Clinical Trials in Myeloma and Related Disorders at PM Cancer Centre
(Version November 2026)

PLEASE SEE ELIGIBILITY CRITERIA AND KEY NOTES AFTER SUMMARY PAGE

MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED:

1. CMRG010 (BOREALIS)- Iberdomide (CELMoD), bortezomib, dex +/- isatuximab -transplant-ineligible.
2. Etentamig (BCMA /CD3) + Rd for Maintenance post ASCT in NDMM -transplant-eligible.

***MULTIPLE MYELOMA TRIALS* – 1-3 PRIOR LINES OF THERAPY**

1. AZD0120, a Dual-Targeting Autologous CAR-T (BCMA and CD19) vs. SOC (DKd, DPd, PVd, Kd), randomized trial.
2. Mezigdomide (CELMOD) + elranatamab (BCMA) single arm trial
3. Autologous CAR-T (GPRC5d) + either mezigdomide or elranatamab.
4. Sonrotoclax (BGB-11417) -(anti- BCL2), Kd for t(11;14), single arm trial
5. Trispecific (BCMA/GPRC5d/CD3) vs. teclistamab (BCMA) randomized trial
6. Cevostamab (FcRH5/CD3) in combination with Pd

MULTIPLE MYELOMA TRIALS 3+ PRIOR LINES OF THERAPY

1. Trispecific (BCMA/GPRC5d/CD3) vs teclistamab (BCMA) randomized trial.
2. Etentamig (BCMA bispecific) + Iberdomide (CELMOD) single arm trial

MULTIPLE MYELOMA TRIALS -EXHAUSTED SOC THERAPY

1. Liposomal curcumin (NF-kB and STAT3 inhibitor).
2. MMSET inhibitor in t(4;14) only.
3. Phase 1 dose escalation study using PF-07994525 (KAT2i)

AMYLOIDOSIS TRIALS

1. CAR-T (CD19/BCMA)-AL RR Amyloidosis.

CHRONIC LYMPHOCYTIC LEUKEMIA & WALDESTROM'S TRIALS

1. MK-1026-003 a reversible non-covalent ATP, competitive BTK inhibitor in Hematologic Malignancies- only for WM patients

MULTIPLE MYELOMA STUDIES – NEWLY DIAGNOSED:

STUDY TITLE: DEVELOPMENT OF NK CELL- AND T CELL- ENGAGING BI- AND MULTI-SPECIFIC BIOLOGICS TO REDIRECT IMMUNE RESPONSES TOWASRDS PLASMA CELLS AND MYELOMA CELLS.
Study Number: NKT vs MM
Contact: Dr. Rodger Tiedemann/ Harjot Vohra- **Open Enrollment**

Inclusion Criteria

1. Age ≥ 18 years
2. Able to give informed consent
3. Diagnosed with or suspected of having multiple myeloma, or is a healthy volunteer
4. Able and willing to donate research specimens

Exclusion Criteria

1. Another active major non-plasma cell malignancy (but permitting non-metastatic skin tumors), previously treated with chemotherapy within the past 2 years
2. Known HIV or HTLV infection
3. Known symptomatic Covid-19 infection in the past 2 weeks
4. Any serious medical condition or psychiatric illness that would prevent the subject from signing the informed consent form.
5. Declined to participate.

AN INTEGRATED APPROACH TO CHARACTERIZE HIGH-RISK DISEASE IN MYELOMA AT PRINCESS MARGARET.
Protocol Number: HiPerMM
Contact: Dr. Suzanne Trudel /Harjot Vohra – **Open Enrollment**

Inclusion Criteria

1. Age ≥ 18 years
2. Ability to give informed consent
3. Newly diagnosed with active multiple myeloma
4. Eligible for autologous stem-cell transplantation (ASCT)
5. Classified as intermediate-high risk (stage III) or high risk (stage IV) risk as per the R2-ISS criteria
6. Able and willing to donate research specimens within the 1st month of induction treatment.

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 questionnaires and follow instructions.

A SINGLE ARM, RESPONSE-ADAPTED, OPEN LABEL STUDY OF IBERDOMIDE, WEEKLY BORTEZOMIB AND DEXAMETHASONE (IBERBD) WITH ISATUXIMAB ADDED ON DEMAND FOR TRANSPLANT-INELIGIBLE, NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: THE BOREALIS TRIAL.
Protocol Number: CMRG010
Contact: Dr. Guido Lancman/Trisha Ramnanan – **Open Enrollment**

Inclusion Criteria

1. Age **≥ 65** years at the time of signing consent
2. Must be able to adhere to the study visit schedule and other protocol requirements.
3. Previously untreated, transplant ineligible, symptomatic multiple myeloma as defined by the criteria below.
   Both criteria A and B must be met:
   A). Clonal bone marrow plasma cells **≥10%** or biopsy proven bony or Extramedullary Plasmacytoma
   B). Any one or more of the following myeloma defining events
   I. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
   - Hypercalcemia: serum calcium **>0.25** mmol/L (>1 mg/dL) higher than the upper limit of normal **or >2.75** mmol/L (>11 mg/dL)
   - Renal insufficiency: creatinine clearance **177** µmol/L (>2 mg/dL)
   - Anemia: hemoglobin value of >**2 g/dL** below the lower limit of normal, or a hemoglobin value **<10g/dL**
   - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

   II. Biomarker criteria or MDE:
   - Clonal bone marrow plasma cell percentage **≥ 60%**
   - Involved: uninvolved serum free light chain (FLC) ratio **≥100**

- **> 1** focal lesions on MRI studies (at least **5 mm in size**)

4. Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
5. Life expectancy of **≥ 3 months.**
6. The following laboratory results must be met within **10 days** prior to first study drug administration:
   - Absolute neutrophil count (ANC) **≥ 1.0 x 109/L**. Growth factors cannot be given within 10 days of study drug administration.
   - Serum AST and ALT **≤ 1.5 x** upper limit of normal (ULN).
   - Creatinine clearance **≥ 30 mL**/min either directly measured via 24-hour urine collection or calculated using MDRD (Appendix 1).
   - Platelet count **≥ 50 x** 109/L. Platelet transfusions to help subjects meet eligibility criteria are not allowed within 10 days before study enrollment.
   - Hemoglobin **≥ 80 g/L.**

Exclusion Criteria

1. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid i.e. less than or equal to dexamethasone 40 mg/day for 4 days not have been given within 14 days of treatment start).
2. Any serious medical condition that places the patient at an unacceptable risk if he or she participates in this study.
3. Pregnant or lactating females.
4. Renal failure requiring hemodialysis or peritoneal dialysis.
5. Prior history of malignancies, other than multiple myeloma, unless the patient has been free of the disease for ≥ 3 years. Except:
   - 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 histological finding of prostate cancer
6. Patients who are unable or unwilling to undergo antithrombotic therapy
7. Peripheral neuropathy of ≥ grade 2 severity.
8. Known HIV positivity or active infectious hepatitis, type A, B, or C.
9. Primary AL (immunoglobulin light chain) amyloidosis and myeloma complicated by amyloidosis.
10. Plasma Cell Leukemia.
11. Evidence of cardiovascular risk including any of the following:
    - QTc interval **≥ 470** msecs. Note that the QT interval should be corrected for heart rate by Fridericia's formula (QTcF).
    - Evidence of current clinically significant uncontrolled arrhythmias; including clinically significant ECG abnormalities; including 2nd degree or 3rd degree atrioventricular (AV) block.
    - History of myocardial infarction, acute coronary syndromes, 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.
12. Patients requiring strong inhibitors or inducers of **CYP3A4/5.**
13. Patients that have undergone major surgery (as defined by the investigator) within 28 days of initiating study treatment
14. Patients with a gastrointestinal disease that may significantly alter the absorption of Iberdomide.
15. Patients that have received a live vaccine within **3 months** of initiating study treatment.

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
Contact: Dr. Anca Prica -**Open for Enrollment**

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.

A PHASE ½, OPEN-LABEL, PLATFORM STUDY TO EVALUATE SAFETY AND EFFICACY OF ETENTAMIG MONOTHERAPY OR ETENTAMIG COMBINATIONS IN SUBJECTS WITH MULTIPLE MYELOMA.
Protocol Number: M25-059 (Sub-Study 4)
Contact: Dr. Guido Lancman/ Olga Levina**–Enrollment on hold by sponsor until release of new enrollment slots**

Inclusion Criteria

1. ≥18 years of age.
2. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
3. Subjects must have NDMM in whom maintenance is part of the intended treatment plan and have:
    - Completed 3-6 cycles of induction therapy, followed by high dose therapy and autologous stem cell transplantation and
    - Must have undergone ASCT within 130 days prior to enrollment (if consolidation therapy is not planned prior to maintenance therapy). Note: For participants who receive consolidation therapy after ASCT, first dose of study treatment must occur within 60 days of consolidation and within 7 months from ASCT.
    - Must have MRD positivity at a threshold of 10^{-5}via NGS (ClonoSEQ assay) or < sCR and achieved at least a partial response or better per 2016 IMWG response criteria without evidence of progression at enrollment.
4. Subjects must have NDMM as defined according to the IMWG criteria with measurable disease at the time of diagnosis. Measurable disease defined as:
    - Serum M-protein ≥ 0.5 g/dL (≥5 g/dL);
    - Urine M-protein level ≥200 mg/24 hours;
    - Serum free light chain (FLC) ≥10 mg/dL (involved light chain) and an abnormal serum kappa lambda ratio only for subjects without measurable serum or urine M-protein.
5. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.
6 Clinical laboratory values:
    - **Hemoglobin** ≥8.0 g/dL; subject may receive red blood cell (RBC) transfusions in accordance with institutional guidelines. Subjects may not have received a red blood cell (RBC) transfusion within 7 days prior to the hemoglobin result used for eligibility.
    - **Platelets** ≥ 75,000/mm3 . For subjects with >50% myeloma involvement in the marrow, a platelet count of ≥ 50,000 mm3 is allowed. Subjects may not have received a platelet transfusion within 7 days prior to the platelet count used for eligibility.
    - Absolute Neutrophil Count (ANC) ≥ 1,000/µL; subject may use growth factor support to achieve ANC eligibility criteria. Subjects may not have received a GCSF within 7 days prior to the ANC results for eligibility.
    - Estimated glomerular filtration rate ≥ 30 ml/min calculated using the Modification of Diet in Renal Disease formula.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)≤3 ×ULN
    - Serum total bilirubin ≤ 2.0 × ULN (except for subjects with documented Gilbert's syndrome, in which case direct bilirubin ≤ 1.5 × ULN is required)
    - Serum calcium corrected for albumin ≤14 mg/dL (≤3.5 mmol/L)
7. Availability of an archival bone marrow biopsy/ aspirate samples to identify the dominant malignant (index) clone by central laboratory/NGS test (clonoSEQ assay) that is used to track MRD status. This sample should preferably be collected before induction treatment (e.g at diagnosis) or before transplant.
Note: acceptable archival samples may include: non-decalcified diagnostic tissue slides (bone marrow aspirate smear, touch preparation or clot section), genomic DNA from bone marrow samples (bone marrow aspirate, bone marrow mononuclear cells, bone marrow clot tissue block or FFPE, or CD138-enriched bone marrow mononuclear cells)
8. Consent to a fresh bone marrow biopsy/aspirate before enrollment (bone marrow aspirate/biopsy performed within 56 days before enrollment without intervening treatment is acceptable).
9. For all female subjects of childbearing potential, 2 negative pregnancy tests must be obtained prior to initiating therapy,
    - The first test (serum) should be performed within 14 days prior to the first etentamig administration or lenalidomide administration.
    - The second test (urine, minimum sensitivity of 25 IU/L) or serum at the discretion of the Investigator per local guidelines should be performed within 24 hours prior to the first dose of etentamig administration or lenalidomide administration.
    - Female subjects who are not of childbearing potential at Screening do not require pregnancy testing.
10. Female subjects of childbearing potential must practice at least 2 protocol-specified methods of birth control from at least 28 days prior to C1D1 through 90 days after the last dose of study treatment.
11. Female subject who is not pregnant or breastfeeding and is not considering becoming pregnant or donating eggs during the study and for at least 90 days after the last dose of etentamig or lenalidomide.
12. Male subjects who are sexually active with female partner(s) of childbearing potential must agree to follow the contraception requirement during lenalidomide treatment and till 28 days after the last dose of study treatment
13. Male subject who is not considering fathering a child or donating sperm during the study or for at least 28 days after the last dose of any study treatment
14. Subject must be registered and must comply with all requirements of the lenalidomide pregnancy prevention program (PPP) or local equivalent.
15. Prior BCMA exposure as part of induction therapy is allowed.

