500/\text{mm}^3$, absolute neutrophil count $\geq 1000/\text{mm}^3$, hemoglobin $\geq 8.5 \text{ g/dL}$ and platelet count $\geq 75,000/\text{mm}^3$ (patients for whom $< 50\%$ of bone marrow nucleated cells are plasma cells) or $\geq 50,000/\text{mm}^3$ (patients for whom $\geq 50\%$ 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 \geq 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 $< 1.4 \text{ m}^2$ at baseline.
11. Life expectancy of < 4 months.

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

AN OPEN-LABEL, RANDOMIZED PHASE 3 STUDY OF COMBINATIONS OF NIVOLUMAB, ELOTUZUMAB, POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol number: CA209-602

Inclusion Criteria:

1. Signed Written Informed Consent
2. Target Population
 - a. Must have received 2 prior lines of therapy which must have included at least 2 consecutive cycles of each immune modulatory drug (IMiD) and a proteasome inhibitor alone or in combination
 - b. Documented refractory or relapsed and refractory (R/R) multiple myeloma
 - c. Refractory (progressed on or within 60 days of treatment) to their last treatment
 - d. Subjects must have failed treatment with a proteasome inhibitor and an IMiD in one of the following ways
 - i. “Double Refractory” = Refractory to a proteasome inhibitor and an IMiD, and to their last treatment
 - ii. “Relapsed and refractory” = patients had achieved at least a partial response to previous treatment with proteasome inhibitor or IMiD, or both, but progressed within 6 months, and were refractory to their last treatment
 - e. Measurable disease at screening, based on central lab results within 28 days of randomization.
 - f. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
3. Age and Reproductive Status
 - a. Males and Females at least 18 years or legal age of consent per local regulations
 - b. Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests.
 - i. Men who are sexually active with WOCBP must agree for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks (except the Pd arm -where only 4 weeks is required) post-treatment completion
 - c. Women must not be breastfeeding
 - d. Male patients must not donate sperm, for up to 180 days (4 weeks only for Pd arm) post treatment completion
 - e. Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section
 - f. All subjects must not donate blood for 90 days post treatment completion

- g. All subjects must be willing and able to comply with Pomalyst® REMS program, where applicable
- h. All subjects must agree not to share study medication

Exclusion Criteria

1. Target Disease Exceptions
 - a. Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
 - b. Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), amyloidosis, Waldenstrom's Macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
 - c. Subjects with active plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of plasma/CD138+ cells or an absolute plasma cell count of $2 \times 10^9/L$)
2. Medical History and Concurrent Diseases
 - a. Women who are of childbearing potential not complying to the above described contraceptive measures or are breastfeeding, and sexually active fertile men whose partners are WOCBP if they are not complying to the above described contraceptive measures
 - b. Any uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator, including:
 - c. NYHA functional classification III or IV, congestive heart failure, unstable or poorly controlled angina, uncontrolled hypertension, arrhythmia, or myocardial infarction in the past 12 months
 - d. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
 - e. Active infection
 - f. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
 - g. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of initiation of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
 - h. Unable to tolerate thromboembolic prophylaxis while on the study
 - i. Hypersensitivity reaction to prior IMiD (thalidomide or lenalidomide)
 - j. Grade ≥ 2 peripheral neuropathy (per NCI CTCAE v4.0)
 - k. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
 - l. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation
 - m. Gastrointestinal disease that may significantly alter the absorption of pomalidomide
 - n. Prior or concurrent invasive malignancy, except for the following:
 - i. Adequately treated basal cell or squamous cell skin cancer
 - ii. Adequately treated in-situ cancer
 - iii. Any cancer (other than those noted above) from which the subject has been disease free for > 3 years prior to study entry
3. Prior Therapy or Surgery
4. Prior treatment with pomalidomide, Nivolumab (or any PD-1 or PD-L1 inhibitor) or Elotuzumab
5. Use of any anti-myeloma drug therapy, within 14 days of the initiation of study drug treatment or use of any experimental drug therapy or plasmapheresis within 28 days (or 5 half-lives of the experimental drug; whichever is longer) of the initiation of study drug treatment (includes dexamethasone). Bisphosphonate use permitted if initiated prior to first dose of study medication
6. Treatment with melphalan or monoclonal antibodies within 4 weeks (or 5 half-lives of the monoclonal antibody; whichever is longer) of the first dose of study drug
7. Prior autologous stem cell transplant within 12 weeks of the first dose of study drug
8. Prior allogeneic stem cell transplant except subjects who have completed the stem cell transplant > 12 months prior to first dose of study drug, have no current or history of graft versus host disease, and are not on topical or systemic immunosuppressive therapy
9. Treatment with corticosteroids within 2 weeks of the first dose of study drug, except for the equivalent of 10 mg prednisone per day or corticosteroids with minimal to no systemic absorption (ie, topical or inhaled steroids) or for short course (4 days) of 40 mg dexamethasone or equivalent for emergency use (baseline M proteins must be drawn after this short course and prior to randomization). Adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

