

Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre
(Version March 2020)

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

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

Non-Interventional

Inclusion criteria:

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

Exclusion criteria:

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

Contact: Dr. Anca Prica/Vinita Dhir -**Open Enrollment**

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

Non-Interventional

Inclusion criteria:

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

Contact: Dr. Donna Reece/Harminder Paul -**Open Enrollment**

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

Non-Interventional

Inclusion criteria:

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

2. Patient must be ≥ 18 years old.
3. Patients are undergoing standard of care blood draw.
4. All patients must have signed and dated an informed consent form.

Healthy Subject Inclusion Criteria

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

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

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

DESENSITIZATION OF IMMUNOMODULATING AGENT-RELATED HYPERSENSITIVITY REACTIONS AS A MEANS TO PROVIDE THERAPEUTIC OPTIONS IN THE MANAGEMENT OF PLASMA CELL DISORDERS (DEHYPERPCD)

Protocol Number: RV-CL-MM-PI-13170

Inclusion Criteria

1. History of HSR to lenalidomide or pomalidomide within 30 days of signing consent.
2. Registered into the mandatory Lenalidomide or Pomalidomide Pregnancy Prevention (PPP) plan for subjects in clinical trials, and be willing and able to comply with the requirements.
3. Females of reproductive potential must adhere to the scheduled pregnancy testing and the contraceptive techniques as required by the Global Pregnancy Prevention plan for subjects in clinical trials
4. Diagnosed with multiple myeloma or amyloidosis, who had experienced moderately-severe (Grade 3 CTCAE v5.0) cutaneous reactions, with or without being symptomatic (itchy rash) to IMiDs OR complained of angioedema or anaphylaxis reactions (in addition to body rash) attributable to lenalidomide or pomalidomide.
5. Afebrile at least 48 hours prior to proposed desensitization day.
6. For patients with existing body rash, a complete resolution of rash is needed at least 7 days prior to desensitization.
7. Patients with other allergy history may also be included.
8. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).
9. Renal function as follows:
 - a. Calculated creatinine clearance ≥ 60 ml/min by Cockcroft-Gault formula for lenalidomide OR Serum creatinine ≤ 2.0 mg/dL (≤ 177 μ mol/L) for Pomalidomide. For those patients who had their lenalidomide or pomalidomide dose previously adjusted, due to renal impairment, and do not meet the stated renal eligibility criteria, could be considered eligible upon discussion with Sponsor Investigator.
 - b. Total bilirubin ≤ 1.5 x ULN
 - c. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

Exclusion Criteria:

1. Female who is pregnant or suspected of being pregnant or who intends to become pregnant, breast feeding or likely to breast feed during the study duration.
2. Male subjects donating semen / sperm, and male and female subjects donating blood
3. Inability to take oral medications, or are unable to tolerate IMiDs (other than hypersensitivity reactions).
4. Disease progression or resistance to IMiDs.
5. History of Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
6. Patients who are taking IMiDs-based therapy for an indication other than MM and/or systemic amyloidosis
7. The development of erythema nodosum, if characterized by a desquamating rash while taking thalidomide, IMiDs or similar drugs.

8. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.
9. Patients who have completed 3 RDPs and continued to have breakthrough HSR post RDP.
10. Patients who had experienced an IMiDs-related hypersensitivity reaction that is less than Grade 3 (Grade 1 and 2) as per CTCAE v5.0.
11. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent participation
12. Peripheral neuropathy > grade 2.
13. In the opinion of the investigator, clinically significant ECG, CHF, MI within 12 months or uncontrolled angina pectoris.

Contact: Dr. Anca Prica/Daniel Socko– **Open for enrollment (tentative end of March 2019)**

A PHASE I/II, RANDOMIZED, OPEN-LABEL PLATFORM STUDY UTILIZING A MASTER PROTOCOL TO STUDY BELANTAMAB MAFODOTIN (GSK2857916) AS MONOTHERAPY AND IN COMBINATION WITH ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) – DREAMM 5.

