

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

**MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:**

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

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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**

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

#### **A PHASE II STUDY OF ELOTUZUMAB, POMALIDOMIDE, & DEXAMETHASONE (ELO-POM-DEX) WITH SECOND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED MULTIPLE MYELOMA**

**WUSM Protocol Number:201701084**

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#### **Key Inclusion Criteria**

1. Received prior autologous stem cell transplantation as first line therapy for multiple myeloma with subsequent disease relapse/progression.
2. Refractory to or intolerant of lenalidomide maintenance following first autologous stem cell transplantation. Refractory is defined as disease relapse/progression on therapy or within 60 days of completing therapy. Intolerance is defined as the inability to administer  $\geq 10$  mg per day due to toxicity.
3. All US study participants must be registered into the mandatory POMALYST REMS® program and be willing and able to comply with the requirements of the POMALYST REMS® program. **For Canadian sites, patients will be followed according to the Pomalidomide pregnancy prevention program**
4. Candidate for second autologous stem cell transplantation per local institution's guidelines with at least  $2 \times 10^6/\text{kg}$  CD34+ autologous stem cells available for transplantation.
5. At least 18 **and no more than 75 years of age at enrollment.**
6. Normal bone marrow and organ function as defined as ALL of the following:
  - Absolute neutrophil count  $\geq 1000/\text{mm}^3$
  - Platelets  $\geq 75,000/\text{mm}^3$  (transfusions not permitted within 7 days of screening)
  - Total bilirubin  $\leq 2.0 \times \text{IULN}$
  - AST(SGOT)/ALT(SGPT)  $\leq 3.0 \times \text{IULN}$
  - Creatinine clearance  $\geq 15 \text{ mL/min}$

#### **Key Exclusion Criteria:**

- 1.** Prior exposure to elotuzumab or pomalidomide.
- 2.** Received systemic multiple myeloma therapy post-relapse/progression. Patients that received 1-2 cycles of salvage therapy, local radiation, and/or corticosteroids post relapse/ progression are eligible if there was no further disease progression following administration.
- 3.** More than one prior transplant prior to study entry with the exception of tandem transplantation. Tandem transplantation is defined as two autologous stem cell transplants that occur within 9 months of one another, and the patient did not have disease progression in the period between the two transplants.
- 4.** History of plasma cell leukemia or MM CNS involvement.
- 5.** Presence of peripheral neuropathy  $\geq$  grade 3 based on NCI CTCAE v 4.0
- 6.** Receiving renal replacement therapy, hemodialysis, or peritoneal dialysis.
- 7.** Diagnosed with another concurrent malignancy requiring treatment.
- 8.** Known HIV or active hepatitis A, B, or C. Antibody testing not required for screening.
- 9.** Known hypersensitivity to pomalidomide, dexamethasone, or any excipients in elotuzumab formulation, or recombinant protein.
- 10.** Receiving any other investigational agents within 14 days prior to enrollment.

- 11.** Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

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

**A PHASE I/II SINGLE ARM OPEN-LABEL STUDY TO EXPLORE SAFETY AND CLINICAL ACTIVITY OF GSK2857916 ADMINISTERED IN COMBINATION WITH PEMBROLIZUMAB IN SUBJECTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (DREAMM 4)**

**Protocol Number: 205207**

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**Inclusion Criteria:**

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
  - a. Have undergone stem cell transplant, or have been considered transplant ineligible;
  - b. Previously undergone at least 3 prior lines of treatment and must have received Pom/lenalidomide and a proteasome inhibitor (eg., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody (in separate regimens or in combination);
2. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
  - a. Transplant was > 100 days prior to study enrolment;
  - b. No active infection
3. Subjects with measurable disease defined as at least one of the following:
  - Serum M-protein  $\geq 5$  g/L;
  - Urine M-protein  $\geq 200$  mg/24 h;
  - Serum free light chains (FLC) assay: Involved FLC level  $\geq 100$  mg/l and an abnormal serum free light chain ratio ( $< 0.26$  or  $> 1.65$ ).
4. Subject has adequate organ system functions defined as:
  - Absolute neutrophil count (ANC)  $> 1.0 \times 10^9/L$  (Without Growth factor support for the past 14 days, excluding erythropoietin)
  - eGFR (MDRD)  $\geq 40$  mL/min
  - Platelet count  $> 75 \times 10^9/L$ .
  - Hemoglobin  $\geq 8.0$  g/dL;
  - Total bilirubin  $\leq 1.5 \times ULN$ . Isolated bilirubin  $> 1.5 \times ULN$  is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ ;
  - Albumin/creatinine ratios (spot urine)  $< 500$ mg/g (56 mg/mmol);
  - ALT and AST  $\leq 2.5 \times$  upper limit of normal (ULN);
  - LVEF (Echo)  $> 50\%$
  - QTcF interval  $< 470$  msec
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, 2010) [NCI, 2010] must be  $\leq$  Grade 1 at the time of enrollment except for alopecia, and Grade 2 neuropathy.

