

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

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

A PHASE 1/2, MULTICENTER, OPEN-LABEL, STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN, AND EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF CC-92480 IN COMBINATION WITH STANDARD TREATMENTS IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM) AND NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

Protocol Number: CC-92480-MM-002

Inclusion Criteria:

1. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Females of childbearing potential (FCBP) must:
 - a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence* from heterosexual contact.
 - b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with two reliable forms of contraception as defined in the Pregnancy Prevention Plan (PPP) without interruption, 28 days prior to starting CC-92480, during the study treatment (including during dose interruptions), and for 28 days after the last dose of CC-92480 or 90 days after the last dose of BTZ (**for Cohorts A, D and G**) or DARA (**for Cohorts B and E**) or 6 months after the last dose of CFZ (**for Cohorts C and F**), whichever is later.

Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point and, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

3. Male subjects must:
 - a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use of a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study (even during dose interruptions) and for at least 3 months following study treatment discontinuation, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and coitus interruptus (withdrawal) are not acceptable methods of contraception.

4. Males must agree to refrain from donating sperm or semen while on study treatment, and for at least 3 months following last dose of study treatment. Females must refrain from egg cell (ova) donation while on study treatment, and for 28 days after the last dose of CC-92480.
5. All subjects must agree to refrain from donating blood while on study treatment and for 28 days after the last dose of study treatment.
6. All male and female subjects must follow all requirements defined in the PPP (Pregnancy Prevention Plan: study nurse will train the subjects on this)

For subjects in Cohorts A, B, C, D, E and F, the following inclusions will also apply:

7. Subject has documented diagnosis of MM and measurable disease, defined as:
 - a. M-protein quantities ≥ 0.5 g/dL by serum protein electrophoresis (sPEP) or ≥ 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP) and/or
 - b. Serum free light chain (FLC) levels > 100 mg/L (10 mg/dL) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in subjects without measurable disease in the serum or urine
8. Subject has received 2 to 4 (**for Cohorts A, B, and C**) or 1 to 3 (**Cohorts D, E and F**) prior anti-myeloma regimens. Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered as one regimen.
9. Subject has received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles.
10. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.

11. Subject must have documented disease progression during or after their last anti-myeloma regimen.
12. **Cohort F:** Prior therapy with a proteasome inhibitor (PI), excluding carfilzomib, is allowed as long as the subject had at least a PR to prior PI therapy, was not removed from PI therapy due to toxicity, and will have at least a 6-month PI treatment-free interval from last dose received until first study treatment (Subjects may receive maintenance therapy with drugs that are not in PI class during this 6-month treatment free interval).

For subjects in Cohort G, the following inclusions will also apply:

13. Considered by the investigator to be eligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT) according to the institution's criteria based on age, medical history, cardiac and pulmonary status, overall health and condition, co-morbid condition(s), physical examination, and laboratory.

14. Subject must have documented diagnosis with previously untreated symptomatic MM as defined by the criteria below (Rajkumar, 2016):

- MM diagnostic criteria;
 - Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma*
 - Any one or more of the following myeloma defining events:
 - one or more of the following Myeloma-related organ dysfunction (at least one of the following);
 - [C] Calcium elevation (serum calcium > 0.25 mmol/L [> 1 mg/dL] higher than the upper limit of laboratory normal or > 2.75 mmol/L (> 11 mg/dL))
 - [R] Renal insufficiency (serum creatinine > 2 mg/dl) [> 177 μ mol/L] or creatinine clearance < 40 ml/min
 - [A] Anemia (hemoglobin < 10 g/dl or > 2 g/dL below the lower limit of laboratory normal)
 - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT
 - one or more of the following biomarkers of malignancy:
 - Clonal bone marrow plasma cell percentage* $\geq 60\%$
 - Abnormal serum free light-chain ratio ≥ 100 (involved kappa) or < 0.01 (involved lambda) and involved FLC level must be ≥ 100 mg/L
 - >1 focal lesion detected by magnetic resonance imaging (MRI) (at least 5 mm in size)

AND have measurable disease, as assessed by central laboratory, defined by any of the following:

- Immunoglobulin (Ig)G myeloma: serum M-protein level ≥ 1.0 g/dL or urine Mprotein level ≥ 200 mg/24 hours; or
- IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in serum or urine: serum FLC ≥ 100 mg/L and abnormal kappa lambda (κ/λ) ratio

Exclusion criteria:

- 1 Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Subject has any condition that confounds the ability to interpret data from the study.
4. Subject has any of the following laboratory abnormalities:
 - a. Absolute neutrophil count (ANC) $< 1,000/\mu$ L (for Phase 1 without growth factor support for ≥ 7 days [≥ 14 days for pegfilgrastim])
 - b. Platelet count: $< 75,000/\mu$ L (it is not permissible to transfuse a subject to reach this level)
 - c. Hemoglobin < 8 g/dL (< 4.9 mmol/L)
 - d. Creatinine clearance (CrCL) < 45 mL/min
 - e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
 - f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN
 - g. Serum total bilirubin > 1.5 x ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
 - h. Prothrombin time (PT)/international normalized ration (INR) > 1.5 x ULN or 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.