Exclusion Criteria

1. Subjects with toxicities from previous anticancer therapies that have not resolved to baseline

levels or to Grade 1 or less except for alopecia or fatigue.

2. Subject who has known active central nervous system involvement of MM.Subjects who has known active central nervous system involvement MM.
3. Subject who has any of the following conditions:
   - Non-secretory MM;
   - Active plasma cell leukemia, i.e., either 5% of peripheral white blood cells or > 5.0 × 108/L circulating plasma cells by standard differential;
   - Waldenstrom's macroglobulinemia;
   - Light chain amyloidosis;
   - POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes);
   - Active and acute viral, bacterial, or systemic fungal infection within 14 days prior to the first dose of study treatment requiring antimicrobial therapy.
4. Subject who has history of clinically significant renal, neurologic, psychiatric, endocrine, metabolic, immunologic, pulmonary, or hepatic disease within the last 6 months that, in Investigator's opinion, would adversely affect the subject's participation in the study.
5. Subject who has history of significant cardiovascular or pericardial disease, including uncontrolled angina, arrhythmia, recent myocardial infarction within 6 months of first dose, congestive heart failure cardiovascular disability status of New York Heart Association Class ≥ 3, or severe cardiac insufficiency.
6. Subject who has known history of other active malignancies within the past 3 years with the following exceptions:
   - Adequately treated in situ carcinoma of the cervix uteri or the breast;
   - Prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen levels
   - Previous malignancy with no evidence of disease confined and surgically resected (or treated with other modalitities) with curative intent and unlikely to impact survival during the duration of the study.
7. Subjects who have had prior maintenance therapy.
8. Subjects who progressed after initiation of 1Ltherapy.
9. Subjects received tandem transplants.
10. Subjects received allogeneic SCT.
11. Subject received treatment with anti-cancer therapy (including chemotherapy, radiotherapy, biologics, immunotherapy, cellular therapies and/or steroids at doses > 20 mg dexamethasone or equivalent) or undergone a major surgical procedure within 21 days or within 5 half-lives of an anticancer therapy, prior to the first dose of study treatment, whichever is shorter.
12. Subject treated with any investigational treatment within 5 half-lives of the treatment (or contact TA MD if half-life is unknown,) prior to the first dose of study treatment
13. Subject who has evidence of active hepatitis B (HBsAg positive) infection based on screening blood testing. Subject with resolved infection (HBsAg negative, but HBcAb or HBsAb positive) must be screened using real-time PCR of HBV DNA. Subjects with positive PCR will be excluded.

Table 1. Substudy 4 Eligibility Based on Hepatitis B Virus Test Results

Action	HBsAg	HBsAb	HBcAB Total
Exclude	+	-or +	-or +
	-	-	+
Include	-	-	-
	-	+	+
	-	+	-

14. Subject who has evidence of active hepatitis C infection based on screening blood testing. Subject may not be seropositive for hepatitis C (except in the setting of a sustained virologic response, defined as aviremia atleast 12 weeks after completion of antiviral therapy)
15. Subject who has known active SARS-CoV-2 infection.
16. Subject who has known active infection with HIV.
17. Known or suspected hypersensitivity or allergic reaction or significant intolerance to constituents of the study treatment etentamig, premedications, anti-cytokine therapy or their excipients. For Phase 2 only, subjects may not have known contraindication to lenalidomide.
18. Subject who has known history of clinically significant (per Investigator's judgment) alcohol abuse within the last 6 months.
19. Subject received any live vaccine within 30 days prior to the first dose of the study treatment

MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY:

***MULTIPLE MYELOMA TRIALS* – SECOND LINE THERAPY**

A Phase 3 Randomized Study Comparing JNJ-79635322 versus Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma after 1 to 3 Prior Lines of Therapy, Including an Anti-CD38 Antibody and Lenalidomide
Protocol Number: 79635322MMY3002
Contact: Dr. Guido Lancman/ Elena Talovikova – Open

Inclusion Criteria

Age

1. ≥18 years of age

Type of Participant and Disease Characteristics

2. Multiple Myeloma diagnosis according to the IMWG diagnostic criteria. Measurable disease by any of the following:
   i. Serum M-protein level ≥5 g/L; or
   ii. Serum Ig FLC ≥100 mg/L and abnormal serum Ig kappa lambda FLC ratio; or
   iii. Urine M-protein level ≥0.2 g/24 hours
3. Received 1 to 3 prior lines of myeloma therapy, including an anti-CD38 antibody and lenalidomide. Have undergone at least 2 consecutive cycles of an anti-CD38 antibody at the approved dosing schedule (or a minimum of 6 doses if the anti-CD38 antibody was only part of a maintenance regimen) in any prior line and 2 consecutive cycles of lenalidomide in any prior line, unless Progressive Disease was the best response to the line of therapy.
4. Relapsed or refractory disease as defined below:
   i. Relapsed disease is defined as an initial response to prior treatment, followed by confirmed PD by IMWG response criteria >60 days after cessation of treatment.
   ii. Refractory disease is defined as failure to achieve a response or confirmed PD by IMWG response criteria during previous treatment or <60 days after cessation of treatment.
5. ECOG performance status of 0 to 2
6. Laboratory values meeting the following criteria:

Hemoglobin	≥75 g/L, without use of transfusion or growth factors within 7 days prior to testing
ANC	≥0.75×103/µL (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF prior to the testing)
Platelets	≥50×103/µL, without use of transfusion or growth factors within 7 days prior to laboratory testing
AST and ALT	<2.5×ULN
Total bilirubin	<1.5×ULN
Bilirubin in case of known congenital nonhemolytic hyperbilirubinemias such as Gilbert's Syndrome	Isolated total bilirubin ≥1.5×ULN with direct bilirubin <1.5×ULN
eGFR, calculated with the CKD-epi creatinine formula using adjusted BSA	>30 mL/min

Sex and Contraceptive/Barrier Requirements

7. Patients must agree, while on study treatment and for 6 months after the last dose of study treatment, to:
   - Not breastfeed or be pregnant.
   - Not donate gametes (ie, eggs or sperm) or freeze for future use for the purposes of
   - assisted reproduction.
   - Wear an external condom
   - if of childbearing potential:
     - negative pregnancy test at screening and within 24 hours before the first dose of study treatment and agree to further pregnancy tests.
     - Practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used.
   - If a participant's partner is of childbearing potential:
     - The partner must practice a highly effective method of contraception unless the participant is vasectomized

Exclusion Criteria

Medical Conditions

1. Serious underlying medical conditions, such as:
   i. Evidence of active systemic viral, fungal or bacterial infection requiring systemic antiviral, antifungal, or antimicrobial therapy.
   ii. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of treatment. EXCEPTION: Patient with vitiligo, Type 1 diabetes, or prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing are eligible regardless of when these conditions were diagnosed.

iii. Overt clinical evidence of dementia or altered mental status.

2. Major surgery, (eg, requiring general anesthesia) or significant traumatic injury within 2 weeks prior to first dose, or not fully recovered from prior surgery, or has major surgery planned during the time the participant is expected to participate in the study.

Note: Patient with planned surgical procedures to be conducted under local anesthesia may participate.

3. Suspected or known allergies, hypersensitivity, intolerance, or other contraindications to the use of JNJ-79635322 or teclistamab, or their excipients.

4. Any of the following within 6 months prior to first dose of study treatment: Seizure, severe or unstable angina, myocardial infarction, major thromboembolic events (eg, pulmonary embolism, cerebrovascular accident [including transient ischemic attack and stroke]), clinically significant ventricular arrhythmias or heart failure New York Heart Association functional classification Class III to IV. Uncomplicated deep vein thrombosis is not considered exclusionary

Prior Malignancies

5. Presence of any of the following

i. Any ongoing myelodysplastic syndrome or B-cell malignancy (other than MM).
ii. Any history of malignancy, other than MM, that is considered at high risk of recurrence requiring systemic therapy.
iii. Any active malignancy (ie, progressing or requiring treatment change in the last 24 months) other than MM

The only allowed exceptions are malignancies treated within the last 24 months that are considered cured:

i. Non-muscle invasive bladder cancer (solitary Ta-papillaryurothelial neoplasm of low malignant potential or low-grade, <3 cm, no carcinoma in situ).
ii. Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone.
iii. Non-invasive cervical cancer.
iv. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, or history of localized breast cancer (anti-hormonal therapy is permitted).
v. Localized prostate cancer (M0, N0) with a Gleason Score ≤7, treated locally only (radical prostatectomy/radiotherapy/focal treatment).
vi. Other malignancy that is considered cured with minimal risk of recurrence in consultation with the sponsor.

