

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

**MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:**

**PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF ORAL IXAZOMIB MAINTENANCE THERAPY AFTER INITIAL THERAPY IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA NOT TREATED WITH STEM CELL TRANSPLANTATION**

**Protocol Number: C16021**

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**Inclusion Criteria:**

Each patient must meet all the following inclusion criteria to be randomized to treatment:

1. Adult male or female patients aged 18 years or older with a confirmed diagnosis of symptomatic NDMM according to standard criteria.
2. Completed 6 to 12 months (+/- 2 weeks) of initial therapy, during which the patient was treated to best response, defined as the best response maintained for 2 cycles after the M-protein nadir is reached.
3. Documented major response (PR, VGPR, and CR) according to the IMWG uniform response criteria, version 2011, after this initial therapy.
4. Female patients who:
  - a. Are postmenopausal for at least 1 year before the screening visit, OR
  - b. Are surgically sterile, OR
  - c. 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 90 days after the last dose of study drug, or
  - d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)
5. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
  - a. Agree to practice effective barrier contraception during the entire study
6. Treatment period and through 90 days after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation,
7. symptothermal, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
8. 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of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
9. Complete documentation of the details of the initial therapy before randomization including cytogenetics and ISS is available.
10. Eastern Cooperative Oncology Group Performance Status of 0 to 2.
11. Suitable venous access for the study-required blood sampling and consent for the specific amounts that will be taken.
12. Patient is willing and able to adhere to the study visit schedule and other protocol requirements including blood sampling and bone marrow aspiration.
13. Patients must meet the following clinical laboratory criteria at study entry:
  - a. Absolute neutrophil count (ANC)  $\geq 1,000/\text{mm}^3$  without growth factor support and platelet count  $\geq 75,000/\text{mm}^3$ . Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before randomization.
  - b. Total bilirubin  $\leq 1.5 \times$  the upper limit of the normal range (ULN).
  - c. Alanine aminotransferase and aspartate amino transferase  $\leq 3 \times$  ULN.
  - d. Calculated creatinine clearance  $\geq 30 \text{ mL/min}$  (using the Cockcroft-Gault equation)

**Exclusion Criteria:**

1. Patients meeting any of the following exclusion criteria are not to be randomized to treatment
2. Multiple myeloma that has relapsed after, or was not responsive to, initial therapy
3. Prior SCT.
4. Radiotherapy within 14 days before randomization.
5. Diagnosed or treated for another malignancy within 5 years before randomization or previous diagnosis with another malignancy. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
6. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

7. Major surgery within 14 days before randomization.
8. Central nervous system involvement.
9. Infection requiring IV antibiotic therapy or other serious infection within 14 days before randomization.
10. Diagnosis of Waldenstrom's Macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
11. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, uncontrolled congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
12. 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 randomization.
13. Ongoing or active infection, known human immunodeficiency virus positive, active hepatitis B or C infection.

Contact: Dr. Vishal Kukreti/Diana Arones– **Open Enrollment**

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

***Protocol Number MMRF-002 (Non-Interventional)***

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### **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**

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### **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)**

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### **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**

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### **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  $\geq$  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**

## **PHASE 1/2 MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN OF DURVALUMAB (MEDI4736) IN COMBINATION WITH LENALIDOMIDE (LEN) WITH AND WITHOUT DEXAMETHASONE (DEX) IN SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA**

***Protocol: MEDI4736-MM-002***

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#### **Inclusion criteria:**

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

1. Subject is  $\geq$  18 years of age at the time of signing the informed consent form (ICF)
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Subject must have documented diagnosis with previously untreated (for cohort C, the induction and consolidation treatment along with the first ASCT are allowed), symptomatic MM as defined by the criteria below ([Rajkumar, 2014](#); [NCCN-MM, 2015](#)): \*MM diagnostic criteria (all 3 required);
  - Monoclonal protein present in the serum and/or urine
  - Clonal bone marrow plasma cells  $\geq$ 10% or biopsy-proven bony or extramedullary plasmacytoma\*
  - Any one or more of the following myeloma defining events:

- one or more of the following Myeloma-related organ dysfunction (at least one of the following);
    - [C] Calcium elevation (serum calcium >11.5 mg/dl [ $> 2.65$  mmol/L])
    - [R] Renal insufficiency (serum creatinine >2 mg/dl [ $177 \mu\text{mol/L}$  or more] or creatinine clearance < 40 ml/min)
    - [A] Anemia (hemoglobin <10 g/dl or >2 g/dL below the lower limit of laboratory normal)
    - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, CT, or PET-CT
      - one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage\*  $\geq 60\%$
    - Abnormal serum free light-chain ratio  $\geq 100$  (involved kappa) or < 0.01 (involved lambda)
    - >1 focal lesions detected by functional imaging including PET/CT and/or whole body magnetic resonance imaging (MRI)
- AND have measurable disease by protein electrophoresis analyses** as defined by the following:
- IgG MM: Serum monoclonal paraprotein (M-protein) level  $\geq 1.0$  g/dl or urine M protein level  $\geq 200$  mg/24 hours
  - IgA MM: Serum M-protein level  $\geq 0.5$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - IgM MM (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level  $\geq 1.0$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - IgD MM: Serum M-protein level  $\geq 0.05$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - Light chain MM: Serum M-protein level  $\geq 1.0$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
  6. Females of childbearing potential (FCBP1) must:
    - a. Have two negative pregnancy tests as verified by the investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence<sup>2</sup> from heterosexual contact.
    - b. She must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and be source documented) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study treatment, during the study therapy (including dose interruptions), and for 90 days after discontinuation of study treatment.
    - c. Refrain from egg cell and blood donation for 90 days after the final dose of Durvalumab.
  7. Male subjects must:
    - a. Practice true abstinence<sup>2</sup> (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions and for at least 90 days following study treatment discontinuation, even if he has undergone a successful vasectomy.
    - b. Refrain from sperm and blood donation for at least 90 days after the final dose of Durvalumab
  8. For Cohort A subject must be transplant non-eligible (TNE) and meet at least one of the following high risk factors:
    - Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q rearrangement; and / or t(14;16); or
    - ISS Stage III; or
    - Serum LDH > 2 x ULN;
  9. For Cohort B subject must be  $\geq 65$  years of age at the time of signing the informed consent form (ICF) and transplant non-eligible (TNE); excluding the subjects who meet the Cohort A criteria
  10. For Cohort C subject must be after first autologous stem cell transplantation (ASCT) for NDMM and meet the following criteria:
    - a. Have a post-transplant response as PR or better at the time of enrollment to this study;
    - b. Have one of the following high risk factors at the time of NDMM diagnosis;
      - Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q rearrangement; and / or t(14; 16); or
      - ISS stage III; or
      - Serum LDH > 2 x ULN;
    - c. MRD positive (defined as more than 1 malignant cell in 10<sup>5</sup> cells) measured by ClonoSIGHT™ NGS assay of a BMA sample) at the time of enrollment to this study; BMA sample collected at the time of multiple myeloma diagnosis, prior to induction therapy available for central MRD assessment by ClonoSIGHT™ NGS assay.

**Exclusion criteria:**

The presence of any of the following will exclude a subject from enrollment:

1. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of Cycle 1 Day 1], for Cohort C, the induction and consolidation treatment along with the first ASCT are allowed)
2. Any of the following laboratory abnormalities:
  - a. Absolute neutrophil count (ANC) < 1,000/ $\mu\text{L}$
  - b. Untransfused platelet count < 75,000 cells/ $\mu\text{L}$

3. Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 2.5 × upper limit of normal (ULN)
  - a. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
  - b. Corrected serum calcium >13.5 mg/dL (> 3.4 mmol/L)
4. Renal failure requiring hemodialysis or peritoneal dialysis
5. Any serious medical condition that places the subject at an unacceptable risk if he or she participates in this study. Examples of such a medical condition are, but are not limited to, subject with unstable cardiac disease as defined by: cardiac events such as myocardial infarction (MI) within the past 6 months, NYHA (New York Heart Association) heart failure class III-IV, uncontrolled atrial fibrillation or hypertension; subjects with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis and lupus, that likely need additional steroid or immunosuppressive treatments in addition to the study treatment
6. Peripheral neuropathy ≥ Grade 2
7. Primary AL (immunoglobulin light-chain) amyloidosis and myeloma complicated by amyloidosis
8. Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies:
  - a. Basal cell carcinoma of the skin
  - b. Squamous cell carcinoma of the skin
  - c. Carcinoma *in situ* of the cervix
  - d. Carcinoma *in situ* of the breast
  - e. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
9. Subjects is positive for human immunodeficiency virus (HIV); chronic or active hepatitis B or active hepatitis A, or C
10. Subject had prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibody or inhibitor, cell-based therapies, or cancer vaccines
11. Subjects has history of organ or allogeneic stem cell transplantation
12. Subjects who have had clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS multiple myeloma, or plasma cell leukemia
13. Known or suspected hypersensitivity to the excipients contained in the formulation of Durvalumab, lenalidomide, or dexamethasone
14. Major surgery (as defined by the investigator) within the 28 days prior to the first dose of study treatment
15. Received prior treatment (for any reason) with a monoclonal antibody within 5 half-lives of initiating study treatment
16. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment.