5. Subject has peripheral neuropathy \geq Grade 2
6. Subject with gastrointestinal disease that may significantly alter the absorption of CC-92480.

7. 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 TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative

8. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or clinically significant amyloidosis.

9. Subject with known central nervous system (CNS) involvement with myeloma.

10. Subject has received immunosuppressive medication within the last 14 days of initiating study treatment. The following are exceptions to this criterion:

- Intranasal, inhaled, topical or local corticosteroid injections (e.g., 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 (e.g., computed tomography [CT] scan premedication).

11. Subject has impaired cardiac function or clinically significant cardiac disease, including any of the following:

- Left ventricular ejection fraction (LVEF) $< 45\%$ as determined by echocardiogram (ECHO) or multigated acquisition (MUGA) scan at Screening.
- Complete left bundle branch, bifascicular block or other clinically significant abnormal electrocardiogram (ECG) finding at Screening
- A prolongation of QT interval on Screening ECG as defined by repeated demonstration of a QTc interval > 470 milliseconds (msec) using Fridericia'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 within 12 months prior to starting study treatment.
- Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris
- History of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, pericardial disease or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker

12. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to enrollment.

13. Concurrent administration of strong CYP3A modulators. For full list of modulators, refer to: <https://drug-interactions.medicine.iu.edu/MainTable.aspx>

14. Subject is a female who is pregnant, nursing or breastfeeding, or who intends to become pregnant during the participation in the study.

15. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B, or active hepatitis A or C.

16. Subject has a history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, pomalidomide, BTZ (**for Cohorts A, D and G**), DARA (**for Cohort B**), CFZ (**for Cohort C**) or dexamethasone.

17. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of CC-92480, BTZ (**for Cohorts A, D and G**), DARA (**for Cohorts B and E**), CFZ (**for Cohorts C and F**) or dexamethasone.

18. Contraindications to the standard treatment regimens, per local prescribing information.

19. Subject is unable or unwilling to undergo protocol required thromboembolism prophylaxis.

For subjects in Cohorts A, B, C, D, E and F, the following exclusions will also apply:

20. Subject received any of the following within the last 14 days of initiating study treatment:

- a. Plasmapheresis
- b. Major surgery (as defined by the Investigator)
- c. Radiation therapy other than local therapy for myeloma associated bone lesions
- d. Use of any systemic anti-myeloma drug therapy

21. **Cohorts A and D:** Subjects who had progression during treatment or within 60 days of the last dose of BTZ or discontinued BTZ due to toxicity.

22. **Cohort B:** Subjects who had progression during treatment or within 60 days of the last dose of DARA or discontinued DARA due to toxicity.

23. **Cohort C:** Subjects who had progression during treatment or within 60 days of the last dose of CFZ or discontinued CFZ due to toxicity.

24. **Cohorts D, E and F:** Previous treatment with pomalidomide (POM).

25. **Cohort E:** Previous treatment with DARA.

26. **Cohort F:** Previous treatment with CFZ.
27. Subject used any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment.
28. **Cohorts B and E:** Subject has received previous allogeneic stem cell transplantation or received autologous stem cell transplantation within 12 weeks prior to starting study treatment.
29. **Cohorts B and E:** 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.
30. **Cohorts B and E:** Subject has known moderate or severe persistent asthma, or currently has uncontrolled asthma of any classification.
31. **Cohorts C and F:** Subject has mild hepatic impairment defined as elevated bilirubin > 1.0 but < 1.5 x ULN or normal bilirubin with any elevation of AST.

For subjects in Cohort G, the following exclusion criteria will also apply

32. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of initiating study treatment]).