6. PC leukemia at the time of screening (≥5% circulating PCs in peripheral blood smear), Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or systemic amyloid light chain amyloidosis (Rajkumar 2014; patients with myeloma who have incidental amyloid deposits on biopsy of an impacted organ, without clinical manifestations of amyloidosis, are not excluded and may participate in the study).

Brain and Central Nervous System Metastases

7. Known active or prior CNS involvement or exhibits clinical signs of meningeal involvement of MM. If either is suspected, negative whole brain MRI and lumbar cytology are required

HIV Status

8. Patients who are HIV-positive and meet any of the following:

i. Detectable viral load (ie, >50 copies/mL) at screening.
ii. CD4+ count <300 cells/mm3 at screening.
iii. AIDS-defining opportunistic infection within 6 months of screening.
iv. Receive treatment other than continued HAART. A change in HAART due to resistance/progression must occur at least 3 months prior to screening. A change in HAART due to toxicityis allowed up to 4 weeks prior to screening.

Note: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

Viral Hepatitis Assessments

9. Active hepatitis of infectious origin.

i. Seropositive for hepatitis B: defined bya positive test for HBsAg. Patient with resolved infection (ie, patients who are HBsAg negative with positive antibodies to total HBc antigen [anti-HBc]) must be screened using RT-PCR measurement of HBV DNA levels. Those who are RT-PCR positive will be excluded. Patients with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR.
ii. Known hepatitis C infection or positive serologic testing for HCV (anti-HCV) antibody. Patients with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained at screening or within 3 months prior to first dose of study treatment.
iii. Other clinically active liver disease of infectious origin

Prior/Concomitant Therapy or Clinical Study Experience

10. Concurrent use of any other anticancer treatment (including non-palliative radiotherapy) or investigational agent. For patients who received an allogeneic stem cell transplant, the transplant must be dated at least 6 months before first dose of study drug. Patients who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks before the start of study treatment administration without signs of graft-versus-host disease. Toxicity related to prior anticancer treatment must have resolved to Grade 1 or better (except alopecia, skin fibrosis or discoloration, dry mouth, hearing loss, endocrinopathy managed with replacement therapy, peripheral neuropathy, which must be Grade 2 or better)
11. Received prior or concurrent exposure to T-cell redirecting therapy (eg, CAR-T, bispecific antibodies), directed at BCMA or GPRC5D.
12. Received a cumulative dose of corticosteroids equivalent to ≥160 mg of dexamethasone within 14 days prior to first dose of study drug.
13. Received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study drug or within 90 days after the last dose of study drug. Non-live and non-replication-competent vaccines approved or authorized for emergency use by local HAs are allowed.

A Phase III Open-label, Randomized, Multicenter Study Comparing AZD0120, a Dual-Targeting Autologous Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against BCMA and CD19, versus Standard Regimens in Participants with Relapsed Refractory Multiple Myeloma (DURGA-4)

Protocol Number: D8311C00001

Contact: Dr. Suzanne Trudel / Trina Wang – **Open to Enrollment (limited slots- please check first with site for any referral)**

Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply

Age

1. 18 years or older.

Type of Participant and Disease Characteristics

2. Diagnosis of MM according to the IMWG diagnostic criteria (Rajkumar et al 2014).
3. Measurable disease criteria:
   (a) Serum M-protein level ≥ 1.0 g/dL
   (b) Urine M-protein level ≥ 200 mg/24 h
   (c) Serum immunoglobulin FLC ≥ 10 mg/dL (100 mg/L) and abnormal FLC ratio.
4. Progressive Disease (PD) by IMWG 2016 criteria during or after the most recent line of therapy. Participants who have had only 1 prior line of therapy must have disease that has progressed within 47 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.
5. Received 1 to 3 lines of prior therapy including an IMiD and either a PI or an anti-CD38 antibody. Must have undergone at least 2 complete cycles of treatment for each line of therapy, unless PD was the best response to the line of therapy.
6. Eligible to receive at least one of the standard regimens (DKd, PVd, DPd, or Kd).
   (a) Participants who are refractory to daratumumab are not eligible to receive DKd or DPd
   (b) Participants who are refractory to carfilzomib are not eligible to receive DKd or Kd
   (c) Participants who are refractory to pomalidomide are not eligible to receive PVd or DPd
   (d) Participants who are refractory to bortezomib are not eligible to receive PVd
7. ECOG performance status score of 0 to 1.
8. **Participant must have screening bone marrow aspirate, or archival sample, adequate for clonal sequence calibration for MRD. An archival sample from any time prior to screening is acceptable.**
9. Adequate organ and bone marrow function. Criteria for Adequate Organ and Bone Marrow Function at Screening[a] (Within 7 days Prior to Randomisation)

Parameter	Parameter	Value
Haematological	Haemoglobin [b]	≥ 8.0 g/dL
	Absolute neutrophil count [c]	≥ 1×10^9/L (1000 per mm^3)
	Platelet count [b]	≥ 75×10^9/L (75,000 per mm^3) in participants with <50% of bone marrow nucleated cells are plasma cells
		≥ 50×10^9/L (50,000 per mm^3) in participants with ≥50% of bone marrow nucleated cells are plasma cells
	Absolute lymphocyte count	≥ 300/µL (0.3×10^9/L)
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome
		≤ 3 × ULN if the participant has Gilbert's syndrome
	AST and ALT	≤ 3 × ULN
Renal	CrCl by Cockcroft and Gault method: CrCl (mL/min) = (140 – age [years]) × weight (kg) × (F) [d] / (72 × serum creatinine mg/dL)	≥ 30 mL/minute

a) Screening laboratory values must demonstrate participant eligibility but may be repeated once within the screening window, if necessary. Participants who fail to meet the absolute neutrophil count or platelet count eligibility criteria during screening should not be retested for the study after being treated with GCSF and/or transfusions.
b) Transfusions (RBC or platelet) are not permitted within 7 days prior to the date of the screening laboratory assessment.
c) Short-acting myeloid growth factors (eg, GCSF) are not permitted within 7 days prior to the date of the screening laboratory assessment. Long-acting myeloid growth factors (eg, Peg-GCSF) are not permitted within 14 days prior to the date of the screening laboratory assessment.
d) Where F = 0.85 for females and F = 1 for males

Sex and Contraceptive/Barrier Requirements

10. Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies, and up to 12 months, and potentially longer, depending on treatment and study arm
11. Male participants must refrain from sperm donation while on-study and for 12 months after receiving AZD0120 infusion or until CAR-T cell DNA is no longer detectable by PCR, whichever is later.

Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has a known active, or prior history of CNS involvement or exhibits clinical signs of meningeal involvement of MM.
2. Has primary amyloidosis, active plasma cell leukaemia (presence of ≥ 5% of circulating plasma cells on a conventional peripheral blood

smear) at time of screening, Waldenstrom macroglobulinemia or Polyneuropathy Organomegaly Endocrinopathy M-protein and Skin (POEMS) syndrome.

3. Has primary refractory MM (failed to generate at least a minimal response to any prior therapy).
4. Has significant neurological or psychiatric condition (active or history of) including but not limited to severe brain injury, dementia, cerebellar disease, Parkinson's disease, clinical evidence of dementia or altered mental status, or stroke, intracranial haemorrhage, or seizure within 6 months before signing ICF. Participants with existing stable, mild neurological conditions that have not progressed in the last 6 months (eg, essential tremor) may be considered eligible at the Investigator's discretion, following appropriate neurological consultation.
5. Has any other significant medical condition (including neurological or psychiatric) which, in the opinion of the Investigator, places the participant at an unacceptable risk for treatment-related complications, could interfere with the successful or safe delivery of therapy, or could interfere with evaluation of study intervention or interpretation of participant safety or study results. These include but are not limited to:
   - Serious active or uncontrolled infection
   - Requirement of supplemental oxygen to maintain oxygen saturation
   - Active autoimmune disease or a history of autoimmune disease within 2 years
   - Inflammatory bowel disease (IBD) requiring treatment within the past 5 years or other clinically significant gastrointestinal condition
6. Has ongoing toxicity from previous anticancer therapy that has not resolved to baseline levels or to Grade 1 or less, with the exception of alopecia.
7. Has a history of a prior non-haematologic malignancy unless the participant has been disease-free with no evidence of recurrence for ≥ 2 years. The following are exceptions:
   - Basal cell carcinoma of the skin that is fully resected
   - Squamous cell carcinoma of the skin that is fully resected
   - Carcinoma in situ of the cervix
   - Carcinoma in situ of the breast
   - Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumour, nodes, metastasis] clinical staging system) or prostate cancer that is curative
8. Has a history of haematologic malignancies, other than MM, regardless of remission status.
9. Positive for any of the following:
   - HIV: Known to be seropositive for HIV (including any history of HIV).
   - Chronic or active hepatitis B: Seropositive for hepatitis B (defined by a positive testfor HBsAg). Participants with resolved infection (ie, HBsAg negative but positive for antibodies to anti-HBc and/or anti-HBs) must be screened using real-time PCR measurement of HBV DNA levels. Those who are PCR positive will be excluded. Exception: Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
   - Active hepatitis C: Hepatitis C infection (defined as anti-HCV antibody positive or HCV RNA positive). For participants with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥ 12 weeks after completion of antiviral therapy. PCR HCV RNA must be undetectable at screening
   - Additional local requirements for the testing for infectious diseases and exclusions of applicable participants should be followed per local regulations.
10. Has clinically significant cardiovascular disease, including but not limited to:
    - Myocardial infarction within 6 months prior to randomisation, or an unstable or uncontrolled disease/condition related to or affecting cardiac function
    - Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities
    - Congestive heart failure class III or IV according to the New York Heart Association standards
    - Impaired cardiac function (LVEF < 45%) as assessed by TTE or MUGA scan performed ≤ 8 weeks before randomisation.
11. Additional exclusion for participants who are planned to receive DKd or DPd as standard therapy in Arm B or as bridging therapy in Arm A: Participant has COPD with a FEV1 < 50% of predicted normal. Note: FEV1 testing is required for participants suspected of having COPD.
12. Additional exclusion for participants who are planned to receive PVd as standard therapy in Arm B or as bridging therapy in Arm A: Participant has peripheral neuropathy Grade 4, Grade 3, Grade 2

Prior/Concomitant Therapy

13. Previously received any BCMA-targeted treatment.
14. Previously received CAR-T or CAR-NK therapy directed at any target.
15. Previously received T-cell engager therapy directed at any target.
16. Previously received allogeneic stem cell transplantation at any time during prior therapy or received ASCT within 12 weeks before randomisation.
17. Received any of the following prior to randomisation:
    - Received any investigational drug within 14 days (or 5 half-lives whichever is shorter)
    - Received any immunomodulatory agent or cereblon E3 ligase modulatory drugs within 7 days, PI therapy within 14 days, monoclonal antibody treatment within 14 days, or other systemic anti-myeloma therapy within 14 days
    - Received radiation therapy within 14 days
18. Received live, attenuated vaccine within 28 days prior to randomisation.
19. Received a cumulative dose of corticosteroids equivalent to ≥ 70 mg of prednisone within the 7 days prior to randomisation (or ≥ 10 mg equivalent prednisone per day).
20. Received major surgery within 28 days prior to randomisation.