Protocol Number: 208887

Inclusion Criteria:

1. Participants who have histologically or cytologically confirmed diagnosis of MM, as defined by the International Myeloma Working Group.
2. Participants who have been treated with at least 3 prior lines of prior anti-myeloma treatments including an IMiD (e.g. Lenalidomide), a proteasome inhibitor (e.g. Bortezomib) and an anti-CD38 monoclonal antibody. Lines of therapy are defined by consensus panel of the International Myeloma Workshop
3. 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 screening
 - b. no active infection(s)
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
5. Measurable disease defined as at least 1 of the following:
 - Serum M-protein ≥ 0.5 g/dL (≥ 5 g/L)
 - Urine M-protein ≥ 200 mg/24 hours
 - Serum free light chain (FLC) assay: Involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal serum FLC ratio (< 0.26 or > 1.65)
6. Have organ system functions as defined by the following laboratory assessments:
 - Absolute neutrophil count (ANC) $> 1.0 \times 10^9/L$
 - Hemoglobin > 8.0 g/dL
 - Platelets $> 50 \times 10^9/L$
 - Total bilirubin $\leq 1.5 \times ULN$ (isolated bilirubin $> 1.5 \times ULN$ is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$)
 - Alanine transaminase (ALT) $< 2.5 \times ULN$
 - Aspartate aminotransferase (AST) $< 2.5 \times ULN$
 - Estimated glomerular filtration rate (eGFR) 40 mL/min/1.73 m²
 - Spot urine (albumin/creatinine ratio) < 500 mg/g (56 mg/mmol)
 - Left ventricular ejection fraction (LVEF) $\geq 50\%$
7. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 5.0, 2017) must be Grade 1 at the time of screening except for alopecia (any grade), neuropathy (Grade 2), or endocrinopathy managed with replacement therapy (any grade).

Exclusion criteria:

1. Symptomatic amyloidosis, active ‘polyneuropathy, organomegaly, endocrinopathy, Myeloma protein, and skin changes’ (POEMS) syndrome, active plasma cell Leukemia at the time of screening.
2. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participant’s safety, obtaining informed consent, or compliance with study procedures.

3. Current corneal epithelial disease except mild punctate keratopathy
4. 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.
5. 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 and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM).
 - Participants with curatively treated non-melanoma skin cancer are not excluded.
6. Evidence of cardiovascular risk including any of the following:
 - a. QTcF interval ≥ 480 msec (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
 - b. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) block.
 - c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting or bypass grafting, all within three months of Screening.
 - d. Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
 - e. Uncontrolled hypertension
 - f. Recent (within the past 6 months) history of symptomatic pericarditis.
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK'916 (belantamab mafodotin) or any of the components of the study treatment. History of severe hypersensitivity to other mAbs.
8. Active infection requiring antibiotic, antiviral, or antifungal treatment.
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 (≤ 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
 - QTcF interval ≥ 470 msec
 - Evidence of current clinically significant uncontrolled arrhythmias;
 - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
 - Class III or IV heart failure as defined by the New York Heart Association functional classification system
 - Uncontrolled hypertension
 - Presence of cardiac pacemaker
 - 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 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF BB2121 VERSUS STANDARD TRIPLET REGIMENS IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) (KARMMA-3)
Protocol BB2121-MM-003

Study Design

Approximately 381 subjects will be randomized 2:1 between Treatment Arm A or Treatment Arm B:

- ~ 254 subjects will be randomized to receive Treatment Arm A: bb2121
- ~ 127 subjects will be randomized to receive Treatment Arm B: standard triplet regimens dependent on the subject's most recent anti-myeloma treatment regimen:

- Daratumumab (DARA) in combination with pomalidomide (POM) and low-dose dexamethasone (dex) (DPd)
- OR
- DARA in combination with bortezomib (BTZ) and low-dose dex (Dvd)
- OR
- Ixazomib (IXA) in combination with lenalidomide (LEN) and low-dose dex (IRd)

Inclusion Criteria

- Subject is willing and able to adhere to the study visit schedule and other protocol requirements within this protocol and for a subject randomized to Treatment Arm A, subject agrees to continued follow-up for up to 15 years as mandated by the regulatory guidelines for gene therapy trials.
- Subject has received at least 2 but no greater than 4 prior MM regimens. Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered as one regimen.
- Subject has received prior treatment with DARA, a proteasome inhibitor- and an immunomodulatory compound-containing regimen for at least 2 consecutive cycles.
- Recovery to Grade 1 or baseline of any non-hematologic toxicities due to prior treatments, excluding alopecia and Grade 2 peripheral neuropathy.
- Adequate vascular access for leukapheresis
- Female and Male subjects must use effective measures of contraception without interruption from screening during study treatment until:
 - Treatment Arm A: at least 1 year following bb2121 infusion and until CAR T cells are no longer present by qPCR on two consecutive tests.
 - Treatment Arm B: at least 90 days after the last dose of DARA, BTZ or IXA or 28 days after last dose of POM or LEN, whichever is later.