Contact: Dr. Suzanne Trudel/Trina Wang – **Open for enrollment**

STUDY TITLE: DOES FRAILTY ASSESSMENT PREDICT IMMEDIATE POST-TRANSPLANT TOXICITY IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANT? A PILOT STUDY
PROTOCOL SHORT NAME: FRAILTY ASSESSMENT PRE-ASCT IN MYELOMA

Non-Interventional

Inclusion criteria:

1. Newly diagnosed MM patients, who are eligible and cleared to proceed with their first ASCT, as determined by the Princess Margaret autologous transplant team
2. Age ≥ 18 years at the time of signing the consent
3. Able to understand the consent and agrees to participate in the study.
4. Subsequent follow up visits must be at Princess Margaret Cancer Centre

Exclusion criteria:

1. Patient deemed unfit or ineligible to proceed with ASCT.
2. Concurrent *plasma cell disorder such as amyloid or POEMS*, or other hematological malignancy
3. Any serious medical condition or psychiatric illness that would prevent the subject from signing the informed consent form.
4. Declined to participate
5. Unable to speak or understand English, necessary for completing the questionnaire and follow instructions

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

IDENTIFICATION OF PATIENTS WITH AGE-RELATED CLONAL HEMATOPOIESIS (ARCH) AMONG CANCER SURVIVORS
PROTOCOL SHORT NAME: ARCH-001

Non-Interventional

Inclusion criteria:

1. Age ≥ 60
2. Completed chemotherapy and/or radiation therapy and are being followed at University Health Network.
3. Patient must be in remission after completing chemotherapy or radiation
4. Peripheral blood counts must have returned to normal as defined by:
 - a. Platelets ≥ 100 x 10⁹/L

- b. PMN $\geq 1 \times 10^9/L$
- c. Ongoing treatment for malignancy allowed, if does not involve the use of conventional cytotoxic chemotherapeutic agents.

Or

5. Prior to chemotherapy and/or radiation therapy at the University Health Network, or prior to a myeloablative dose of chemotherapy such as autotransplant, even if already commenced treatment with chemotherapy and/or radiation at non-myeloablative doses.
6. All histologically/cytologically proven tumour types (solid tumours and hematologic malignancies) will be eligible.
7. Received or will receive regimens of chemotherapy or radiation with doses expected to produce transient myelosuppression (PMN $< 1.0 \times 10^9/L$) (The identification and definition of appropriate myelosuppressive chemotherapy and radiation regimens will be at the discretion of the treating physician and will vary among disease sites).
8. Patients must have the ability to understand the requirements of the study and provide written informed consent, which includes authorization for release of protected health information
9. Patient must be willing to provide a peripheral blood sample.

Exclusion criteria:

1. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

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

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

Non-Interventional

Inclusion criteria:

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

Exclusion criteria:

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

Contact: Dr. Anca Prica/Ping Li (16-2007) -**Open for Enrollment**

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

Non-Interventional

Inclusion criteria:

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

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

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

Non-Interventional

Inclusion criteria:

1. Patients must have or be suspected of a diagnosis of AL amyloidosis, MM, or related clonal plasma cell disorder (PCD) such as smoldering myeloma or MGUS.
2. Patient must be ≥ 18 years old.
3. Patients are undergoing standard of care blood draw.
4. All patients must have signed and dated an informed consent form.

Healthy Subject Inclusion Criteria

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

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

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

STUDY TITLE: A PHASE 1/2 DOSE ESCALATION AND COHORT EXPANSION STUDY OF SAFETY AND EFFICACY OF ANTI-BCMA ALLOGENEIC CRISPR-CAS9-ENGINEERED T-CELLS (CTX120) IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CRSP-ONC-002

Inclusion Criteria:

1. Age ≥ 18 years.
2. Able to understand and comply with protocol-required study procedures and voluntarily sign a written informed consent document.
3. Diagnosis of multiple myeloma with relapsed or refractory disease, as defined by IMWG response criteria, and at least 1 of the following:
 - Have had at least 2 prior lines of therapy, including an IMiD (e.g., lenalidomide, pomalidomide), PI (e.g., bortezomib, carfilzomib), and a CD38-directed monoclonal antibody (e.g., daratumumab; if approved and available in country/region).
 - MM that is 'double-refractory' to IMiD and PI combination, defined as progression on or within 60 days of treatment with these agents.
 - MM relapsed within 12 months after autologous stem cell transplant.
4. Measurable disease, including at least 1 of the following criteria:
 - Serum monoclonal protein (M-protein) ≥ 0.5 g/dL.
 - Urine M-protein ≥ 200 mg/24 hours.
 - Serum free light chain (FLC) assay: Involved FLC level ≥ 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal.
5. Eastern Cooperative Oncology Group performance status 0 or 1.
6. Meets criteria to undergo LD chemotherapy and CAR T cell infusion.
7. Adequate organ function:
 - Renal: Estimated glomerular filtration rate >50 ml/min/1.73 m².

- Liver: Aspartate transaminase or alanine transaminase <3 x upper limit of normal (ULN); total bilirubin <2 x ULN.
- Cardiac: Hemodynamically stable and left ventricular ejection fraction ≥45% by echocardiogram.
- Pulmonary: Oxygen saturation level on room air >91% per pulse oximetry.