Prior/Concurrent Clinical Study Experience

21. Concurrent enrolment in another clinical study (unless the study is observational, or the participant is in the follow-up period of an interventional study).
22. Has a known hypersensitivity or a contraindication to any study intervention (AZD0120, fludarabine, cyclophosphamide, daratumumab, carfilzomib, dexamethasone, pomalidomide, bortezomib, dexamethasone) or their excipients. A participant with known hypersensitivity or contraindication to daratumumab, carfilzomib, pomalidomide, or bortezomib may receive a regimen that does not contain these agents. For example, a participant who has a hypersensitivity or contraindication to pomalidomide may receive DKd or Kd, per Investigator selection.
23. Involvement in the planning and/or conduct of the study (both AstraZeneca staff and/or staff at the study site).
24. Judgement by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
25. Previous randomisation in the present study.
26. For female participants: currently pregnant (confirmed with positive pregnancy test) or who are planning to become pregnant while enrolled in this study or within the required contraception period detailed in inclusion criteria.
27. Female participants should refrain from breastfeeding from randomisation, throughout the study and until at least 12 months after receiving AZD0120 infusion or until CAR T-cell DNA is no longer detectable by PCR, whichever is later. Refer to local prescribing information for further details on lactation and breastfeeding restrictions for daratumumab (during treatment), bortezomib (for at least 2 months after last dose), pomalidomide (during treatment), and carfilzomib (during treatment).
28. For male participants: planning to father a child while enrolled in this study or within the required contraception period detailed in inclusion criteria.

Impact of Clonal Hematopoiesis (CHIP) on Toxicity and Outcomes in Lymphoma and Multiple Myeloma Patients Receiving CAR-T Cell Therapy or T-cell engaging Antibodies

Protocol: CHIP-IMPACTS

Contact: Dr. Christine Chen/Harjot Vohra– **Open for Enrollment**

Inclusion Criteria:

1. Age ≥18 years
2. Diagnosis of lymphoma or multiple myeloma
3. Planned to receive standard of care CAR T-cell therapy or TCE (myeloma patients only) as next line of therapy
4. Provides informed consent for serial blood sampling and clinical data collection

Exclusion Criteria:

1. History of myeloid malignancy (e.g., MDS, AML)
2. Individuals who have previously received CAR-T or T-cell engaging antibody (TCE) therapy.
3. Inadequate baseline blood sample for CHIP mutation will preclude further study participation

PHASE 1B/2A, MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE RECOMMENDED DOSE AND SCHEDULE, AND EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF MEZIGDOMIDE IN COMBINATION WITH ELRANATAMAB IN PARTICIPANTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Protocol Number: CA0571040

Contact: Dr Guido Lancman / Olga Levina– **Enrollment on hold due to SAE-Expected to reopen at the end of November**

Inclusion Criteria

Type of Participant and Target Disease Characteristics

1. Participant with a history of RRMM, and must:
   a) **Phase 1**: Have received 2 to 4 prior lines of anti-myeloma therapy. Participants must have previously received a regimen that included an immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide) and a PI (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination. Participants must have undergone at least 2 complete cycles of treatment unless progressive disease was the best response to the regimen. (Note: One line can contain several phases [eg, induction with or without hematopoietic stem cell transplant (HSCT) and with or without consolidation, and/or with or without maintenance therapy]).
   b) **Phase 2**: Have received 1 to 3 prior lines of anti-myeloma therapy.
      i) Achieved a response of minimal response or better to at least 1 prior anti-myeloma therapy.
      ii) A regimen that included lenalidomide and a PI (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination.
   c) Have documented disease progression by the IMWG Uniform Response Criteria during or after their last anti-myeloma regimen.
   d) Participants must have measurable disease (as determined by local laboratory), including at least 1 of the following criteria:
      i) M-protein quantities ≥ 0.5 g/dL by sPEP
      ii) M-protein quantities ≥ 200 mg/24-hour urine collection by uPEP
      iii) Serum FLC levels > 100 mg/L (milligrams/liter) involved light chain and an abnormal kappa/lambda (κ/λ) ratio in participants without detectable serum or urine M protein
      iv) For participants with IgA myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA level ≥ 0.50 g/dL

2. Participant consents to hospitalization requirements for elranatamab.
3. Participant consents to serial BMAs and/or BMBs during screening, study treatment, and at EOT.
4. Participant has an ECOG PS of 0 to 1.50

Age of Participant

5. Participant must be 18 years of age, inclusive, at the time of signing the ICF.

Reproductive Status

6. The investigator or designee shall counsel individuals of childbearing potential (IOCBP) participants (as defined in APPENDIX 3) and male (as assigned at birth) participants who are sexually active with IOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention present in seminal fluid to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
   a) IOCBP must have 2 negative highly sensitive urine or serum, as required by local regulations, pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). The first pregnancy test must be performed within 10 to 14 days prior to the planned start of mezigdomide and the second pregnancy test must be within 24 hours prior to the start of study intervention. IOCBP must agree and adhere to all testing requirements in APPENDIX 3.
   b) A female (as assigned at birth) is eligible to participate if they are not pregnant or breastfeeding and at least 1 of the following conditions applies:
      i) Is not an IOCBP
      OR
      ii) Is an IOCBP and agree to use, and be able to comply with 2 forms of contraceptive methods including one that is highly effective (with a failure rate of < 1% per year) and one additional effective (barrier) method without interruption, as described in Protocol APPENDIX 3, during the intervention period and for at least 28 days after the last dose of mezigdomide or 115 days after the last dose of elranatamab, whichever is longer, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction while taking mezigdomide, during dose interruption, and for 28 days after the last dose of mezigdomide
      OR
      iii) Is an IOCBP and commits to complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the individual. Periodic abstinence [eg, calendar, symptothermal or post-ovulation methods], withdrawal [coitus interruptus] from heterosexual contact that could lead to pregnancy [based on sex assigned at birth], spermicide only, and lactation amenorrhea method [LAM] are not acceptable methods of contraception), and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction while taking mezigdomide, during dose interruption, and for 28 days after the last dose of mezigdomide.
   c) Male (as assigned at birth) participants will be required to:
      i) Always use a condom (male and female condoms must not be used together) during any sexual activity (eg, vaginal, anal, oral) with a pregnant partner or an IOCBP, even if the participant has undergone a successful vasectomy (i.e., with documented azoospermia 90 days after the procedure) as described in Appendix 3. Male (as assigned at birth) participants should continue to use a condom during the intervention period, during dose interruption, and for at least 28 days after the last dose of mezigdomide or 115 days after the last dose of elranatamab, whichever is longer, and agrees not to donate sperm while taking mezigdomide, during dose interruption, and for 28 days after the last dose of mezigdomide. Note: azoospermic males are not exempt from contraceptive requirements.
      OR
      ii) Practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the individual. Periodic abstinence [eg, calendar, symptothermal or post-ovulation methods], withdrawal [coitus interruptus] from heterosexual contact that could lead to pregnancy [based on sex assigned at birth], spermicide only, and LAM are not acceptable methods of contraception), and agrees not to donate sperm while taking mezigdomide, during dose interruption, and for 28 days after the last dose of mezigdomide.
   d) All participants regardless of reproductive status must agree to refrain from donating blood while taking mezigdomide, during dose interruptions, and for at least 28 days after the last dose of mezigdomide.
   e) All participants must follow all other requirements defined in Protocol APPENDIX 3.

<u>Exclusion Criteria</u>

Medical Conditions

1. Participant with known current or history of CNS involvement of MM.
2. Participant has non-secretory MM, plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, or amyloidosis.
3. Participant cannot tolerate oral medications and/or has gastrointestinal disease (within 3 months of screening) or any gastrointestinal surgery that may significantly alter the absorption of oral study treatment.
4. Ongoing Grade ≥ 2 peripheral sensory or motor neuropathy.
5. History of GBS or GBS variants, or history of any Grade ≥ 3 peripheral motor polyneuropathy.
6. Participant has impaired cardiac function or clinically significant cardiac disease, including any of the following:
   a) LVEF < 45% as determined by ECHO or MUGA scan at screening
   b) Myocardial infarction within 6 months before study treatment, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure New York Heart Association Class III-IV)
   c) Uncontrolled clinically significant cardiac arrhythmia or clinically significant ECG abnormalities

7. Known HIV positive with an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the last year or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if:
   a) Participants are established on ART for at least 4 weeks and have an HIV viral load of < 400 copies/mL prior to enrollment.
   b) Participants continue taking ART as clinically indicated and while enrolled on study.
   c) Participants' CD4 counts and viral load are monitored per SoC by a local health care provider.

Note: HIV-positive participants must be excluded where mandated locally.

8. Participant has known chronic, active HBV/HCV infection. Participants who had HCV but have received an antiviral treatment and show no detectable HCV viral RNA for 6 months are eligible. Participants with no active hepatitis B infection (eg, HBsAg negative, anti-HBc positive) who are under adequate prophylaxis per local SoC against HBV re-activation may be eligible; such participants must be screened using real-time PCR measurement of HBV levels; those who are PCR positive will be excluded. HBV prophylactic medication must not be strong CYP3A modulator. Participants who have received HBV vaccine and are HBsAb positive, HBcAb negative, and HBsAg negative are eligible for study entry.
9. Participant has a history of a VTE within 3 months prior to study entry (eg, deep-vein thrombosis or pulmonary embolism). Participants with VTE occurring > 6 months prior to study entry who require ongoing treatment with chronic therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) are eligible for study entry.
10. Participant has a prior history of malignancies other than MM, except if the participant has been free of the disease for ≥ 3 years or if the participant had 1 of the following malignancies treated with curative intent without known recurrence:
    a) Basal cell carcinoma of the skin
    b) Squamous cell carcinoma of the skin in situ (stage 0)
    c) Carcinoma in situ of the cervix
    d) Carcinoma in situ of the breast
    e) Low-risk prostate cancer in active surveillance; low risk is defined as T1-T2a, Gleason ≤ 6 (Grade Group 1) and prostate-specific antigen ≤ 10 ng/mL (per the National Comprehensive Cancer Network [NCCN] and the European Society of Medical Oncology [ESMO] risk groups) or prostate cancer that has been treated with curative intent
11. Participant has a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, subarachnoid hemorrhage or CNS bleed, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
12. Participant has inadequate pulmonary function as defined as SpO2 < 92% on room air.
13. Participant has active, uncontrolled, bacterial, viral, or fungal infection. Active infections must be resolved at least 21 days prior to enrollment. Treatment with systemic anti-infective agents must be completed at least 28 days prior to enrollment. Prophylactic use of systemic agents is permitted.
14. Lung imaging (eg, chest x-ray or lung CT) and SARS-CoV-2 PCR testing is mandated within 14 days prior to enrollment. Participants with a positive PCR test result within 14 days prior to enrollment or those suspected of having SARS-CoV-2 or evidence of active respiratory infection should be excluded from study enrollment.
15. Participant has any medical condition (eg, the presence of laboratory abnormalities), psychiatric, and/or social reason that places the participant at unacceptable risk or could confound interpretation of the data if he/she were to participate in the study per investigator or the sponsor discretion.