Exclusion Criteria:

- Subject has nonsecretory MM.
- Subject has any of the following laboratory abnormalities: a. Absolute neutrophil count (ANC) < 1,000/μL; b. Platelet count: < 75,000/μL in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/μL in subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells (it is not permissible to transfuse a subject to reach this level); c. Hemoglobin < 8 g/dL (< 4.9 mmol/L) (it is not permissible to transfuse a subject to reach this level)
- Subject has 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:
 - Basal cell carcinoma of the skin
 - Squamous cell carcinoma of the skin
 - Carcinoma in situ of the cervix
 - Carcinoma in situ of the breast
 - Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system) or prostate cancer that can be treated with curative intent
- Subject has active or history of plasma cell leukemia, Waldenstrom's Macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
- Subject with known central nervous system (CNS) involvement with myeloma.
- Subject has clinical evidence of pulmonary leukostasis and disseminated intravascular coagulation.
- Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that forced expiratory testing (FEV1) is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal.
- Subject was treated with DARA in combination with POM with or without dex (DP±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DPd as bridging therapy but may receive Dvd or IRd as bridging as per Investigator's discretion if randomized to Treatment Arm A.
- Subject was treated with DP±d as part of their most recent anti-myeloma treatment regimen, cannot receive DPd if randomized to Treatment Arm B but may receive Dvd or IRd as per Investigator's discretion.

- Subject was treated with DARA in combination with BTZ with or without dex (DV±d) as part of their most recent anti-myeloma treatment regimen, cannot receive DVd as bridging therapy but may receive DPd or IRd as bridging as per Investigator's discretion if randomized to Treatment Arm A.
- Subject was treated with DV±d as part of their most recent anti-myeloma treatment regimen, cannot receive DVd if randomized to Treatment Arm B but may receive DPd or IRd as per Investigator's discretion.
- Subject was treated with IXA in combination with LEN with or without dex (IR±d) as part of their most recent anti-myeloma treatment regimen, cannot receive IRd as bridging therapy but may receive DPd or DVd as bridging as per Investigator's discretion if randomized to Treatment Arm A.
- Subject was treated with IR±d as part of their most recent anti-myeloma treatment regimen, cannot receive IRd if randomized to Treatment Arm B but may receive DPd or DVd as per Investigator's discretion
- Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine or systemic steroids at any dose). Intermittent topical, inhaled or intranasal corticosteroids are allowed.
- Hypersensitivity to DARA, thalidomide, lenalidomide, POM, BTZ, IXA or dex. This includes rash ≥ Grade 3 during prior thalidomide, POM or lenalidomide therapy.
- Subject with known hypersensitivity to any component of bb2121 product, cyclophosphamide, Fludarabine, and/or tocilizumab or hypersensitivity to the excipients contained in the formulation of DARA, POM, LEN, IXA, BTZ or dex.
- Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study.
- For a subject randomized to Treatment Arm B and will be on a POM- or LEN-containing regimen; unable or unwilling to undergo protocol required thromboembolism prophylaxis.
- Subject is intolerant to bortezomib, subject cannot receive DVd as bridging therapy if randomized to Treatment Arm A or cannot receive DVd if randomized to Treatment Arm B.
- Subject is positive for human immunodeficiency virus (HIV-1), chronic or active hepatitis B or active hepatitis A or C.
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- Previous history of an allogeneic hematopoietic stem cell transplantation, treatment with any gene therapy-based therapeutic for cancer, investigational cellular therapy for cancer or BCMA targeted therapy.
- Subject has received autologous stem cell transplantation (ASCT) within 12 weeks prior to randomization.
- Subject has received any of the following within the last 14 days prior to randomization:
 - Plasmapheresis
 - Major surgery (as defined by the Investigator)
 - Radiation therapy other than local therapy for myeloma-associated bone lesions
 - Use of any investigational agents and systemic anti-myeloma drug therapy