10. Major cardiac surgery within 8 weeks prior to the first dose of study drug; all other major surgery within 4 weeks prior to the first dose of study drug. (Kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities
11. Physical and Laboratory Test Findings
12. Screening Laboratory evaluations within the following parameters:
 - a. Absolute neutrophil count (ANC) < 1,000 cells/ μ L (1.0 x 10⁹/L) (Growth factors cannot be used within 1 week of first drug administration. No pegylated growth factors within 3 weeks of first drug administration)
 - b. Platelet count < 75,000 cells/ μ L (75 x 10⁹/L) (< 30 x 10⁹/L if \square 50% of bone marrow nucleated cells were plasma cells). Qualifying laboratory value must occur at most recent measurement prior to study entry. No transfusions are allowed within 72 hours prior to qualifying laboratory value
 - c. Hemoglobin < 8 g/dl (No transfusions are allowed within 72 hours prior to qualifying laboratory value)
 - d. Total Bilirubin > 1.5 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin up to 3.0 X ULN)
 - e. AST (SGOT) and ALT (SGPT) > 3.0x ULN
 - f. Renal function: Estimated creatinine clearance by Cockcroft-Gault formula < 30 mL/min
 - g. Corrected serum calcium \geq 11.5 mg/dl within 2 weeks of initiation of study drug (despite appropriate measures such a short course of steroids, bisphosphonates, hydration, calcitonin)
13. Allergies and Adverse Drug Reaction a) History of allergy or hypersensitivity to study drug components

Contact: Dr. Anca Prica/Susi Snitzler– **Enrollment on HOLD BY THE SPONSOR**

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

Inclusion Criteria:

1. Written informed consent
2. Age \geq 18 years.
3. Histologically confirmed diagnosis, measurable disease and evidence of disease Progression of MM, based on IMWG guidelines.
4. Patients must have measurable disease as Defined by at least one of the following:
5. Serum M-protein \geq 0.5 g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or
6. Urinary M-protein excretion at least 200 mg/24 hours; or FLC \geq 100 mg/L, provided that FLC ratio is abnormal
7. If serum protein electrophoresis is felt to be unreliable for routine M-protein
 - a. measurement (e.g., for IgA MM), then quantitative Ig levels by nephelometry
 - b. or turbidometry are acceptable.
8. No evidence of prior drug-related toxicities to \geq Grade 2.

SdP (Selinexor Dexamethasone Pomalidomide) Only:

Relapsed *and* refractory MM with:

- Documented evidence of PD after achieving at least SD for \geq 1 cycle during previous MM treatment (i.e., relapsed MM).
- Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
- Previously undergone \geq 2 cycles of lenalidomide and a proteasome inhibitor (in separate regimens or in combination).

SdB (Selinexor Dexamethasone Bortezomib) Only:

- Relapsed or refractory MM with
- Documented evidence of relapse after \geq 1 previous line of therapy.
- Not refractory to bortezomib in their most recent line of therapy.

Both SdP and SdB:

- Eastern Cooperative Oncology Group (ECOG) Performance Status of \leq 2.
- Adequate hepatic function within 21 days prior to Cycle 1 Day 1 (i.e., Day -21 to Day -1): Total bilirubin < 2x ULN, AST < 2.5x ULN and ALT < 2.5x ULN.
- Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of \geq 45 mL/min, calculated using the formula of Cockroft and Gault: (140-Age) • Mass (kg)/ (72 • creatinine mg/dL) multiply times 0.85 if the patient is female.

- Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.
- Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1: total WBC count $\geq 1,500/\text{mm}^3$, ANC $\geq 1000/\text{mm}^3$, hemoglobin (Hb) $\geq 8.0 \text{ gm/dL}$, and platelet count $\geq 75,000/\text{mm}^3$ for patients with plasma cells of $< 50\%$ of bone marrow nucleated cells; or $\geq 30,000/\text{mm}^3$ for patients with plasma cells of $\geq 50\%$ of bone marrow nucleated cells.
- Patients receiving hematopoietic growth factor support, including erythropoietin (EPO), darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophagecolony stimulating factor (GM-CSF), and platelet stimulators (e.g., eltrombopag or romiplostim or IL-11) may continue to do so.