Prior/Concomitant Therapy

16. Inability to comply with restrictions and prohibited treatments as listed in Protocol Section 7.7.
17. Participant received prior therapy with mezigdomide.
18. Participant received prior treatment with TCE.
19. Participant received prior treatment with BCMA-targeting therapy, with the exception of participants who have received autologous BCMA-targeted CAR T-cell therapy > 6 months from the start of study therapy.
20. Participants have received prior allogeneic or autologous CAR T-cell therapy within 6 months, regardless of antigen target.
21. Participant has previously received allogeneic stem cell transplantation at any time or received autologous stem cell transplantation within 12 weeks of initiating study treatment.
22. Participant had prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting study treatment, whichever is shorter. Participants must have recovered from any clinically significant non-hematologic toxicities (i.e., to Grade ≤ 1) of prior systemic anti-cancer directed treatments unless otherwise specified.
23. Participant received any of the following:
    a) Plasmapheresis within the last 28 days of initiating study treatment
    b) Radiation therapy, other than local palliative therapy for myeloma-associated bone lesions, within 14 days of initiating study treatment
    c) Participant had major surgery ≤ 2 weeks prior to starting study treatment. Participants must have recovered from any clinically significant effects of recent surgery.
24. Participant is on chronic systemic immunosuppressive therapy or corticosteroids (eg, prednisone or equivalent exceeding a total of 140 mg over the last 14 days). Intranasal, inhaled, topical, or local corticosteroid injections (eg, intra-articular injection), or steroids as premedication for ISRs (eg, CT scan premedication) are exceptions to this criterion.
25. Concurrent administration of strong CYP3A modulators (see Protocol Section 7.7.1) within 14 days of initiating study treatment.
26. Live vaccines are prohibited within 4 weeks prior to first dose of study drug.
27. Participant is unable or unwilling to undergo protocol-required thromboembolism prophylaxis (see Protocol Section 9.3.10.2).
28. Concurrent administration of proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole) within 7 days or PCABs (eg, vonoprazan) within 2 days prior to initiating study treatment.

Physical and Laboratory Test Findings

29. Evidence of organ dysfunction or any clinically significant deviation from normal in PE, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population, and in addition to the other inclusion/exclusion criteria.
30. Participant has any of the following laboratory values (determined by local lab); qualifying laboratory value must occur at most recent measurement prior to cohort assignment and must be no more than 14 days prior to cohort assignment:
    a) ANC < 1.0 × 109/L (< 1000/ µL) and growth factor support is not allowed within 7 days prior to screening CBC (14 days if pegfilgrastim is used)
    b) Platelets < 75 × 109/L (< 75,000/µL) and platelet transfusions are not allowed within 7 days prior to screening CBC
    c) Hemoglobin < 8 g/dL (< 4.9 mmol/L)
    d) Potassium outside normal limits and cannot be corrected with supplements
    e) Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
    f) Serum AST/SGOT and/or ALT/SGPT > 2.5 × ULN
    g) Serum bilirubin > 1.5 × ULN; > 3.0 mg/dL is allowed for participants with documented Gilbert's Syndrome
    h) eGFR < 30 mL/min or requiring dialysis. GFR will be calculated using the MDRD formula or measured in 24-hour urine collection (see Protocol Section 9.2.4), or
        i) INR ≥ 1.5× ULN and/or PTT ≥ 1.5× ULN (only for participants who are not on anticoagulants).

Allergies and Adverse Drug Reactions

31. History of severe allergic or anaphylactic reactions or hypersensitivity to monoclonal antibodies and related excipients, human proteins in the study interventions, or to other IMiDs (eg, lenalidomide, pomalidomide, thalidomide) or CELMoDs (eg, iberdomide).

Other Exclusion Criteria

32. Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)
33. Inability to be venipunctured and/or tolerate venous access

A PHASE 1, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF BMS-986393 IN NOVEL COMBINATIONS IN PARTICIPANTS WITH RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA AND DETERMINE THE RECOMMENDED DOSE FOR EACH ADD-ON INVESTIGATIONAL COMPONENT
Protocol: CA0881005 (JUNO)
Contact: Dr. Christine Chen / Trisha Ramnanan **Enrollment on Hold by Sponsor until the end of November (for Part 2)**

Inclusion Criteria

1) Signed Written Informed Consent
2) Type of Participant and Target Disease Characteristics
    a) Participant has a diagnosis of MM with relapsed and/or refractory disease. Participants must have confirmed progressive disease (as per IMWG criteria) on or within 12 months (measured from the last dose) of completing treatment with the last antimyeloma treatment regimen before study entry or have confirmed progressive disease within 6 months prior to Screening and who are subsequently determined to be refractory or non-responsive to their most recent anti-myeloma treatment regimen, except for participants with cellular therapy (eg, CAR T-cell therapy) as their last treatment, who may enroll beyond 12 months.
    b) **For Part 1** and first 10 participants in each Part 2 arm: Participants must have received at least 3 prior anti-myeloma treatment regimens (note: induction with or without hematopoietic stem cell transplantation [HSCT] and with or without maintenance therapy is considered 1 regimen).
        i) A regimen that included an immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide) and a proteasome inhibitor (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination. Participants must have undergone at least 1 complete cycle of treatment unless progressive disease was the best response to the regimen.
        ii) A regimen that included anti-CD38 (eg, daratumumab), alone or in combination.
        iii) Autologous HSCT, unless the participant was ineligible.
        iv) Prior therapy targeting BCMA and/or GPRC5D is permitted in all arms.
    c) **For Part 2**: Participants must have received at least 1 but not greater than 3 prior antimyeloma treatment regimens, including a proteasome and immunomodulatory agent.
        i) A regimen that included an immunomodulatory agent (eg, thalidomide, lenalidomide, pomalidomide) and a proteasome inhibitor (eg, bortezomib, carfilzomib, ixazomib), either alone or in combination. Participants must have undergone at least 1 complete cycle of treatment unless progressive disease was the best response to the regimen.
        ii) Prior therapy targeting BCMA is permitted in Arms B and C only.
3) Physical and Laboratory Test Findings
    a) Participant has adequate vascular access for leukapheresis.
    b) Participant has Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
    c) Participant must have measurable disease, as determined by the central or local laboratory, defined as meeting at least 1 of the criteria below:
        i) M-protein ≥ 0.5 g/dL by serum protein electrophoresis (sPEP).
        ii) M-protein ≥ 200 mg/24-hour urine collection by urine protein electrophoresis (uPEP).
        iii) Serum free light chain (sFLC): levels of the involved light chain > 100 mg/L and an abnormal kappa/lambda (κ/λ) ratio in

participants without measurable serum or urine M-protein.

iv) Immunoglobulin A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement: a serum IgA level ≥ 0.5 g/dL.

d) Participant has recovery to Grade ≤ 1 or baseline of any non-hematologic toxicities due to previous therapy, except alopecia (any Grade acceptable) and peripheral neuropathy (Grade ≤ 2 acceptable).

e) Adequate organ function as determined by site's local laboratory defined as:

i) Peripheral blood ANC ≥ 1.0 × 109/L without growth factor support within 7 days (14 days if pegfilgrastim), and platelet count ≥ 50 × 109/L without platelet transfusion support within 7 days of screening.

ii) Creatinine clearance (CrCl) ≥ 45 mL/min, measured in 24-hour urine collection or calculated from serum creatinine using the Cockcroft-Gault equation, without the support of hydration within 3 days of renal assessment.

iii) Aspartate aminotransferase/alanine aminotransferase ≤ 3.0× upper limit of normal (ULN) and total bilirubin < 1.5× ULN (or direct bilirubin < 1.5× ULN with documented Gilbert's syndrome).

iv) Prothrombin time (PT) or international normalized ratio (INR), or partial thromboplastin time (PTT) ≤ 1.5×ULN.

v) Adequate pulmonary function, defined as ≤ CTCAE Grade 1 dyspnea and saturated oxygen (SaO2 ≥ 92%) on room air.

vi) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 45% as assessed by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan performed within 8 weeks prior to or during the screening period.

4) Age of Participant

a) Participant must be 18 years of age at the time of signing the ICF.

5) Reproductive Status

a) Female of childbearing potential (FCBP) is a female who:

1) has achieved menarche at some point,

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 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). FCBPs must:

i) Have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. They must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the participant practices complete abstinence* from heterosexual contact.

ii) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a person with an undetected pregnancy.

iii) Female participants must have documented proof that they are not of childbearing potential.