Contact: Dr. Christine Chen/Rebecca Noronha— **Open for enrollment (limited enrollment, please check with site before sending referral)**

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

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 ≥ 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 2x10⁶/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 $\geq 15 \text{ mL/min}$

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

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 (e.g., 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 $\geq 5 \text{ g/L}$;
 - Urine M-protein $\geq 200 \text{ mg/24 h}$;
 - Serum free light chains (FLC) assay: Involved FLC level $\geq 100 \text{ mg/l}$ 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) $> 1.0 \times 10^9/\text{L}$ (Without Growth factor support for the past 14 days, excluding erythropoietin)
 - eGFR (MDRD) $\geq 40 \text{ mL/min}$
 - Platelet count $> 75 \times 10^9/\text{L}$.
 - Hemoglobin $\geq 8.0 \text{ g/dL}$;
 - Total bilirubin $\leq 1.5 \times \text{ULN}$. Isolated bilirubin $> 1.5 \times \text{ULN}$ is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$;
 - Albumin/creatinine ratios (spot urine) $< 500 \text{ mg/g}$ (56 mg/mmol);
 - ALT and AST $\leq 2.5 \times$ upper limit of normal (ULN);
 - LVEF (Echo) $> 50\%$
 - QTcF interval $< 470 \text{ msec}$

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 (≤ 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 ≥ 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

Inclusion Criteria:

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
 - a. Have undergone stem cell transplant, or have been considered transplant ineligible
 - b. Previously undergone at least 2 prior lines of treatment and must have received lenalidomide and a proteasome inhibitor (in separate regimens or in combination);
 - c. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for ≥ 1 cycle during a previous MM treatment (i.e., relapsed MM); and/or
 - d. Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).

2. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
 - a. Transplant was > 100 days prior to study enrolment
 - b. No active infection
3. Subjects with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):
 - Serum M-protein ≥ 5 g/L;
 - Urine M-protein ≥ 200 mg/24 h;
 - Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/l and an abnormal serum free light chain ratio (< 0.26 or > 1.65).
4. The following laboratory results must be met within 10 days of first study drug administration:
 - Absolute neutrophil count (ANC) $> 1.0 \times 10^9/L$. Growth factors cannot be given within 10 days of study drug administration;
 - Serum ALT ≤ 2.5 x upper limit of normal (ULN);
 - eGFR (MDRD) ≥ 40 mL/min a (Appendix 2);
 - Platelet count $> 75 \times 10^9/L$. Platelet transfusions to help subjects meet eligibility criteria are not allowed within 10 days before study enrollment;
 - Hemoglobin ≥ 8.0 g/dL;
 - Total bilirubin ≤ 1.5 x ULN, unless known to have Gilbert's disease. If Gilberts, isolated bilirubin > 1.5 and < 3 x ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$;
 - Albumin/creatinine ratios (spot urine) < 500 mg/g (56 mg/mmol);
 - Albumin ≥ 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 ≥ 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 II, OPEN LABEL STUDY OF AN ACCELERATED INFUSION RATE OF DARATUMUMAB IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA.

Protocol Number: MCRN 009

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Males or females, age 18 years or older.
2. ECOG performance status score of 0, 1 or 2.
3. Life expectancy of at least 3 months
4. Measurable disease according to the IMWG criteria defined below (These baseline laboratory studies for determining eligibility must be obtained during the screening period within 28 days prior to start of study drug):
 - a. Serum monoclonal paraprotein (M-protein) ≥ 10 g/L (if IgG) or ≥ 5 g/L (if IgA, D, E or M).
 - b. Urine M-protein ≥ 200 mg/24 h.
 - c. Serum free light chains (FLC) assay: Involved FLC level ≥ 100 mg/L and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
5. Received at least 3 prior lines of therapy including a proteasome inhibitor (≥ 2 cycles or 2 months of treatment) and an IMiD (≥ 2 cycles or 2 months of treatment) in any order or in combination during the course of treatment or subjects whose disease is double refractory to a PI and an IMiD. For subjects who have received more than 1 type of PI, their disease must be refractory to the most recent one. Similarly, for those who have received more than 1 type of IMiD, their disease must be refractory to the most recent one.
 **A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy (refer to Appendix 2). Radiotherapy, bisphosphonate, or a single short course of steroids (i.e. less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy. Have achieved at least a minimal response (MR) or better to at least one previous line of therapy as per EBMT response criteria.
6. Have achieved at least a minimal response (MR) or better to at least one previous line of therapy as per EBMT response criteria.
7. The following laboratory results must be met within 10 days of first study drug administration:
 - a. ANC $\geq 1.0 \times 10^9/L$
 - b. Hemoglobin ≥ 80 g/L
 - c. Platelets $\geq 70 \times 10^9/L$ (or $\geq 50 \times 10^9/L$ if $\geq 50\%$ plasmacytosis in bone marrow)
 - d. Calculated or measured CrCl ≥ 30 mL/min
 - e. AST and ALT $\leq 3.0 \times$ ULN
 - f. Total bilirubin $\leq 2 \times$ ULN unless known to have Gilbert's disease
 - g. Corrected serum calcium ≤ 3.5 mmol/L