**Exclusion criteria:**

- 1 Systemic anti-myeloma therapy or an investigational drug  $< 14$  days or five half-lives, whichever is shorter, preceding the first dose of study drug.
2. Has had an allogenic tissue/solid organ transplant
3. Pregnant or lactating females.
4. Subjects with previous or concurrent malignancies are allowed only if the second tumor is not contributing to the subject's illness.
5. Plasmapheresis within 7 days prior to the first dose of study drug
6. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs
7. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune related adverse event (irAE)
8. Current corneal epithelial disease except mild punctate keratopathy

9. Any major surgery within the last four weeks prior to the first dose of study therapy
10. Presence of active renal condition. Subjects with isolated proteinuria resulting from MM are eligible.
11. Has received prior radiotherapy within 2 weeks of start of study therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation ( $\leq 2$  weeks of radiotherapy) to non-central nervous system (CNS) disease.
12. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
13. Current active liver or biliary disease
14. Evidence of any cardiovascular risk defined in the protocol
  - o QTcF interval  $\geq 470$  msec
  - o Evidence of current clinically significant uncontrolled arrhythmias;
  - o History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
  - o Class III or IV heart failure as defined by the New York Heart Association functional classification system
  - o Uncontrolled hypertension
  - o Presence of cardiac pacemaker
  - o Abnormal cardiac valve morphology ( $\geq$  Grade 2)
15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or Pembrolizumab, or any of the components of the study treatment.
16. Known active infection requiring antibiotic, antiviral, or antifungal treatment
17. Active autoimmune disease that has required systemic treatment in past 2 years
18. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy

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

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

***Protocol Number: MCRN 007***

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**Inclusion Criteria:**

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
  - a. Have undergone stem cell transplant, or have been considered transplant ineligible;
  - b. Previously undergone at least 2 prior lines of treatment and must have received lenalidomide and a proteasome inhibitor (in separate regimens or in combination);
  - c. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for  $\geq 1$  cycle during a previous MM treatment (i.e., relapsed MM); and/or
  - d. Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
2. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
  - a. Transplant was  $> 100$  days prior to study enrolment;
  - b. No active infection
3. Subjects with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):
  - Serum M-protein  $\geq 5$  g/L;
  - Urine M-protein  $\geq 200$  mg/24 h;
  - Serum free light chains (FLC) assay: Involved FLC level  $\geq 100$  mg/l and an abnormal serum free light chain ratio ( $< 0.26$  or  $> 1.65$ ).
4. The following laboratory results must be met within 10 days of first study drug administration:
  - Absolute neutrophil count (ANC)  $> 1.0 \times 10^9/L$ . Growth factors cannot be given within 10 days of study drug administration;
  - Serum ALT  $\leq 2.5 \times$  upper limit of normal (ULN);
  - eGFR (MDRD)  $\geq 40$  mL/min a (Appendix 2);
  - Platelet count  $> 75 \times 10^9/L$ . Platelet transfusions to help subjects meet eligibility criteria are not allowed within 10 days before study enrollment;
  - Hemoglobin  $\geq 8.0$  g/dL;

- Total bilirubin  $\leq 1.5 \times$  ULN, unless known to have Gilbert's disease. If Gilbert's, isolated bilirubin  $> 1.5$  and  $< 3 \times$  ULN is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ ;
- Albumin/creatinine ratios (spot urine)  $< 500$  mg/g (56 mg/mmol);
- Albumin  $\geq 2.0$  g/dL (20 g/L).