Exclusion Criteria

1) Medical Conditions

a) Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the investigator; or unwillingness or inability to follow the procedures required in the protocol.

b) Any condition that confounds the ability to interpret data from the study.

c) Known active or history of central nervous system (CNS) involvement of MM.

d) Active or history of plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, or clinically significant amyloidosis.

e) Active autoimmune disease requiring immunosuppressive therapy.

f) Prior history of malignancies, other than MM, unless the participant has been free of the disease for ≥ 2 years except for the following non-invasive malignancies:

i) Basal or squamous cell carcinoma of the skin

ii) Carcinoma in situ of the cervix or breast

iii) Incidental histologic finding of prostate cancer (T1a or T1b using the TNM (tumor, nodes, metastasis) clinical staging system or prostate cancer that is curative

iv) Other completely resected Stage 1 solid tumor with low risk for recurrence

g) Active hepatitis B, hepatitis C, or any evidence of human immunodeficiency virus (HIV) infection at the time of Screening.

h) Participant has uncontrolled or active systemic fungal, bacterial, viral, or other infection despite appropriate anti-infective treatment at the time of leukapheresis.

i) Participant has impaired cardiac function or clinically significant cardiac disease, including any of the following:

i) A history of any 1 of the following cardiovascular conditions within 6 months prior to screening: Class III or IV heart failure as defined by the New York Heart Association, myocardial infarction, unstable angina, angioplasty or stenting, or other clinically significant cardiac disease.

ii) Uncontrolled clinically significant cardiac arrhythmia or clinically significant ECG abnormalities.

j) Participant cannot tolerate oral medications and/or has gastrointestinal disease that may significantly alter the absorption of oral study treatment.

k) Participant has a history or presence of clinically significant CNS pathology such as seizure disorder, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, or cerebellar disease, or presence of clinically active psychosis.

l) Participant has deep vein thrombosis or pulmonary embolism (non-infusion lineassociated) within 3 months prior to leukapheresis. Participants with venous thromboembolism (VTE) occurring > 3 months prior to leukapheresis who require ongoing treatment with chronic therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) are eligible for study

entry.

m) Participant has a history of Grade ≥ 2 hemorrhage within 30 days of Screening

n) Participant has received any live vaccines against infectious disease within 8 weeks before BMS-986393 administration. Participant has received an approved or authorized SARS CoV-2 vaccine within 14 days prior to leukapheresis or initiation of LD chemotherapy. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed at least 14 days prior to leukapheresis when feasible and when a delay in leukapheresis would not put the study participant at risk.

o) Participant in other interventional trial, including SARS-CoV-2 non-vaccine trials. If previously in another interventional trial, the participant may not have leukapheresis until the washout period of the investigational agent is achieved ≥ 28 days, or 5 half-lives, whichever is shorter (minimum 14 days).

2) Reproductive Status

a) FCBP who is pregnant, nursing (lactating), or breastfeeding, or who intends to become pregnant during participation in the study.

3) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy.

b) Participant is unable or unwilling to undergo protocol-required thromboembolism prophylaxis.

c) Arm B: Concurrent administration of proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole) including within 14 days prior to initiating mezigdomide.

d) Participant received prior therapy with alnuctamab (Arm A), mezigdomide (Arm B), or iberdomide (Arm C).

e) Arm B and Arm C: Concurrent administration of strong cytochrome P450 (CYP) 3A modulators within 14 days of initiating mezigdomide or iberdomide.

f) Participant has received prior treatment for MM with the following therapies, within the specified period:

i) Bendamustine within 6 months before leukapheresis

ii) Therapeutic doses of corticosteroids (defined as > 10 mg/day prednisone or equivalent) within 14 days before leukapheresis. Physiologic replacement, topical, intranasal, and inhaled steroids are permitted.

iii) Approved anti-MM antibody (eg, daratumumab) within 14 days before leukapheresis

iv) Any other systemic therapy approved for the treatment of MM within 14 days before leukapheresis, except T cell engaging agents, which are within 28 days

v) Any experimental biologics or any other therapy within 28 days or 5 half-lives before leukapheresis, whichever is shorter (minimum 14 days)

vi) Autologous HSCT (i.e., day of hematopoietic stem cell infusion) within 9 months before leukapheresis

vii) Allogeneic HSCT (i.e., day of hematopoietic stem cell infusion) within 12 months before leukapheresis, or has ongoing symptoms or treatment for chronic graft-versus-host disease (GVHD)

viii) Prior CAR T cell therapy administered within 3 months before leukapheresis

ix) Immunosuppressive therapies within 4 weeks before leukapheresis (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, immunosuppressive antibodies such as anti-TNF, anti-IL6, or anti-IL6R)

x) Donor lymphocyte infusions within 6 weeks before leukapheresis

xi) Plasmapheresis within 14 days before leukapheresis

xii) Radiation that includes a large bone marrow field such as the pelvis or sternum within 14 days before leukapheresis

4) Allergies and Adverse Drug Reactions

a) History of allergy to fludarabine or cyclophosphamide (for participants receiving fludarabine/cyclophosphamide LDC) and bendamustine (for participants receiving bendamustine LDC).

b) History of allergy to monoclonal antibodies and related excipients (eg, tocilizumab) or known components of BMS-986393.

c) Arm B and Arm C: history of severe or clinically significant allergy to other IMiDs (eg, lenalidomide, pomalidomide, thalidomide) or CELMoDs (eg, iberdomide).

AN OPEN-LABEL, MULTICENTER, PHASE Ib TRIAL EVALUATING THE SAFETY, PHARMACOKINETICS, AND ACTIVITY OF CEVOSTAMAB AS MONOTHERAPY AND CEVOSTAMAB PLUS POMALIDOMIDE AND DEXAMETHASONE OR CEVOSTAMAB PLUS DARATUMUMAB AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (CAMMA 1)

Protocol Number: GO42552

Contact: Dr. Suzanne Trudel/ Trisha Ramnanan – Open Enrollment – Arm B- Cohort B4E (Cevos+Pd) only

Inclusion Criteria (All Arms):

Patients must meet the following criteria for study entry:

- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, including study procedures and collecting of bone marrow biopsy and aspirate samples,
- Life expectancy of at least 12 weeks with ECOG Performance Status of 0 or 1
- Resolution of adverse events from prior anti-cancer therapy to Grade ≤ 1, with the following exceptions: Any grade alopecia is allowed.
- Measurable disease defined as at least one of the following
- Serum M-protein ≥ 0.5 g/dL (≥5 g/L); Urine M-protein ≥ 200 mg/24 hr; SFLC assay: Involved SFLCs ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal SFLC ratio (< 0.26 or > 1.65)
- Laboratory values as follows:
- Hepatic function

a) AST and ALT ≤ 2.5 x ULN
b) Total bilirubin ≤ 1.5 x ULN
Patients with a documented history of Gilbert syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible if total bilirubin ≤ 3.0 x ULN.

- Hematologic function (requirement prior to first dose of study treatment)
  a) Platelet count ≥ 75,000/mm^3 without transfusion within 7 days prior to first dose
  b) ANC ≥ 1000/mm3
  c) Total hemoglobin ≥ 8 g/dL
  Note: Patients may receive supportive care (e.g., blood transfusion, G-CSF, etc.) except for platelet transfusions as detailed above to meet hematologic function eligibility criteria.
  d) Creatinine ≤ 2.0 mg/dL and creatinine clearance (CrCl) ≥ 30 mL/min (either calculated using modified Cockcroft-Gault equation [see Appendix 13] or per 24-hour urine collection)
  e) Serum calcium (corrected for albumin) level ≤ 11.5 mg/dL (treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to Grade ≤ 1 with standard treatment)

Additional Arm B-Specific Inclusion Criteria:

For Cohort B4E (Cevostamab/POM/DEX): Patients with R/R MM who have received one to four lines of prior therapy that included at least two consecutive cycles of the following:

- Anti-CD38 therapy, Lenalidomide and PI

and received either:

- Prior BCMA-directed CAR T cell or BCMA-ADC therapy
- Only one prior line of CAR T-cell therapy or BCMA-ADC therapy in any prior treatment line is allowed.
- At least 6 months must have elapsed since the CAR T-cell administration or 3 months have elapsed since the last administration of BCMA-ADC therapy before first dose of study treatment.
- Patient must have documented clinical response of VGPR or better under prior CAR T-cell or BCMA-ADC therapy.
- Patient must have received a commercially available BCMA-ADC product or CAR T-cell product or an investigational CAR T agent administered at the determined RP2D.

For Cohort B2S, B1E, B3E, B4E, and additional cohorts: Prior pomalidomide exposure is allowed, provided patients are not refractory to pomalidomide. Refractory means that the patients did not achieve at least a PR to most recent therapy with pomalidomide or if their disease relapsed within 60 days of the last dose of pomalidomide treatment.

The risk minimization plan should be followed by patients using pomalidomide.

- Agreement to avoid donating blood or breast feeding during the treatment period (including treatment interruptions) and for at least 28 days after the last dose of pomalidomide
- For **women of childbearing potential**: agreement to use two reliable methods of contraception or practice complete abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.
- **For men:** agreement to remain completely abstinent (refrain from heterosexual intercourse; True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject.
  - To refrain from donating sperm and blood during this same period.
  - If a pregnancy or positive pregnancy test occurs in the partner of a male patient while taking pomalidomide, the study investigator must be notified immediately.

Exclusion Criteria (All Arms):

Patients who meet any of the following criteria will be excluded from study entry:

- Prior treatment with cevostamab or another agent targeting FcRH5
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the last dose of cevostamab or within 3 months after the last dose of tocilizumab (if applicable)
- Prior use of any monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate as anti-cancer therapy within 4 weeks before first study treatment, except for the use of non-myeloma therapy (e.g., denosumab for hypercalcemia is allowed).
- 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 study treatment
- Known treatment-related, immune-mediated adverse events associated with prior checkpoint inhibitors as follows:
- Prior PD-L1/PD-1 or CTLA-4 inhibitor: Grade ≥ 3 adverse events with the exception of Grade 3 endocrinopathy managed with replacement therapy
  - Grade 1-2 adverse events that did not resolve to baseline after treatment discontinuation
- Treatment with radiotherapy within 4 weeks (systemic radiation) or 14 days (focal radiation) prior to first study treatment
- Treatment with any chemotherapeutic agent or other anti-cancer agent (investigational or otherwise) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to first study treatment
- Autologous SCT within 100 days prior to first study treatment; Prior allogeneic SCT
- Circulating plasma cell count exceeding 500/µL or 5% of the peripheral blood white cells; Prior solid organ transplantation
- 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, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 18 for a more comprehensive list of autoimmune diseases and immune deficiencies)

- Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
- History of confirmed progressive multifocal leukoencephalopathy; History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- Known history of amyloidosis (e.g., positive Congo Red stain or equivalent in tissue biopsy)
- Lesions in proximity of vital organs that may develop sudden decompensation/deterioration in the setting of a tumor flare
- History of other malignancy within 2 years prior to screening, except those with negligible risk of metastasis or death (e.g., expected 5-year OS ≥ 90%), such as ductal carcinoma in situ not requiring chemotherapy, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, low-grade, localized prostate cancer (Gleason score ≤7) not requiring treatment or appropriately treated Stage I uterine cancer.
- Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM; 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.
- 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.
- Significant cardiovascular disease (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, uncontrolled arrhythmias, or unstable angina) that may limit a patient's ability to adequately respond to a CRS event.
- Additionally, patients enrolling to Arm B must not have a history of myocardial infarction within the last 12 months.
- Known history of Grade ≥3 CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) with prior bispecific therapies; Known history of HLH or IEC-HS; Symptomatic active pulmonary disease or requiring supplemental oxygen; 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 antimicrobials where the last dose of IV antimicrobial was given within 14 days prior to first study treatment
- Active symptomatic COVID-19 infection at study enrollment or requiring treatment with IV antiviral where the last dose of IV antiviral treatment was given within 14 days prior to first study treatment. Patients with active COVID-19 infection must have clinical recovery and two negative antigen tests at least 24 hours apart prior to first study treatment.
- Positive and quantifiable EBV PCR or CMV PCR prior to first study treatment; Known or suspected chronic active EBV infection; Positive serologic or PCR test results for acute or chronic HBV infection [Guidelines for diagnosing chronic active EBV infection are provided by Okano et al. (2005)].
- Recent major surgery within 4 weeks prior to first study treatment
- Patients whose HBV infection status cannot be determined by serologic test results (www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf) must be negative for HBV by PCR to be eligible for study participation.
- Acute or chronic HCV infection; Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.
- Known history of HIV seropositivity; Administration of a live, attenuated vaccine within 4 weeks before first study treatment or anticipation that such a live attenuated vaccine will be required during the study
- Influenza vaccination may be given during influenza season (approximately October to May in the Northern Hemisphere; approximately May to October in the Southern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist) at any time during the study treatment period.
- COVID-19 vaccines, may be given in accordance with the approved/authorized vaccine label and official/local immunization guidance. COVID-19 vaccines must not be administered within 1 week before first study treatment, or during pre-phase (Arm B) or Cycle 1 (Arms A and C).
- Treatment with 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 study treatment
    - The use of inhaled corticosteroids is permitted; The use of mineralocorticoids for management of orthostatic hypotension is permitted.
    - The use of physiologic doses of corticosteroids for management of adrenal insufficiency is permitted.
- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study, or which could affect compliance with the protocol or interpretation of results.

Additional Arm B-Specific Exclusion Criteria:

- Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential.
- Women of childbearing potential must have two negative pregnancy test results prior to initiation of study treatment. The first pregnancy test must be performed between 10 and 14 days prior and the second test must be performed within 24 hours prior to the first dose of study treatment. The study investigator must verify that both pregnancy tests are negative before the patient may initiate study treatment.
- Significant cardiovascular disease (such as, but not limited to, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 12 months, uncontrolled arrhythmias, or unstable angina)
- History of erythema multiforme, Grade ≥ 3 rash, blistering, or severe hypersensitivity to prior treatment with immunomodulatory drugs such as thalidomide, lenalidomide, or pomalidomide

- Inability to tolerate thromboprophylaxis, or contraindication to thromboprophylaxis
- GI disease that might significantly alter absorption of oral drugs; Known history of interstitial lung disease

For Cohort B4E:

- For patients with prior exposure to BCMA-directed CAR T or BCMA-ADC therapy: prior exposure to any prior BMCA-directed therapy other than BCMA-directed CAR T therapy or BCMA-ADC therapy (i.e., BCMA-ADC or BCMA-directed CAR T therapy and anti BCMA-CD3 bispecific antibody therapy)
- Bridging therapy with a GPRC5D-directed bispecific antibody (up to 2 treatment cycles) administered during the CAR T-cell manufacturing period is permitted and is not considered a new line of therapy. The participant must not have developed progression on bridging therapy.

MULTIPLE MYELOMA TRIALS - FOURTH LINE OF THERAPY

AN OPEN-LABEL PHASE 1 STUDY TO EVALUATE PF-07994525 IN PARTICIPANTS WITH ADVANCED MALIGNANCIES
Protocol Number: C6331001
Contact: Dr. Suzanne Trudel / Olga Levina – Open Enrollment

Inclusion Criteria

Participants eligible for inclusion in this study must be relapsed or refractory to existing treatment. The definition of relapsed/refractory disease is as follows:
The following disease-specific criteria must be met according to the WHO classification of hematological malignancies
1. Type of Participant and Disease Characteristics:
-Prior diagnosis of MM as defined according to IMWG criteria
-Serum M-protein ≥0.5 g/dl by serum protein electrophoresis (SPEP)
-Urinary M-protein excretion ≥200mg/24 hours by urine protein electrophoresis (UPEP)
-Serum immunoglobulin FLC ≥10 mg/dl (≥100 mg/dl) and abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)
-Participants must be refractory to, or intolerant to, all established therapies known to provide clinical benefit in Multiple myeloma that are an appropriate therapeutic option, in the judgement of the investigator. A minimum Of 3 prior lines of therapy are required.
-ECOG Performance status 0-1
2. **Informed Consent:**
- Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at the time of informed consent.
- Provide documented informed consent and willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations and other study procedures
3. Other Inclusion Criteria:
Resolved acute effects of any prior therapy to either baseline severity or CTCAE Grade ≤1, with the exception of AEs not constituting a safety risk (e.g, alopecia) in the investigator's judgement and agreed to by the Sponsor
4. Male Participants:
Male participants are eligible to participate if they agree to the following requirements during the study intervention period and for at least 95 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) plus an additional 90 days (a spermatogenesis cycle):
-Refrain from donating sperm PLUS either:
-Be persistently abstinent from heterosexual intercourse and agree to remain abstinent OR
-Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person
-The participant should be advised of the benefit for an IOCBP partner using a highly effective method of contraception with a failure rate of <1% per year
5. Female Participants
A participant is eligible to participate if the participant (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for 28 days after the last dose of PF-07994525 and (c) at least 1 of the following conditions applies:
-Is not an IOCBP (see definition in Section 10.4.3) OR
-Is an IOCBP and agrees to use a contraceptive method that is highly effective (failure rate of <1% per year) with low user dependency during the intervention period and for at least for 28 days after the last dose of PF-07994525, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should confirm the use of the appropriate contraceptive method in relationship to the first dose of study intervention OR
-Is an IOCBP and agrees to use a highly effective (failure rate of <1% per year) user dependent method of contraception during the intervention period and for at least for 28 days after the last dose of PF-07994525, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to use of the highly effective method above (with the exception of abstinence), the participant agrees to concurrently use an effective barrier method. The investigator should confirm the use of the appropriate contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of an individual with an early undetected pregnancy.

Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Active plasma cell leukemia, Smoldering MM, Waldenstroms macroglobulinemia, Amyloidosis, POEMS syndrome

All Participants (unless otherwise specified):

2. Autologous stem cell transplant within 12 weeks prior to enrollment or active GVHD.
3. History of allogeneic stem cell transplant
4. Any medical or psychiatric condition including recent (within the past year), or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgement, make the participant inappropriate for the study.
5. Active or suspected cerebral/meningeal disease related to the underlying malignancy.
6. History of another malignancy within 3 years before the first dose of study intervention, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g, 5 year OS ≥ 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
7. Documented history of any of the following within 6 months prior to the first dose of study intervention:
    a. Acute myocardial infarction or acute coronary syndromes (e.g, unstable angina, coronary artery bypass, coronary angioplasty or stenting, symptomatic pericardial effusion)
    b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia). Participants on appropriate therapy with stable symptoms for >6 months may be eligible following consultation with the sponsor
    c. Thromboembolic or cerebrovascular events (eg transient ischemic attack, cerebrovascular accident, deep vein, thrombosis or pulmonary embolism)
    d. Symptomatic congestive heart failure (CHF), New York Heart Association Class III-IV)
    e. Prolonged QT syndrome (or QTcF >470 msec at screening per local evaluation); If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 ms, the participant may be considered eligible.
    f. Pulmonary compromise requiring continuous oxygen support.
8. Other surgical (including major surgery within 14 days or minor surgery within 7days prior to first dose of study intervention). Participants must have recovered adequately from any AEs or complications from the surgery prior to starting study drug.
9. Active clinically significant Grade ≥3 GI disease (including but not limited to inflammatory GI disease [eg, ulcerative colitis, Crohn's disease, inflammatory bowel disease, immune-mediated colitis], previous gastric resection, ongoing gastroparesis or lap band surgery that may increase the risk associated with study participation or study treatment administration.
10. Other serious or clinically significant underlying medical condition that, in the opinion of the investigator, would impair the participant's ability to receive or tolerate the planned treatment and follow-up.

Prior/Concomitant Therapy

11. Live or live-attenuated vaccines received within 30 days prior to the first dose of study intervention
12. A condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone or equivalent to ≥140 mg of prednisone within the 14 day period) or other immunosuppressive medications within 2 weeks of the first dose of study intervention. Inhaled, topical, intraocular, intranasal, and intra-articular steroids are permitted in the absence of active immune disease.
13. Use of any prohibited concomitant medication(s) within 14 days of the first dose of study intervention, unless otherwise stated, or unwillingness or inability to use a required concomitant medication(s).

Prior/Concurrent Clinical Study Experience:

14. Previous administration with an investigational product (e.g, drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half lives preceding the first dose of study intervention used in this study (whichever is longer). A participant may be eligible if they are in the follow-up phase of an investigational study if they meet the criterion for time elapsed from previous administration of investigational product.
15. Chemotherapy, radiotherapy, biologics, and/or other anti-cancer treatment that is not completed 4 weeks prior to first dose of study intervention, or within 2 weeks prior to first dose of study intervention if the underlying disease has progressed on treatment.

Diagnostic Assessment:

16. **Hepatic function defined by the following:**
    a. Total bilirubin >1.5xULN (>3xULN for participants with documented Gilbert's syndrome or documented hepatic tumor involvement);
    b. AST and ALT >2.5xULN or>5xULN if AST/ALT elevation is attributed to underlying disease or concomitant medication
17. Renal function as defined by an estimated BSA adjusted glomerular filtration rate (eGFR) as calculated using 2021 CKD-EPI equation. eGFR < 45 mL/min (Part 1) and eGFR <30 mL/min (Part 2), unless otherwise specified by the Sponsor. BSA adjusted eGFR will be calculated by multiplying the patient's eGFR by the patient's BSA and dividing by 1.73 to determine eligibility. A 24 hour urine collection for CrCl may also be used in equivocal cases.
18. BM function characterized by the following:
    a. ANC <1000/ μ L (use of granulocyte-colony stimulating factors is permitted if completed at least 14 days prior to planned start of dosing)

b. Platelets <50,000/ μ L (transfusion support is permitted if completed at least 14 days prior to planned start of dosing) and
c. Hemoglobin <8g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing)

19. Corrected serum calcium >14 mg/dL (>3.5 mmol/L) or free ionized calcium >6.5 mg/dL (>1.6 mmol/L)
20. Any active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) COVID-19, HBV, HCV, known HIV or AIDS related illness, unless deemed not clinically significant by the investigator (eg, onychomycosis). Routine antimicrobial prophylaxis is permitted(assuming no drug interaction potential). Active infections must be resolved at least 14 days prior to enrollment. Comments regarding specific infections are listed:
    a. Known acquired immunodeficiency syndrome (AIDS)-related illness or HIV disease
    b. Known to be positive for hepatitis B by surface antigen expression and/or hepatitis B core antibody; participants with a negative PCR assay are permitted with appropriate antiviral prophylaxis (assuming no drug interaction potential)
    c. Known to have active hepatitis C infection (positive by PCR or on antiviral therapy for hepatitis C within the last 6 months). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks prior to the first dose of study intervention.