Exclusion Criteria:

1. Prior exposure to daratumumab (or other anti-CD38 monoclonal antibody).
2. History of prior allogeneic stem cell transplantation and showing evidence of active graft-versus-host disease or graft-versus-host disease that requires immunosuppressive therapy.
3. Chemotherapy or other anti-myeloma therapy within 14 days prior to the first dose of study drug.
4. Treatment-related toxicity that has not recovered \leq Grade 1 unless deemed to be irreversible (an example of an irreversible toxicity would include steroid induced cataracts).

5. Subjects who have received steroids within 2 weeks prior to starting study treatment or who have not recovered from side effects of such therapy. Concomitant therapy medications that include corticosteroids are allowed if subject receive ≤ 10 mg of prednisone per day, or equivalent, as indicated for other medical conditions, or up to 100 mg of hydrocortisone as pre-medication for administration of certain medications or blood products prior to enrolment in this study.
6. Subjects who have received any investigational agents within 28 days or 5 half-lives (whichever is shorter, however the minimum allowed timeframe is 14 days) of the first dose (Cycle 1 Day 1).
7. Prior history of malignancies, other than MM, unless the subject has been free of the disease for 3 years or longer. Exceptions include the following:
 - a. Basal or squamous cell carcinoma of the skin
 - b. Carcinoma in situ of the cervix or breast
 - c. Adenocarcinoma of the prostate (TNM stage of T1a or T1b)
8. Other concurrent severe and/or uncontrolled medical conditions (i.e. uncontrolled diabetes, active or uncontrolled infection, acute diffuse pulmonary disease, pericardial disease, uncontrolled thyroid dysfunction) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol.
9. Known chronic obstructive pulmonary disease (COPD), defined as a FEV1 < 50% predicted value.
10. Known moderate or severe persistent asthma within the last 2 years, or currently has uncontrolled asthma of any classification.
11. History of or current uncontrolled cardiovascular disease including:
 - a. Unstable angina, myocardial infarction, or known congestive heart failure Class III/IV (Appendix 4) within the preceding 12 months
 - b. Transient ischemic attack within the preceding 3 months, pulmonary embolism within the preceding 2 months.
 - c. Any of the following: sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, cardiac arrest, Mobitz II second degree heart block or third-degree heart block; known presence of dilated, hypertrophic, or restrictive cardiomyopathy.
 - d. QTc prolongation as confirmed by ECG assessment at screening (QTc >470 milliseconds).
12. Known HIV positivity or active infectious hepatitis B or C.
13. Known allergies, hypersensitivity to mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Daratumumab IB), or known sensitivity to mammalian-derived products.
14. Known CNS involvement, amyloidosis, or currently active plasma cell leukemia.
15. Subjects who are receiving any other investigational agent.
16. Autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug.
17. Any other condition that, in the Investigator's opinion, would contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

Contact: Dr. Vishal Kukreti/Diana Arones or Olga Levina– **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 ≥ 0.5 g/dL by sPEP or
 - b. ≥ 200 mg/24-hour urine collection by uPEP or
 - c. Serum FLC levels > 100 mg/L (milligrams/liter) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in subjects without detectable serum or urine M-protein or
 - d. for subjects with immunoglobulin class A (IgA), myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 0.50 g/dL.
3. All subjects must:
 - a. have documented disease progression on or within 60 days from the last dose of their last myeloma therapy and,
 - b. have failed treatment with, are intolerant to or are not otherwise candidates for available therapies that are known to confer clinical benefit to subjects with RRMM.