8. Female subjects of childbearing potential (postmenarcheal with an intact uterus and at least 1 ovary, who are less than 1 year postmenopausal) must agree to use acceptable method(s) of contraception from enrollment through at least 12 months after CTX120 infusion.

9. Male subjects must agree to use effective contraception from enrollment through at least 12 months after CTX120 infusion.

Exclusion criteria:

1. Prior allogeneic SCT.
2. Less than 60 days from autologous SCT at time of screening and with unresolved serious complications.
3. Plasma cell leukemia (>2.0 × 10⁹/L circulating plasma cells by standard differential), or nonsecretory MM, or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis with end organ involvement and damage.
4. Prior treatment with any of the following therapies:
 - a. Any gene therapy or genetically modified cell therapy, including CAR T cells or natural killer cells.
 - b. Prior treatment with BCMA-directed therapy, including BCMA-directed antibody, bispecific T-cell engager, or antibody-drug conjugate.
 - c. Radiation therapy within 14 days of enrollment. Palliative radiation therapy for symptom management is permitted.
5. Known contraindication to cyclophosphamide, fludarabine, or any of the excipients of CTX120 product.
6. Evidence of direct central nervous system (CNS) involvement by multiple myeloma.
7. History or presence of clinically relevant CNS pathology such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, or another condition that in the opinion of the investigator may increase CAR T cell-related toxicities.
8. Unstable angina, clinically significant arrhythmia, or myocardial infarction within 6 months of enrollment.
9. Presence of bacterial, viral, or fungal infection that is uncontrolled or requires IV anti-infectives.
10. Positive for presence of human immunodeficiency virus type 1 or 2, or active hepatitis B virus or hepatitis C virus infection. Subjects with prior history of hepatitis B or C infection who have documented undetectable viral load (by quantitative polymerase chain reaction or nucleic acid testing) are permitted.
11. Previous or concurrent malignancy, except basal cell or squamous cell skin carcinoma, adequately resected and in situ carcinoma of cervix, or a previous malignancy that was completely resected and has been in remission for ≥5 years.
12. Received live vaccine within 28 days of enrollment.
13. Use of systemic anti-tumor therapy or investigational agent within 14 days prior to enrollment. Use of physiological doses of steroids (e.g., ≤10 mg/day prednisone or equivalent) will be permitted for subjects previously on steroids if clinically indicated.
14. Primary immunodeficiency disorder or active autoimmune disease requiring steroids and/or other immunosuppressive therapy.
15. Diagnosis of significant psychiatric disorder or other medical condition that, in the opinion of the investigator, could impede the subject's ability to participate in the study.
16. Women who are pregnant or breastfeeding.

Contact: Dr. Christine Chen/ Daniel Socko– **Open for enrollment**

A PHASE 1/2 OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF AMG 701 MONOTHERAPY, OR IN COMBINATION WITH POMALIDOMIDE, WITH AND WITHOUT DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (PARADIGMM-1B)

Protocol Number: 20170122 (AMG 701)

Inclusion Criteria:

1. Multiple myeloma meeting the following criteria:
 - Pathologically-documented diagnosis of multiple myeloma that is relapsed or is refractory (see Section 12.13) as defined by the following:
 - Relapsed after ≥ 3 lines of prior therapy that must include a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and a CD38-directed antibody in combination in the same line or separate lines of treatment OR refractory to PI, IMiD and CD38-directed antibody

- Note: Subjects enrolled in dose-confirmation Group C must be relapsed/refractory or intolerant to GSK2857916 (belantamab mafodotin)

- Measurable disease, defined by 1 or more of the following at time of screening (Note: extramedullary disease in the absence of medullary disease will be allowed in Group B of dose-confirmation):
 - a serum M protein ≥ 0.5 g/dL measured by serum protein electrophoresis (SPEP)
 - urinary M protein excretion ≥ 200 mg/24 hours
 - involved sFLC measurement > 10 mg/dL, provided that the sFLC ratio is abnormal as per IMWG response criteria

2. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2

3. Life expectancy of at least 3 months as per investigator's judgment at time of screening

4. Hematological function without transfusion support as follows:

- absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$ (without growth factor support)
- platelet count $\geq 50 \times 10^9/L$ (without transfusions within 7 days from screening assessment)
- hemoglobin ≥ 8.0 g/dL (transfusions permitted no later than 48 hours before screening)

5. Renal function as follows:

- calculated or measured creatinine clearance ≥ 30 mL/min using:
 - the Cockcroft-Gault equation OR
 - via 24-hour urine collection with plasma and urine creatinine concentrations

6. Hepatic function as follows:

- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 3 \times$ upper limit of normal (ULN)
- total bilirubin (TBIL) $< 1.5 \times$ ULN (unless considered due to Gilbert's syndrome)

Additional Inclusion Criteria For AMG701 combination therapy with pomalidomide and dexamethasone:

7. Subjects must have received ≥ 2 lines of prior therapy that must include a proteasome inhibitor (PI), lenalidomide, and where approved and available a CD38-directed antibody. These therapies may be in the same line or separate lines of treatment.