Contact: Dr. Donna Reece/Olga Levina—enrollment on **HOLD BY THE SPONSOR**

### **MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:**

**A PHASE II, OPEN LABEL, RANDOMIZED, TWO-ARM STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF TWO DOSES OF THE ANTIBODY DRUG CONJUGATE GSK2857916 IN PARTICIPANTS WITH MULTIPLE MYELOMA WHO HAD 3 OR MORE PRIOR LINES OF TREATMENT, ARE REFRACTORY TO A PROTEASOME INHIBITOR AND AN IMMUNOMODULATORY AGENT AND HAVE FAILED AN ANTI-CD38 ANTIBODY (DREAMM 2)**

**Protocol Number: 205678**

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#### **Inclusion Criteria:**

Each patient must meet all the following inclusion criteria to be randomized to treatment:

14. Histologically or cytologically confirmed diagnosis of MM as defined in IMWG, 2014 criteria, and
  - a. Has undergone stem cell transplant or is considered transplant ineligible, and
  - b. Has failed at least 3 prior lines of anti-myeloma treatments, including an antiCD38 antibody (e.g., daratumumab) alone or in combination, and is refractory to an IMiD (i.e. Lenalidomide or pomalidomide), and to a proteasome inhibitor (i.e., bortezomib, ixazomib or carfilzomib).
15. Has measurable disease with at least one of the following:
  - a. Serum M-protein ≥0.5 g/dL (≥5 g/L)
  - b. Urine M-protein ≥200 mg/24h

- c. Serum FLC assay: Involved FLC level  $\geq 10$  mg/dL ( $\geq 100$  mg/L) and an abnormal serum free light chain ratio ( $< 0.26$  or  $> 1.65$ )
16. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met: a. transplant was  $> 100$  days prior to study enrolment b. no active infection(s) c. participant meets the remainder of the eligibility criteria outlined in this protocol
  17. All prior treatment-related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03 must be  $\leq$  Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy.
  18. Patients must meet the following clinical laboratory criteria at study entry:
    - a. Absolute neutrophil count (ANC)  $\geq 1.00 \times 10^9/L$ , Hb  $\geq 8$  g/dL and platelet count  $\geq 50 \times 10^9/L$ .
    - b. Total bilirubin  $\leq 1.5 \times$  the upper limit of the normal range (ULN).
    - c. Alanine aminotransferase  $\leq 2.5 \times$  ULN.
    - d. Calculated eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> and spot urine (Albumin/creatinine ratio  $< 500$  mg/g)
    - e. LVEF (Echo)  $\geq 45\%$

### **Exclusion Criteria:**

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Systemic anti-myeloma therapy within  $< 14$  days, or plasmapheresis within 7 days prior to the first dose of study drug
2. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening.
3. Prior allogeneic stem cell transplant
4. Current corneal epithelial disease except mild punctate keratopathy
5. 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 drugs. Prior BCMA targeted therapy.
6. Evidence of active mucosal or internal bleeding
7. Any major surgery within the last four weeks
8. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety)
9. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities)
10. 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
11. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years
12. Evidence of cardiovascular risk including any of the following:
  - a. QTcF interval  $\geq 470$  msec (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
  - b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 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
  - e. Uncontrolled hypertension
13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916
14. Active infection requiring antibiotic, antiviral, or antifungal treatment.
15. Known HIV infection.
16. 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
17. 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.

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

## **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  $\geq 0.5$  g/dL by sPEP or
  - b.  $\geq 200$  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 ( $\kappa/\lambda$ ) 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  $\geq 0.50$  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  $\geq 7$  days ( $\geq 14$  days for pegfilgrastim).
- Hemoglobin (Hgb)  $\geq 8$  g/dL.
- Platelets (plt)  $\geq 75 \times 10^9/L$  without transfusion for  $\geq 7$  days ( $\geq 50 \times 10^9/L$  for subjects with  $> 50\%$  plasma cells in bone marrow).
- Corrected serum calcium  $\leq 13.5$  mg/dL ( $\leq 3.4$  mmol/L).
- 24-hr creatinine clearance (CrCl)  $\geq 45$  mL/min.
- AST/SGOT and ALT/SGPT  $\leq 3.0 \times$  upper limit of normal (ULN).
- Serum bilirubin  $\leq 1.5 \times$  ULN.
- Uric acid  $\leq 7.5$  mg/dL (446  $\mu\text{mol/L}$ ).
- PT/INR  $< 1.5 \times$  ULN and partial thromboplastin time (PTT)  $< 1.5 \times$  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  $\leq 6$  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)  $\leq$  5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
12. Subject had major surgery  $\leq$  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. Subject has a history of prior malignancy other than MM, unless the subject has been free of disease for  $\geq$ 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**