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

7. Subjects must have the following laboratory values:

- Absolute neutrophil count (ANC) $\geq 1.25 \times 10^9/L$ without growth factor support for ≥ 7 days (≥ 14 days for pegfilgrastim).
- Hemoglobin (Hgb) ≥ 8 g/dL.
- Platelets (plt) $\geq 75 \times 10^9/L$ without transfusion for ≥ 7 days ($\geq 50 \times 10^9/L$ for subjects with $> 50\%$ plasma cells in bone marrow).
- Corrected serum calcium ≤ 13.5 mg/dL (≤ 3.4 mmol/L).
- 24-hr creatinine clearance (CrCl) ≥ 45 mL/min.
- AST/SGOT and ALT/SGPT ≤ 3.0 x upper limit of normal (ULN).
- Serum bilirubin ≤ 1.5 x ULN.
- Uric acid ≤ 7.5 mg/dL (446 μ mol/L).
- PT/INR < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN, (for subjects not receiving therapeutic anticoagulation).

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

Exclusion criteria:

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

If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
11. Subject had prior systemic myeloma treatment (approved or investigational) ≤ 5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
12. Subject had major surgery ≤ 2 weeks prior to starting CC-92480. Note: Subjects must have recovered from any clinically significant effects of recent surgery.
13. HIV
14. Known active chronic hepatitis B or C virus (HBV/HCV) infection
15. A history of concurrent second cancer requiring ongoing systemic treatment
16. Subjects has a history of prior malignancy other than MM, unless the subject has been free of disease for ≥ 3 years except for the following noninvasive malignancies treated with curative intent:
 - Basal or squamous cell carcinoma of the skin.
 - Carcinoma in situ of the cervix or breast.
 - Stage 1 bladder cancer.
 - Incidental histological findings of localized prostate cancer such as tumor stage 1a or 1b (T1a or T1b) using the Tumor/Node/Metastasis (TNM) classification of malignant tumors OR prostate cancer that has been treated with curative intent.
17. Subject has a history of anaphylaxis to thalidomide, lenalidomide, pomalidomide or dexamethasone

18. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480 or dexamethasone
19. Subject has undergone either of the following within 14 days of initiating CC-92480:
 - Plasmapheresis.
 - Radiation therapy other than local therapy for symptomatic relief of MM associated bone lesions.
20. Subject has received immunosuppressive medication within 14 days prior to the first dose of CC-92480. The following are exceptions to this criterion:
 - Intranasal, inhaled, topical or local corticosteroid injections (eg, intra-articular injection).
 - Systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or the equivalent.
 - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
21. Subject is unable or unwilling to undergo protocol required venous thromboembolism (VTE) prophylaxis. Thromboembolism prophylaxis consisting of low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects as part of the study beginning 48 hours prior to Cycle 1, Day 1 until 48 hours after last CC-92480 administration.

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

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

Protocol Number: GO39775

Key Inclusion Criteria:

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

Key Exclusion Criteria:

1. Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate within 4 weeks before first BFCR4350A infusion
2. Prior treatment with systemic immunotherapeutic agents, including, but not limited to, cytokine therapy and anti-CTLA4, anti-PD-1, and anti-PD-L1 therapeutic antibodies, within 12 weeks or 5 half-lives of the drug, whichever is shorter, before first BFCR4350A infusion