8. Subjects must have responded to at least 1 prior line with at least a PR

9. Subjects that have previously received pomalidomide must not have been removed from therapy due to toxicity attributable to pomalidomide and must be at least 6 months from their last dose of pomalidomide

10. Subjects must not have known intolerance to doses of dexamethasone up to 40 mg weekly (20 mg weekly if > 75 years).

Exclusion criteria:

1. Known extramedullary relapse in the absence of any measurable medullary involvement (exception: inclusion of these subjects will be allowed in Group B of dose-confirmation- and dose-expansion)

2. Known central nervous system involvement by multiple myeloma

3. Previously received an allogeneic stem cell transplant and the occurrence of 1 or more of the following:

- received the transplant within 6 months prior to study day 1
- received immunosuppressive therapy within the last 3 months prior to study day 1
- any active acute graft versus host disease (GvHD) requiring systemic therapy within the last 4 weeks prior to start of study treatment
- any systemic therapy against GvHD within 4 weeks prior to start of investigational product treatment

4. Autologous stem cell transplantation less than 90 days prior to study day 1

5. **Recent** history of primary plasma cell leukemia (**within last 6 months prior to enrollment**) or evidence of primary or secondary plasma cell leukemia at the time of screening

6. Waldenstrom's macroglobulinemia

7. Prior amyloidosis (patients with multiple myeloma with asymptomatic deposition of amyloid plaques found on biopsy would be eligible if all other criteria are met)

8. Treatment with systemic immune modulators including, but not limited to, nontopical systemic corticosteroids (unless the dose is ≤ 10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus within 2 weeks before study day 1

9. Last anticancer treatment (chemotherapy, IMiD, PI, molecular targeted therapy) < 2 weeks prior to study day 1

10. Last treatment with a therapeutic antibody less than 4 weeks prior to study day 1

11. Radiation therapy to multiple anatomic sites within 28 days prior to study day 1. Focal radiotherapy within 14 days prior to study day 1.

12. Major surgery defined as surgery requiring general anesthesia with endotracheal intubation within 28 days prior to study day 1, unless discussed with and eligibility approved by Amgen medical monitor

13. Prior treatment with any drug or construct that targets BCMA on tumor cells (eg, other bispecific antibody constructs, antibody drug conjugates, or CAR-T cells), other than group C where prior treatment with GSK2857916 (belantamab mafodotin) is required.

14. Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study. Other investigational procedures while participating in this study are excluded.

15. Treatment with medications known to cause QTc interval prolongation within the washout periods described in Section 12.9. unless approved by the Amgen medical monitor

16. Unresolved toxicities from prior anticancer therapy, defined as not having resolved to CTCAE version 4.0 grade 1 or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia or toxicities from prior anticancer therapy that are considered irreversible (defined as having been present and stable for > 4 weeks) which may be allowed if they are not otherwise described in the exclusion criteria and there is agreement to allow by both the investigator and Amgen medical monitor.

17. Clinically-not controlled chronic or ongoing bacterial, fungal, viral or other infectious disease requiring treatment at the time of study day 1 or within the 14 days before study day 1

18. Active hepatitis B and C based on the following results:

- Positive for hepatitis B surface antigen (HepBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B)
- Negative HepBsAg and positive for hepatitis B core antibody: Negative hepatitis B virus DNA by polymerase chain reaction (PCR) result is necessary.
- Positive Hepatitis C virus antibody (HepCAb): Negative hepatitis C virus RNA by PCR result is necessary.

19. Positive results for human immunodeficiency virus (HIV)

20. Baseline ECG QTc > 470 msec (applying Fridericia correction), defined as the average of individual baseline ECGs

21. History of malignancy other than multiple myeloma within the past 3 years with the following exceptions:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 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
- Breast ductal carcinoma in situ with full surgical resection (ie, negative margins) and without evidence of disease
- Prostate cancer with a Gleason score < 7 with undetectable prostate specific antigen (PSA) over 12 months
- Treated medullary or papillary thyroid cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Similar neoplastic conditions with an expectation of > 95% five-year disease-free survival
- See Exclusion Criterion 5 for exclusion of subjects with plasma cell leukemia

22. Known hypersensitivity to immunoglobulins or to any components of the study drug

23. Current or known history of autoimmune diseases requiring systemic treatment in past 5 years, excluding autoimmune thyroid disease, for which treatment should be completed 6 months prior to enrollment.