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**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/mm<sup>3</sup>** in the absence of growth factor support (Filgrastim within 7 days or pegfilgrastim within 14 days of screening)
  - **Platelet count < 50,000 mm<sup>3</sup>** 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 (SaO<sub>2</sub>) < 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***

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### **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  $\geq 75,000/\text{mm}^3$  without transfusion within 14 days prior to first dose of BFCR4350A, ANC  $\geq 1000/\text{mm}^3$ , Total hemoglobin  $\geq 8 \text{ g/dL}$
  - c. Creatinine  $\leq 2.0 \text{ mL/dL}$  and creatinine clearance (CrCl)  $\geq 30 \text{ mL/min}$  (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  $\geq 3$  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  $2000/\mu\text{L}$  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 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  $\geq 2$  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  $\leq 10$  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**

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**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  $\geq 0.5$  g/dL
  - Urine M-protein  $\geq 200$  mg/24 hours
  - In subjects without detectable serum or urine M-protein: serum Free Light Chain (sFLC)  $\geq 10$  mg/dL ( $\geq 100$  mg/L) and an abnormal sFLC ratio
3. Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$
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 m<sup>2</sup>
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
  - 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  $\geq 2$ ) 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**

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**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  $\leq 14$  days prior to registration.
  - a. Calculated creatinine clearance  $\geq 30$  mL/min
  - b. AST (SGOT) and ALT (SGPT)  $\leq 3.0$  x upper limit of normal (ULN)
  - c. Total bilirubin  $\leq 1.5$   $\times$  the upper limit of the normal range (ULN)
  - d. Absolute neutrophil count (ANC)  $\geq 1500/\text{mm}^3$
  - e. Platelet count  $\geq 75,000/\text{mm}^3$
  - f. Hemoglobin  $\geq 8.0$  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  $\geq 1.0$  g/dL by protein electrophoresis
  - b.  $>200$  mg of monoclonal protein in the urine on 24-hour electrophoresis
  - c. Serum immunoglobulin free light chain  $\geq 10$  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  $\geq 7$  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  $\geq 7$  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  $\leq 14$  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**

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**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  $\geq 0.5$  g/dl ( $\geq 5$  g/l)
  - b. Urine M-protein  $\geq 200$  mg/24 h
  - c. Serum free light chains (FLC) assay: Involved FLC level  $\geq 10$  mg/dl ( $\geq 100$  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  $\leq 2.5$  x upper limit of normal (ULN).
  - c. Creatinine clearance  $\geq 40$  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  $\geq 8.0$  g/dL.
  - f. Total bilirubin  $\leq 1.5$  x ULN, unless known to have Gilbert's disease.
  - g. Albumin  $\geq 2.0$  g/dL (20 g/L).
  - h. Electrolytes: Magnesium within 0.85 to 1.25 x institutional ULN; Sodium  $\geq 130$  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)**

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## **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  $\geq 20$  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  $\geq 8.5$  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  $\leq 2$  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  $< 1.4$  m<sup>2</sup> 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***

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### **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  $\leq 2$
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  $\geq 2$  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/ $\mu$ L ( $1.0 \times 10^9$ /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/ $\mu$ L ( $75 \times 10^9$ /L) (<  $30 \times 10^9$ /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 2, MULTICENTER, OPEN-LABEL, STUDY TO DETERMINE THE SAFETY AND EFFICACY FOR THE COMBINATION OF DURVALUMAB (DURVA) AND DARATUMUMAB (DARA) (D2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM)**