3. Treatment-related, immune-mediated adverse events associated with prior immunotherapeutic agents as follows:
 - a. Grade ≥ 3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy
 - b. Grade 1–2 adverse events that did not resolve to baseline after treatment discontinuation
4. Treatment with radiotherapy, any chemotherapeutic agent, or treatment with any other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first BFCR4350A infusion
5. Autologous stem cell transplantation (SCT) within 100 days prior to first BFCR4350A infusion
6. Prior allogeneic SCT
7. Primary or secondary plasma cell leukemia as defined by an absolute plasma cell count exceeding 2000/ μ L or 20% of the peripheral blood white cells
8. Prior solid organ transplantation
9. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener’s granulomatosis, Sjögren’s syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
10. Patients with history of confirmed progressive multifocal leukoencephalopathy
11. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
12. History of other malignancy that could affect compliance with the protocol or interpretation of results. - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed.
 - a. Patients with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for ≥ 2 years prior to first BFCR4350A infusion.
13. Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
 - a. Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.
 - b. Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed.
14. Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
15. Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
16. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics within 4 weeks prior to first BFCR4350A infusion
17. Known or suspected chronic active EBV infection.
18. Recent major surgery within 4 weeks prior to first BFCR4350A infusion
19. Positive serologic or PCR test results for acute or chronic HBV infection: Patients whose HBV infection status cannot be determined by serologic test results
20. Acute or chronic HCV infection
21. Known history of HIV seropositivity
22. Administration of a live, attenuated vaccine within 4 weeks before first BFCR4350A infusion or anticipation that such a live attenuated vaccine will be required during the study.
23. Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of corticosteroid treatment ≤ 10 mg/day prednisone or equivalent within 2 weeks prior to first dose of BFCR4350A
 - a. Patients who received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval of the Medical Monitor
 - b. The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
24. History of illicit drug or alcohol abuse within 12 months prior to screening,

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

AMYLOIDOSIS TRIALS:

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

Protocol Number: Millennium Rollover C16027

Inclusion Criteria:

7.1 Inclusion Criteria

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

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

Exclusion criteria:

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

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

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

CHRONIC LYMPHOCYTIC LEUKEMIA TRIALS:

A RANDOMIZED, MULTICENTER, OPEN-LABLE, 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 ≥ 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/ μ 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 ≥ 750 cells/ μL ($0.75 \times 10^9/\text{L}$); ANC ≥ 500 cells/ μL ($0.50 \times 10^9/\text{L}$) in subjects with documented bone marrow involvement of CLL
 - Platelet count $\geq 50,000$ cells/ μL ($50 \times 10^9/\text{L}$); platelet count $\geq 30,000$ cells/ μL ($30 \times 10^9/\text{L}$) 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 ≥ 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 ≥ 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 ≥ 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 – **Enrollment temporarily on hold by Sponsor**

WALDESTROM'S MACROGLOBULINEMIA TRIALS:

STUDY TITLE: EXTENDED TREATMENT PROTOCOL FOR SUBJECTS CONTINUING TO BENEFIT FROM IBRUTINIB AFTER COMPLETION OF IBRUTINIB CLINICAL TRIALS

PROTOCOL NUMBER: PCYC-1145-LT

Inclusion Criteria

1. Subject must currently be participating in an ibrutinib clinical trial, deriving clinical benefit from treatment with ibrutinib in the opinion of the treating physician and do not have access to commercial ibrutinib within their region (e.g., no regulatory approval, insufficient reimbursement, and/or insufficient insurer coverage for the indication).
2. Ongoing continuous treatment with ibrutinib: ibrutinib treatment may be on temporary hold at the time of enrollment with less than 28 continuous doses missed, however, the decision cannot have been made to permanently discontinue ibrutinib treatment.
3. Subject must have completed all assessments in their parent protocol (e.g., End-of-Treatment Visit is completed) and want to continue treatment with ibrutinib.
4. Subject has provided informed consent to the long-term treatment extension protocol and not withdrawn consent from the parent study.
5. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, cervical ring, or sponge) during the period of therapy and for 90 days for females and males after the last dose of drug.

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from enrolling in this treatment protocol:

1. Meeting any requirement in the parent protocol to permanently discontinue ibrutinib treatment.
2. Any condition or situation which, in the opinion of the treating physician, may interfere significantly with a subject's participation in the protocol.
3. Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this protocol or within 90 days of last dose of drug treatment. Male subjects who plan to father a child while enrolled in this protocol or within 90 days after the last dose of drug treatment.
4. Unwilling or unable to participate in all required evaluations and procedures.
5. Unable to understand the purpose and risks of the protocol and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

This is an open-label protocol. The dosing regimen of ibrutinib will be the same dose and schedule as received at the end of the respective parent study protocol.

Contact: Dr. Christine Chen/ Rebecca Noronha -**Open Enrollment**

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

Non-Interventional

Inclusion criteria:

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

Exclusion criteria:

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

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

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