24. Males and females of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study through 75 days (females) and 135 days (males) after receiving the last dose of study drug. Refer to Section 12.5 for additional contraceptive information.

25. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 75 days after receiving the last dose of study drug

26. Females with a positive pregnancy test

27. Females planning to become pregnant while on study through 75 days after receiving the last dose of study drug

28. Males who are unwilling to abstain from sperm donation while on study through 135 days after receiving the last dose of study drug

29. Subjects likely to not be available to complete all protocol-required study visits or procedures including BM aspirates/biopsies, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

30. History or evidence of any other clinically-significant disorder, condition or disease (eg, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring therapy at time of screening) with the exception of those outlined above that, in the opinion of the investigator or Amgen medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Additional Exclusion Criteria for AMG701 combination therapy with pomalidomide and dexamethasone:

31. History of serious hypersensitivity associated with thalidomide, pomalidomide, or lenalidomide (> grade 3)

32. Multiple myeloma with IgM subtype
33. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
34. Contraindication to pomalidomide or dexamethasone
35. Glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent dose of other corticosteroids
36. Treatment with systemic immune modulators including, but not limited to, non-topical systemic corticosteroids (unless the dose is ≤ 10 mg/day prednisone or equivalent), cyclosporine, and tacrolimus within 2 weeks before study day 1 or 4 weeks before study day 1 for Phase 1 dose-confirmation
37. Female subjects of childbearing potential with a positive pregnancy test assessed within 14 days prior to first dose of study drugs and/or a positive urine pregnancy test within 24 hours prior to first dose. In addition, females of childbearing potential unwilling to undergo pregnancy testing weekly during the first 4 weeks of pomalidomide use followed by pregnancy testing every 4 weeks in females with regular menses or every 2 weeks in females with irregular menstrual cycles.
38. Male subjects with a female partner of childbearing potential and female subjects of childbearing potential who are unwilling to use 2 methods of contraception (1 of which must be highly effective during the study and for an additional 75 days (females) and 135 days (males) after receiving the last dose of AMG 701, or 28 days after the last dose pomalidomide (males and females) or dexamethasone (females), whichever occurs later. Refer to Section 12.5 for additional contraceptive information.
39. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 75 days after receiving the last dose of AMG 701, or 28 days after the last dose pomalidomide or dexamethasone, whichever occurs later
40. Females planning to become pregnant while on study through 75 days after receiving the last dose of AMG 701 or 28 days after the last dose pomalidomide or dexamethasone, whichever occurs later
41. Male subjects with a pregnant partner who are unwilling to practice abstinence or use a latex or synthetic condom (even if they have had a vasectomy with medical confirmation of surgical success) during treatment (including during dose interruptions) and for an additional 135 days after the last dose of AMG 701, or 28 days after the last dose pomalidomide, whichever occurs later.
42. Males who are unwilling to abstain from sperm donation while on study through 135 days after receiving the last dose of AMG 701 or 28 days after the last dose pomalidomide, whichever occurs later

Contact: Dr. Suzanne Trudel/Daniel Socko – **Open for enrollment for Monotherapy only currently** (AMG701+Pom+Dex and AMG701+Pom will open later, once REB approval is received)

A PHASE 1, MULTICENTER, OPEN-LABEL, DOSE FINDING STUDY OF CC-99712, A BCMA ANTIBODYDRUG CONJUGATE, IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol Number: CC-99712-MM-001

Inclusion Criteria:

1. Documented diagnosis of MM and relapsed and/or refractory disease with:
 - a. Have disease that is nonresponsive while on their last antimyeloma therapy
 - b. Previously undergone at least 3 prior lines of treatment and must have received an immunomodulatory agent and a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib) and an anti-CD38 antibody (in separate regimens or in combination);
2. Subjects with measurable disease defined as at least one of the following:
 - Serum M-protein ≥ 0.5 g/dL by sPEP;
 - 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
 - a serum IgA level ≥ 0.50 g/dL.
3. Subject consents to serial bone marrow aspirations and/or biopsies
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)
 - Serum creatinine clearance ≥ 60 mL/min
 - Platelet count $> 75 \times 10^9/L$.
 - Hemoglobin ≥ 8.0 g/dL;
 - Total bilirubin $\leq 1.5 \times ULN$.
 - Potassium within normal limits or correctable with supplements
 - ALT and AST $\leq 2.5 \times$ upper limit of normal (ULN);

- International normalized ratio (INR) < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN.