Exclusion Criteria:

1. Smoldering MM.
2. Multiple myeloma that does not express M-protein or FLC (i.e., non-secretory MM is excluded), and quantitative Ig levels cannot be used instead.
3. Documented systemic amyloid light chain amyloidosis.
4. Active MM involving the central nervous system (CNS).
5. Plasma cell leukemia.
6. Pregnant or breastfeeding.
7. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1, and radio-immunotherapy within 6 weeks prior to Cycle 1 Day 1. However, dexamethasone, up to 40 mg per week, is allowed as monotherapy up to the start of study treatment on Cycle 1 Day 1.
8. Treatment with an investigational anti-cancer therapy within 3 weeks prior to receiving first dose of study drug on Cycle 1 Day 1.

SdB arm only:

- Prior history of neuropathy Grade > 2 , or Grade 2 neuropathy with pain at screening (within 21 days prior to Cycle 1 Day 1).
- Prior autologous stem cell transplantation < 1 month, or allogeneic stem cell transplantation < 3 months prior to Cycle 1 Day 1.
- Active graft versus host disease after allogeneic stem cell transplantation. A life expectancy of < 3 months.
- Major surgery within four weeks prior to Cycle 1 Day 1.
- Unstable cardiovascular function:
- Symptomatic ischemia, Or
- Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on anti arrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
- Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3 , or
- Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1. Ejection fraction (EF) $< 40\%$ at screening.
- Uncontrolled hypertension.
- Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
- Known active hepatitis A, B or C.
- Known HIV infection or HIV seropositivity.
- Prior malignancies except treated cervical carcinoma *in situ*. Cancer treated with curative intent > 5 years before study enrollment and without evidence of recurrence will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the medical monitor.
- Any GI dysfunction that prevents the patient from swallowing tablets, or interferes with absorption of study treatment.
- A serious psychiatric or medical condition that, in the opinion of the investigator, could interfere with treatment.

Contact: Dr. Christine Chen/Susi Snitzler – **Open for enrollment (by cohort)**

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) $\geq 1.0 \times 10^9/L$
 - Hemoglobin ≥ 8.0 g/dL
 - Platelets $\geq 50 \times 10^9/L$
 - PT/INR and PTT $\leq 1.5 \times ULN$
 - Total bilirubin $\leq 1.5 \times ULN$ (isolated bilirubin $> 1.5 \times ULN$ is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$)
 - AST and ALT $\leq 3 \times ULN$. If liver involvement is present and ALT and AST levels are $> 3 \times ULN$ and $< 5 \times ULN$, enrollment into PKB115131 can occur as long as there is no concurrent bilirubin or INR elevation
 - Serum creatinine OR Calculated creatinine clearance $\leq ULN \geq 30$ mL/min
 - Ejection Fraction (LVEF) $\geq 50\%$ 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 msec 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:

A PHASE 3, RANDOMIZED, CONTROLLED, OPEN-LABEL, MULTICENTER, SAFETY AND EFFICACY STUDY OF DEXAMETHASONE PLUS MLN9708 OR PHYSICIAN'S CHOICE OF TREATMENT ADMINISTERED TO PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC LIGHT CHAIN (AL) AMYLOIDOSIS.

Protocol Number: C16011

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, \leq 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 $\geq 1000/\mu\text{L}$
 - b. Platelet count $\geq 75,000/\mu\text{L}$
 - c. Total bilirubin $\leq 1.5 \times \text{ULN}$
 - d. Alkaline phosphatase $\leq 5 \times \text{ULN}$,
 - e. ALT or AST $\leq 3 \times \text{ULN}$
 - 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 $\geq 10\%$ to $\geq 30\%$, 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, 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 birefringent 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 $\geq 1.0 \times 10^9/L$;
 - b. Hemoglobin level ≥ 8.0 g/dL (≥ 5 mmol/L); red blood cell transfusion allowed until 7 days before randomization
 - c. Platelet count $\geq 50 \times 10^9/L$; 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 $\leq 1.5 \times$ ULN except for subjects with Gilbert syndrome, in which case direct bilirubin $\leq 2 \times$ 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, $\geq 60\%$ 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, fludrocortisone) 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. Known 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 (at the end of October 2018)**