**Exclusion criteria:**

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

Contact: Dr. Suzanne Trudel/Daniel Socko– **Open Enrollment**

**A Phase 1 First in Human Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 176 in Subjects with Relapsed or Refractory Multiple Myeloma and Subjects with Relapsed or Refractory Acute Myeloid Leukemia\***  
**Protocol Number: AMG 176 20150161**

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**Inclusion Criteria:**

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

1. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Subjects must have a documented diagnosis of MM and measurable disease at enrollment. Measurable disease per the IMWG response criteria (assessed within 28 days prior to enrollment), as indicated by one or more of the following:
  - a. Serum M-protein  $\geq 0.5$  g/dL
  - b. Urine M-protein  $\geq 200$  mg/24 hours
  - c. Subjects who do not meet 1 of the 2 prior criteria: serum Free Light Chain (sFLC)  $\geq 10$  mg/dL ( $\geq 100$  mg/L) and an abnormal sFLC ratio ( $< 0.26$  or  $> 1.65$ )
2. All subjects must have Pathologically documented, definitively diagnosed, multiple myeloma relapsed or refractory disease after at least 2 lines of therapy including a proteasome inhibitor and an immunomodulatory agent. The investigator must be of the opinion that no other treatment option will result in a durable response.
3. Subjects must have the following hematological values without transfusion or growth factor support
  - a. Absolute neutrophil count  $\geq 1.0 \times 10^9/L$
  - b. Platelet count  $\geq 50 \times 10^9/L$  (in patients where  $< 50\%$  of bone marrow nucleated cells were plasma cells) or  $\geq 30 \times 10^9/L$  (in patients where  $\geq 50\%$  of bone marrow nucleated cells were plasma cells)
  - c. Subjects should not have received platelet transfusions for at least 1 week prior to screening
  - d. Hemoglobin  $> 8$  g/dL
  - e. Subjects may receive RBC transfusions or receive supportive care with erythropoietin or darbepoetin
4. Subjects must have the following lab values
  - Hepatic function, as follows; TBA  $< 5 \times$  ULN,
  - AST and ALT  $< 3 \times$  ULN,
  - Total bilirubin  $< 1.5 \times$  ULN (except subjects with Gilbert's syndrome)
  - Left ventricular ejection fraction (LVEF)  $> 50\%$  2-D (ECHO) is the preferred method of evaluation.
  - Calculated or measured creatinine clearance (CrCl) of  $\geq 30$  mL/minute

#### **Exclusion criteria:**

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

19. Prior systemic radiation therapy must have been completed at least 28 days before study drug administration. Prior focal radiotherapy completed at 14 days before study drug administration.
20. Major surgery within 28 days of study Day 1
21. Men and women of reproductive potential who are unwilling to practice an acceptable method of effective birth control
22. Use of any medications (except anti-tumor medications), including herbal medicines (eg, St. John's wort), vitamins, or supplements consumed by the subject within the 30 days prior to receiving the dose of study drug
23. Use of known strong inhibitors of cytochrome P450 (CYP) 3A4/P-gp within the 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days
24. Use of known CYP1A2, CYP2D6, CYP2C9 sensitive substrates with a narrow therapeutic window within 3 half-lives of the drug or its major active metabolite, whichever is longer, following the last dose of the drug to receiving the first dose of AMG 176
25. Use of known cytochrome P450 (CYP) 3A4 sensitive substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer
26. Use of known organic anion polypeptide transporters (OATP) OATP1B1 and/or OATP1B3 or Breast Cancer Resistance Protein (BCRP) substrates with a narrow therapeutic window within 5 half-lives of the drug or its major active metabolite, whichever is longer.

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

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

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

***Protocol Number: CelMod CC-92480-MM-001***

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**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:**

27. Subject has non- or oligosecretory multiple myeloma
28. Subject has plasma cell leukemia or active leptomeningeal myelomatosis.
29. Subject has documented, systemic light chain amyloidosis or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes (POEMS) Syndrome.
30. Subject has immunoglobulin class M (IgM) myeloma
31. Subject has a history of allogeneic bone marrow transplantation
32. Subject is undergoing dialysis.
33. Subjects with peripheral neuropathy  $\geq$  Grade 2.
34. Subjects with gastrointestinal disease that may significantly alter the absorption of CC-92480
35. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:
  - LVEF < 45% as determined by ECHO or MUGA scan at Screening.
  - Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiographic (ECG) finding at Screening.
  - A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval >480 milliseconds (ms) using Frederica's QT correction formula; a history of or current risk factors for Torsades de Pointe (eg. heart failure, hypokalemia, or a family history of Long QT Syndrome); and concurrent administration of medications that prolong the QT/QTc interval.
  - Congestive heart failure (New York Heart Association Class III or IV).
  - Myocardial infarction  $\leq$  6 months prior to starting CC-92480.
  - Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris.
36. Concurrent administration of strong CYP3A modulators. Examples of these drugs include (but are not limited to):
  - CYP3A inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
  - CYP3A inducers: carbamazepine, phenytoin, and rifampin.If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
37. Subject had prior systemic myeloma treatment (approved or investigational)  $\leq$  5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
38. 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.
39. HIV
40. Known active chronic hepatitis B or C virus (HBV/HCV) infection
41. A history of concurrent second cancer requiring ongoing systemic treatment
42. Subjects has a history of prior malignancy other than MM, unless the subject has been free of disease for  $\geq$  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.
43. Subject has a history of anaphylaxis to thalidomide, lenalidomide, pomalidomide or dexamethasone
44. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480 or dexamethasone
45. Subject has undergone either of the following within 14 days of initiating CC-92480:
  - Plasmapheresis.
  - Radiation therapy other than local therapy for symptomatic relief of MM associated bone lesions.
46. Subject has received immunosuppressive medication within 14 days prior to the first dose of CC-92480. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection).
  - Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent.
  - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).