***Protocol Number: MEDI4736-MM-003***

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**Inclusion Criteria**

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

1. Subject received at least 3 prior anti-myeloma regimen including a PI and an immunomodulatory agent or is double-refractory to a PI and an immunomodulatory agent.
  - *Induction, bone marrow transplant with or without maintenance therapy is considered one regimen*
  - *Refractory is defined as disease that is nonresponsive on therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.*
  - *For subjects who received more than 1 regimen containing a PI their disease must be refractory to the most recent PI containing regimen.*
  - *For subjects who received more than 1 regimen containing an immunomodulatory agent their disease must be refractory to the most recent immunomodulatory agent containing regimen*
2. Subject has measurable disease defined as:
  - a. M-protein (serum protein electrophoresis (sPEP) or urine protein electrophoresis (uPEP): sPEP  $\geq$  0.5 g/dL or uPEP  $\geq$  200 mg/24 hours) and/or
  - b. Light chain MM without measurable disease in the serum or the urine: serum immunoglobulin free light chain  $\geq$  10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio
3. Subject achieved a response (MR or better) to at least 1 prior treatment regimen
4. Subject has evidence of PD on or within 60 days of the most recent prior treatment regimen



5. Subject received an alkylating agent alone or in combination with other myeloma treatment
6. Subject has an Eastern Cooperative Oncology Group performance-status score of 2 or less
7. Subject's toxicities resulting from previous therapy (including peripheral neuropathy) have resolved or stabilized to  $\leq$  Grade 1.

**Exclusion Criteria:**

The presence of any of the following will exclude a subject from enrollment:

1. Subject has had prior exposure to anti-CTLA-4, anti-PD-1, anti-PD-L1 mAbs, cell-based therapies (eg, CAR-T cells), or cancer vaccines
2. Subject received DARA or other anti-CD38 therapies previously
3. Subject received prior treatment with a monoclonal antibody within 5 half-lives of initiating study treatment
4. Subject used any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment
5. History of organ or allogeneic stem cell transplantation
6. Subject has any of the following laboratory abnormalities:
  - a. Absolute neutrophil count (ANC)  $< 1,000/\mu\text{L}$
  - b. Platelet count:  $< 75,000/\mu\text{L}$
  - c. Hemoglobin  $< 8 \text{ g/dL}$  ( $< 4.9 \text{ mmol/L}$ )
  - d. Creatinine Clearance (CrCl)  $< 45 \text{ mL/min}$
  - e. Corrected serum calcium  $> 13.5 \text{ mg/dL}$  ( $> 3.4 \text{ mmol/L}$ )
  - f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $> 2.5 \times$  upper limit of normal (ULN)
  - g. Serum total bilirubin  $> 1.5 \times$  upper limit of normal (ULN) or  $> 3.0 \text{ mg/dL}$  for subjects with documented Gilbert's syndrome
7. Subject has clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS MM
8. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal.
9. Subject has known moderate or severe persistent asthma within the past 2 years or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.
10. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, or amyloidosis
11. **Subject has nonsecretory MM**
12. Subject has active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener syndrome; myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc.) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
  - a. Subjects with vitiligo or alopecia.
  - b. Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
  - c. Psoriasis not requiring systemic treatment.
13. Subject has history of primary immunodeficiency
14. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B or active hepatitis A or C.
15. Clinically significant abnormal electrocardiogram (ECG) finding at screening
16. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for  $\geq 5$  years with the exception of the following noninvasive malignancies:
  - a. Squamous cell carcinoma of the skin
  - b. Carcinoma in situ of the cervix
  - c. Carcinoma in situ of the breast
  - d. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative

***For subjects who will have POM + dex added to the D2 and subjects who will be enrolled into the PD3 cohort, the following exclusions will also apply:***

17. Subject has history of anaphylaxis or hypersensitivity to thalidomide, LEN, POM, or dex
18. Subject has history of rash  $\geq$  Grade 3 during prior thalidomide, LEN, or POM therapy
19. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of POM or dex
20. **Subject is a current smoker**

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

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## **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 Cockcroft and Gault:  $(140 - \text{Age}) \cdot \text{Mass (kg)} / (72 \cdot \text{creatinine mg/dL})$  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/mm<sup>3</sup>, ANC  $\geq$  1000/mm<sup>3</sup>, hemoglobin (Hb)  $\geq$  8.0 gm/dL, and platelet count  $\geq$  75,000/mm<sup>3</sup> for patients with plasma cells of  $<$  50% of bone marrow nucleated cells; or  $\geq$  30,000/mm<sup>3</sup> 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  $\leq$  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  $\geq$  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)***

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**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  $\geq$  8.0 g/dL
  - Platelets  $\geq$   $50 \times 10^9/L$
  - PT/INR and PTT  $\leq$  1.5x ULN
  - Total bilirubin  $\leq$  1.5x ULN (isolated bilirubin  $>$  1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin  $<$  35%)
  - AST and ALT  $\leq$  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  $\leq$  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 3<sup>rd</sup> 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**

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### **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])  $\geq 50$  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  $\leq 2$
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  $\geq 30$  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, 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**