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Exclusion criteria:

1. In Part A only, subject has received prior investigational therapy directed at BCMA including, but not limited to, antibody-drug conjugates (BCMA-ADC), bispecific T cell-engaging antibodies or molecules, or BCMA-directed T cell therapy (e.g., BCMA chimeric antigen receptor [CAR] T cells).
2. Subject has symptomatic central nervous system involvement of MM.
3. Subject has nonsecretory MM, plasma cell leukemia, Waldenstrom's Macroglobulinemia, POEMS syndrome
4. Subjects with a history of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, unstable angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months
5. Subject had a prior autologous stem cell transplant ≤ 3 months prior
6. Subject had a prior allogeneic stem cell transplant ≤ 6 months prior to starting CC-99712.
7. Subject had a prior chimeric antigen receptor T (CAR T) cell product ≤ 4 weeks prior to starting CC-99712.
8. Subject had a prior systemic cancer-directed treatments 2 weeks prior to starting CC-99712
9. Subject has known human immunodeficiency virus (HIV) infection or Hepatitis B or C infection.
10. . Subject has a history of concurrent second cancers or history of Cirrhosis.
11. Subject has a history of clinically significant corneal disease requiring therapy or ongoing active corneal disease. 17. Subject has active peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0).

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

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 ≥ 60ml/min by Cockcroft-Gault formula for lenalidomide OR Serum creatinine ≤ 2.0 mg/dL (≤177 μmol/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**

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/Olga Levina– **Open for 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/ μ L; b. Platelet count: < 75,000/ μ L in subjects in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/ μ L in subjects in whom \geq 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 \geq 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.
-
- 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**

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 Gilbert's, 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 for enrollment**

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

Protocol Number: CelMod CC-92480-MM-001

Inclusion Criteria:

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

1. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
2. Subjects must have a documented diagnosis of MM and measurable disease at enrollment. Measurable disease is defined as:
 - a. M-protein quantities \geq 0.5 g/dL by sPEP or
 - b. \geq 200 mg/24-hour urine collection by uPEP or
 - c. Serum FLC levels $>$ 100 mg/L (milligrams/liter) involved light chain and an abnormal kappa/lambda (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 \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 x 10⁹/L without growth factor support for \geq 7 days (\geq 14 days for pegfilgrastim).
- Hemoglobin (Hgb) \geq 8 g/dL.
- Platelets (plt) \geq 75 x 10⁹/L without transfusion for \geq 7 days (\geq 50 x 10⁹/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 x upper limit of normal (ULN).
- Serum bilirubin \leq 1.5 x ULN.
- Uric acid \leq 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 \leq 6 months prior to starting CC-92480.
 - Unstable or poorly controlled angina pectoris, including the Prinzmetal variant of angina pectoris.
10. Concurrent administration of strong CYP3A modulators. Examples of these drugs include (but are not limited to):
 - CYP3A inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
 - CYP3A inducers: carbamazepine, phenytoin, and rifampin.

If use of one of these drugs is necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-92480.
11. Subject had prior systemic myeloma treatment (approved or investigational) \leq 5 half-lives or 4 weeks prior to starting CC-92480, whichever is shorter
12. Subject had major surgery \leq 2 weeks prior to starting CC-92480. Note: Subjects must have recovered from any clinically significant effects of recent surgery.
13. HIV
14. Known active chronic hepatitis B or C virus (HBV/HCV) infection
15. A history of concurrent second cancer requiring ongoing systemic treatment
16. 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.
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 for 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 $2000/\mu\text{L}$ 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 ≥ 2 years prior to first BFCR4350A infusion.
13. Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
 - a. Patients with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits as judged by the investigator are allowed.
 - b. Patients with a history of epilepsy who have had no seizures in the past 2 years while not receiving any anti-epileptic medications are allowed.
14. Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina)
15. Significant active pulmonary disease (e.g., bronchospasm and/or obstructive pulmonary disease)
16. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics within 4 weeks prior to first BFCR4350A infusion
17. Known or suspected chronic active EBV infection.
18. Recent major surgery within 4 weeks prior to first BFCR4350A infusion
19. Positive serologic or PCR test results for acute or chronic HBV infection: Patients whose HBV infection status cannot be determined by serologic test results
20. Acute or chronic HCV infection
21. Known history of HIV seropositivity
22. Administration of a live, attenuated vaccine within 4 weeks before first BFCR4350A infusion or anticipation that such a live attenuated vaccine will be required during the study.
23. Received systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) with the exception of corticosteroid treatment ≤ 10 mg/day prednisone or equivalent within 2 weeks prior to first dose of BFCR4350A
 - a. Patients who received acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval of the Medical Monitor
 - b. The use of inhaled corticosteroids, mineralocorticoids for management of orthostatic hypotension, physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
24. History of illicit drug or alcohol abuse within 12 months prior to screening,

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

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

Interventional

Inclusion criteria:

1. Patients must have measurable disease as defined by at least one of the following: a. Serum M-protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA b. Urinary M-protein excretion at least 200 mg/24 hours c. Serum FLC ≥ 100 mg/L, provided that FLC ratio is abnormal d. If SPEP is felt to be unreliable for routine M-protein measurement (e.g., for IgA MM), then quantitative Ig levels by nephelometry or turbidometry are acceptable
2. Any non-hematological toxicities (except for peripheral neuropathy as described in exclusion criterion #22) that patients had from treatments in previous clinical studies must have resolved to \leq Grade 2 by Cycle 1 Day 1.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
4. Adequate hepatic function within 28 days prior to C1D1: Total bilirubin $< 2x$ upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of $\leq 3x$ ULN) and both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 2.5x$ ULN
5. Adequate renal function within 28 days prior to C1D1. Estimated creatinine clearance (CrCl) calculated using the formula of Cockcroft and Gault (1976): $\bullet \geq 20$ mL/min for SVd, SDd, and SKd arms $\bullet \geq 30$ mL/min for SNd arm $\bullet \geq 45$ mL/min for SPd, SPVd, and SPEd arms
6. Adequate hematopoietic function within 28 days prior to C1D1: total white blood cell (WBC) count $\geq 1,500/mm^3$, ANC $\geq 1,000/mm^3$, hemoglobin (Hb) ≥ 8.0 g/dL, and platelet count $\geq 150,000/mm^3$
7. **SPd (Arm 1) Only**: Relapsed and or refractory MM with:
 - a. Documented evidence of progressive disease (PD) after achieving at least stable disease (SD) for ≥ 1 cycle during a previous MM regimen (i.e., relapsed MM)
 - b. $\leq 25\%$ response (i.e., patients never achieved $\geq MR$) or PD during or within 60 days from the end of the most recent MM regimen (i.e., refractory MM)
 - c. Previously undergone ≥ 2 cycles of lenalidomide and a PI (in separate therapeutic regimens [not for maintenance] or in combination)
 - d. In the expansion arm at RP2D, patients must not be pomalidomide refractory
8. **SVd (Arm 2)** Relapsed or refractory MM with:
 - a. Documented evidence of relapse after ≥ 1 previous line of therapy
 - b. Not refractory to bortezomib in their most recent line of therapy

Exclusion criteria:

1. Smoldering MM
2. MM that does not express M-protein or FLC (i.e., non-secretory MM is excluded), and quantitative immunoglobulin levels cannot be used instead
3. Documented active systemic amyloid light chain amyloidosis
4. Active plasma cell leukemia
5. Red blood cell (RBC) and platelet transfusions and blood growth factors within 14 days of C1D1
6. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks prior to C1D1, and radio-immunotherapy within 6 weeks prior to C1D1. Prior radiation is permitted
7. Treatment with an investigational anti-cancer therapy within 3 weeks prior to C1D1
8. Prior autologous stem cell transplantation < 1 month, or allogeneic stem cell transplantation < 3 months prior to C1D1
9. Active graft versus host disease after allogeneic stem cell transplantation
10. Life expectancy < 3 months
11. Major surgery within 4 weeks prior to C1D1
12. Active, unstable cardiovascular function: a.Symptomatic ischemia, or b.Uncontrolled clinically significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or c.Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3 , or d.Myocardial infarction (MI) within 3 months prior to C1D1, or e.Ejection fraction (EF) $< 50\%$ at Screening
13. Uncontrolled active hypertension
14. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to first dose
15. Known active hepatitis A, B, or C
16. Known human immunodeficiency virus (HIV) infection or HIV seropositivity
17. Any active gastrointestinal dysfunction that prevents the patient from swallowing tablets, or interferes with absorption of study treatment
18. Prior exposure to a SINE compound, including Selinexor

Contact: Dr. Christine Chen/Rebecca Noronha - **Enrollment only for 2 arms: Selinexor + Pom + Dex (SPD) & Selinexor + Bortezomib + Dexamethasone (SVD)- Enrollment on Hold pending PA approval.**

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 ≥ 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. Polymphocytes 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/ μ L (0.75x10⁹/L); ANC ≥ 500 cells/ μ L (0.50x10⁹/L) in subjects with documented bone marrow involvement of CLL
 - Platelet count $\geq 50,000$ cells/ μ L (50x10⁹/L); platelet count $\geq 30,000$ cells/ μ L (30x10⁹/L) in subjects with documented bone marrow involvement of CLL
 - b) Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 xULN.
 - c) Total bilirubin ≤ 2 xULN, 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, $[140 \text{Age}] \times \text{Mass (kg)} / [72 \times \text{creatinine mg/dL}]$; 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, polymphocytic 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– **Open for Enrollment**

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 abstinence², 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 for 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/Harjinder Paul -**Open Enrollment**

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