47. Subject is unable or unwilling to undergo protocol required venous thromboembolism (VTE) prophylaxis. Thromboembolism prophylaxis consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study beginning 48 hours prior to Cycle 1, Day 1 until 48 hours after last CC-92480 administration.

Contact: Dr. Suzanne Trudel/Diana Arones– **Open Enrollment**

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

**Protocol Number: GO39775**

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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  $\leq 1$ , with the following exceptions:
  - a. Any grade alopecia, peripheral sensory or motor neuropathy must have resolved to Grade  $\leq 2$
4. Measurable disease defined as at least one of the following:
  - a. Serum monoclonal protein (M-protein)  $\geq 0.5$  g/dL ( $\geq 5$  g/L)
  - b. Urine M-protein  $\geq 200$  mg/24 hr.
  - c. Serum free light chain (SFLC) assay: Involved SFLCs  $\geq 10$  mg/dL ( $\geq 100$  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  $\geq 8$  g/dL
  - c. Creatinine  $\leq 2.0$  mL/dL and creatinine clearance (CrCl)  $\geq 30$  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  $\geq 3$  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**

## **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)  $\leq 3.0 \times$  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- **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])  $\geq 50$  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/ $\mu$ L
    - b. Platelet count  $\geq$  75,000/ $\mu$ L
    - c. Total bilirubin  $\leq$  1.5 X ULN
    - d. Alkaline phosphatase  $\leq$  5 X ULN,
    - e. ALT or AST  $\leq$  3 X 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**

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## **AN OPEN-LABEL, ROLLOVER PROTOCOL FOR PATIENTS PREVIOUSLY ENROLLED IN MILLENNIUM-SPONSORED IXAZOMIB STUDIES**

***Protocol Number: Millennium Rollover C16027***

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### **Inclusion Criteria:**

#### 7.1 Inclusion Criteria

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

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

### **Exclusion criteria:**

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

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

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

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## **CHRONIC LYMPHOCYTIC LEUKEMIA TRIALS:**

**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III STUDY TO COMPARE THE EFFICACY AND SAFETY OF ACALABRUTINIB (ACP-196) IN COMBINATION WITH VENETOCLAX WITH AND WITHOUT OBINUTUZUMAB COMPARED TO INVESTIGATORS CHOICE OF**

# CHEMOIMMUNOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA WITHOUT DEL(17P) OR TP53 MUTATION

**Protocol Number: ACE– CL-311**

## **Inclusion criteria**

1. Men and women  $\geq 18$  years of age.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
3. Diagnosis of CLL that meets published diagnostic criteria (Hallek et al. 2018):
  - a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing B-cell marker (CD19, CD20, and CD23) and CD5.
  - b. Prolymphocytes may comprise  $< 55\%$  of blood lymphocytes.
  - c. Presence of  $\geq 5 \times 10^9$  B lymphocytes/L ( $5000/\mu\text{L}$ ) in the peripheral blood (at any point since the initial diagnosis).
4. Active disease per IWCLL 2018 criteria that requires treatment (see Section 4.5.6)
5. Meet the following laboratory parameters:
  - a) Adequate bone marrow function independent of growth factor or transfusion support within 1 week of Screening, as follows:
    - ANC  $\geq 750$  cells/ $\mu\text{L}$  ( $0.75 \times 10^9/\text{L}$ ); ANC  $\geq 500$  cells/ $\mu\text{L}$  ( $0.50 \times 10^9/\text{L}$ ) in subjects with documented bone marrow involvement of CLL
    - Platelet count  $\geq 50,000$  cells/ $\mu\text{L}$  ( $50 \times 10^9/\text{L}$ ); platelet count  $\geq 30,000$  cells/ $\mu\text{L}$  ( $30 \times 10^9/\text{L}$ ) in subjects with documented bone marrow involvement of CLL
  - b) Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times \text{ULN}$ .
  - c) Total bilirubin  $\leq 2 \times \text{ULN}$ , unless directly attributable to Gilbert's syndrome
  - d) Estimated creatinine clearance of  $\geq 50$  mL/min, calculated using the formula of Cockcroft and Gault (if male,  $[\text{140Age}] \times \text{Mass (kg)} / [72 \times \text{creatinine mg/dL}]$ ; multiply by 0.85 if female); estimated creatinine clearance of  $\geq 70$  mL/min for subjects selected by investigator to receive FCR in Arm C
6. Women who are sexually active and can bear children must agree to use highly effective forms of contraception while on the study and for 2 days after the last dose of acalabrutinib, 30 days after the last dose of venetoclax, 6 months after the last dose of fludarabine or bendamustine, 12 months after the last dose of rituximab or cyclophosphamide, or 18 months after the last dose of Obinutuzumab, whichever is longer. Highly effective forms of contraception are defined in Section 5.1.2.8.2.
7. Men who are sexually active must agree to use highly effective forms of contraception with the addition of a barrier method (condom) during the study and for 90 days after the last dose of venetoclax, Obinutuzumab, or rituximab, or 6 months after the last dose of fludarabine, cyclophosphamide, or bendamustine, whichever is longer. Highly effective forms of contraception are defined in Section 5.1.2.8.2.
8. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of venetoclax, Obinutuzumab, or rituximab, or 6 months after the last dose of fludarabine, cyclophosphamide, or bendamustine, whichever is longer.
9. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules and tablets without difficulty.
10. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

## **Exclusion Criteria**

1. Any prior CLL-specific therapies (except corticosteroid treatment administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents up to 20 mg prednisone daily are permitted).
2. Detected del(17p) or TP53 mutation.
3. Transformation of CLL to aggressive non-Hodgkin lymphoma (NHL) (e.g., Richter's transformation, prolymphocytic leukemia [PLL], or diffuse large B cell lymphoma [DLBCL]), or central nervous system (CNS) involvement by leukemia.
4. Any comorbidity or organ system impairment rated with a single Cumulative Illness Rating Scale (CIRS) score of 4 (excluding the eyes/ears/nose/throat/larynx organ system), or a total CIRS score of  $> 6$ .
5. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.
6. History of confirmed progressive multifocal leukoencephalopathy (PML).
7. Received any investigational drug within 30 days before first dose of study drug.
8. Major surgical procedure within 30 days before the first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
9. History of prior malignancy that could affect compliance with the protocol, or interpretation of results, except for the following: a) Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or carcinoma in situ of the prostate at any time prior to study. b) Other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which subject is disease-free for  $\geq 3$  years without further treatment
10. Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification at Screening. Note: subjects with controlled, asymptomatic atrial fibrillation are allowed to enroll on study.
11. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
12. Received a live virus vaccination within 28 days of first dose of study drug.
13. Known history of infection with human immunodeficiency virus (HIV).
14. Any active significant infection (e.g., bacterial, viral or fungal, including subjects with positive cytomegalovirus [CMV] DNA polymerase chain reaction [PCR]).
15. Serologic status reflecting active hepatitis B or C infection.

16. History of known hypersensitivity or anaphylactic reactions to study drugs or excipients, xanthine oxidase inhibitors, or rasburicase
17. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.
18. History of bleeding diathesis (e.g., hemophilia, von Willebrand disease).
19. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists
20. Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor. The use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited.
21. Concurrent participation in another therapeutic clinical trial.

Contact Dr. Christine Chen /Olga Levina– **Open for enrollment**

### **WALDESTROM'S MACROGLOBULINEMIA TRIALS:**

#### **THE USE OF PERIPHERAL BLOOD CELL-FREE DNA (CFDNA) FOR GENETIC PROFILING IN PATIENTS WITH LYMPHOPLASMACYTIC LYMPHOMA (LPL) AND WALDENSTROM'S MACROGLOBULINEMIA (WM)**

***Protocol Number: PM-WM001***

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#### **Non-Interventional**

##### **Inclusion criteria:**

5. Males or females aged 18 years or older at the time of signing consent
6. A confirmed diagnosis of lymphoplasmacytic lymphoma or Waldenstrom's Macroglobulinemia
7. Treatment-naïve or previously treated
8. Known to Princess Margaret Cancer Centre with routine standard of care laboratory testing available

##### **Exclusion criteria:**

3. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form
4. Currently undergoing treatment for active malignancy, NOT indolent lymphoma

Contact: Dr. Christine Chen/Harminder Paul -**Open Enrollment**

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