Other Exclusions

21. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

PHASE I DOSE ESCALATION STUDY OF LIPOSOMAL CURCUMIN IN RELAPSED REFRACTORY MULTIPLE MYELOMA
Protocol Number: LipoCurc
Contact: Dr. Guido Lancman /Olga Levina – **Enrollment on Hold by Sponsor**

Inclusion Criteria

1. Is the patient able to understand and voluntarily sign an informed consent form (ICF)?
2. Is the patient ≥ 18 years of age at the time of signing the ICF?
3. Is the patient able to adhere to the study visit schedule and other protocol requirements?
4. Does the patient have documented diagnosis of relapsed and/or refractory MM with: (check one)
    a. 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) OR Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
    b. Previously undergone treatment with an immunomodulatory drug (lenalidomide or pomalidomide), a proteasome inhibitor (bortezomib, ixazomib, carfilzomib) and an anti-CD38 drug (daratumumab or isatuximab), and exhausted available standard of care options.
5. Does the patient have a history of autologous stem cell transplant provided the transplant was > 12 weeks prior to study enrolment with no active infection?
6. Does the patient have a measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug)?
    a. Serum M-protein ≥ 0.5 g/dl (≥ 5 g/l)
    b. Urine M-protein ≥ 200 mg/24 h
    c. Serum free light chains (FLC) assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) and an abnormal serum free light chain ratio (< 0.26 or > 1.65)
    d. If the serum protein electrophoresis is unreliable for routine M-protein measurement, quantitative immunoglobulin levels on nephelometry or turbidometry will be followed. N/A
7. Does the patient have Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2? ECOG = ____
8. If patient is of childbearing potential, does serum pregnancy test have a negative result?
    Patient commits to continued abstinence from heterosexual intercourse Or
    Patient abides by birth control requirements as described in protocol
9. If the patient is a man with a female partner of childbearing potential, does patient agree to use effective contraception from the time of first dose of study until 90 days after the last dose of study treatment to allow for clearance of any altered sperm.
10. Is the patient able to take oral medications?
11. Does all prior treatment-related toxicities [defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5] ≤ Grade 1 at the time of enrollment except for alopecia or be deemed to be irreversible (for example, steroid induced cataracts or peripheral neuropathy).
12. Are the following laboratory results met within 7 days of first study drug administration?
    a. Absolute neutrophil count (ANC) >1000 cells/dL (1.0 x 10^9/L). Growth factors cannot be given within 7 days of study drug administration.
    b. Serum AST and ALT ≤ 3 x upper limit of normal (ULN).
    c. Creatinine clearance ≥ 20 mL/min either directly measured via 24-hour urine collection or calculated using Cockroft-Gault
    d. Platelet count ≥ 50 x 109 /L. For subjects with > 50% myeloma involvement in the marrow, a platelet count of ≥30 x 109 /L is allowed. Subjects may not have received a platelet transfusion within 72 hours prior to the platelet count used for eligibility
    e. Hemoglobin ≥ 80 g/L. subject may receive red blood cell (RBC) transfusions in accordance with institutional guidelines to meet this criterion. Subjects may not have received a red blood cell (RBC) transfusion within 72 hours prior to the hemoglobin result used for eligibility; use of growth factors is allowed.
    f. Total bilirubin ≤ 1.5 x ULN, unless known to have Gilbert's disease.
    g. Albumin ≥ 2.0 g/dL (20 g/L).
    h. Calcium <1.2xULN.

Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from enrolment in the study:

1. Known history of clinically active amyloidosis, POEMS syndrome, or patients with plasma cell leukemia defined as circulating plasma cell count exceeding 500/uL or 5% of the peripheral blood white cells 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 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. The following are allowed:
   a. Adequately treated in situ carcinoma of the cervix uteri or the breast;
   b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
   c. In situ malignancy;
   d. Prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen levels off treatment;
   e. Previous malignancy with no evidence of disease confirmed and surgically resected (or treated with other modalities) with curative intent and unlikely to impact survival during the duration of the study.
5. Evidence of cardiovascular risk including any of the following:
   a. QTc interval ≥ 470 m secs.
   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
   e. Uncontrolled hypertension
   f. Ejection fraction <40% as determined by echocardiogram
6. Active human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Presence of hepatitis B surface antigen (HBsAg) or positive HBV PCR test at screening or within 3 months prior to first dose of study treatment. Participants with positive hepatitis B core antibody (HBcAb) can be enrolled, only if confirmatory negative Hepatitis B DNA is obtained AND patient is on hepatitis B prophylaxis (e.g. tenofovir or entecavir) before first dose of study drugs. Presence of isolated Hep B surface antibody (HBsAb) indicating previous vaccination will not exclude a participant. 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. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing. Patients with HIV with detectable viral load or with AIDS-defining features or illnesses will be excluded.
7. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).
8. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease).
9. Current or past history of clinically significant CNS disease, such as stroke, epilepsy, CNS vasculitis, neurodegenerative disease, or CNS involvement by MM
   - Note that 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.
   - Note that 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.
10. Known active infection requiring treatment.
11. Receiving systemic immunosuppressive medications (including, but not limited to, azathioprine, methotrexate, and anti-tumor necrosis factor agents), with the exception of corticosteroid treatment <10mg/day prednisone or equivalent within 2 weeks. Inhaled corticosteroids for respiratory diseases are allowed.
12. Evidence of active mucosal or internal bleeding.
13. Significant urinary outflow obstruction
14. Radiotherapy or systemic therapy (standard or biologic anticancer agent) within 14 days of initiation of study drug treatment.
15. Use of an investigational drug within 21 days or five half-lives, whichever is shorter, preceding the first dose of study drug.
16. Major surgery within 28 days
17. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to liposomal curcumin.

A PHASE 1B/2 DOSE-ESCALATION AND COHORT-EXPANSION STUDY TO DETERMINE THE SAFETY AND EFFICACY OF BGB-11417 AS MONOTHERAPY, IN COMBINATION WITH DEXAMETHASONE, DEXAMETHASONE/CARFILZOMIB, DEXAMETHASONE/DARATUMUMAB, AND DEXAMETHASONE/POMALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND t(11;14)

Protocol Number: BGB-11417-105

Contact: Dr. Christine Chen / Olga Levina – **Open for Enrollment (ONLY cohorts 6 & 7)-Part 2**

Inclusion Criteria

1. ≥ 18 years old
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
3. A confirmed diagnosis of multiple myeloma (must have an M-component in serum and/or urine)
4. Measurable disease defined as:
   a. M-spike ≥ 500 mg/dL, or
   b. Urine protein M-spike of ≥ 200 mg/day, or
   c. Serum free light chains ≥ 10 mg/dL, and an abnormal κ:λ ratio
5. Participant has documented relapsed or progressive MM on or after any regimen or who are refractory to the most recent line of therapy.
   Note:
   - Relapsed MM is defined as previously treated MM that progresses and requires initiation of salvage therapy but does not meet the criteria for refractory MM.
   - Refractory MM is defined as disease that is nonresponsive (failure to achieve minimal response or development of progressive disease) while on primary or salvage therapy or progresses within 60 days of last therapy.

   a. Patients in Part 1 should have relapsed or progressive disease and have had≥ 3 prior lines of therapy including a proteasome inhibitor, IMiD agent, and an anti-CD38 monoclonal antibody.
   b. Patients in Part 2 (Cohorts 1 and 2):
      i. Patients should have relapsed or progressive disease and have had ≥ 3 prior lines of therapy including a proteasome inhibitor, an IMiD, and an anti-CD38 monoclonal antibody.
   c. **Part 2 (Cohorts 3-7):**
      i. Patients should have relapsed or progressive disease and have had ≥ 1 prior line of therapy.
      ii. Patients must have been exposed to a combination therapy containing an anti-CD38 monoclonal antibody.
      iii. Prior treatment with carfilzomib is allowed, but the patient must not be considered carfilzomib refractory by the investigator and not have received carfilzomib within the past 6 months.
6. Positivity for t(11;14) by a validated fluorescence in situ hybridization (FISH) assay in a predefined central laboratory:
   a. A fresh bone marrow aspirate sample must be collected at screening and sent to central laboratory for t(11;14) FISH testing.
   b. Enrollment requires centrally confirmed t(11;14) results.
7. Either > 100 days after autologous stem cell transplant or ≥ 6 months after allogeneic transplant and without active graft-versus-host disease (ie, requiring treatment)
8. At least 2 months should have elapsed after previous chimeric antigen receptor T-cell therapy
9. Adequate organ function defined as:
   a. Hemoglobin ≥ 8.0 g/dL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
   b. Platelet count ≥ 75,000/µL within 7 days before first dose of study treatment, independent of growth factor support and transfusions
   c. Absolute neutrophil count (ANC) ≥ 1000/mm^3 [ANC = (% of segmented neutrophils + % of segmented bands) x total WBC count] within 7 days before first dose of study treatment
      NOTE: The screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim (or other pegylated myeloid growth factors) and at least 7 days following the most recent administration of filgrastim or other myeloid growth factors
   d. ALT and AST ≤ 3 x upper limit of normal (ULN) and total bilirubin ≤ 2.0 x ULN
   e. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 45 mL/min/1.73 m^2 calculated by the MDRD-6 formula.
      Web-based calculator available at:
      https://qxmd.com/calculate/calculator_141/mdrd-egfr-6-variable
10. Women of childbearing potential must have a negative serum pregnancy test ≤ 7 days before the first dose of study drug(s). In addition, they must use a highly effective method of birth control initiated before the first dose of study drug(s), for the duration of the study treatment period, and for 90 days after the last dose of sonrotoclax, dexamethasone, daratumumab, or pomalidomide, or 180 days after the last dose of carfilzomib, whichever is longer. See Appendix 10 for highly effective methods of birth control and the definition of childbearing
11. Nonsterile men must use a highly effective method of birth control along with barrier contraception for the duration of the study treatment period and for ≥ 90 days after the last dose of study drug. During this same period, they must not donate sperm. Sterile men must use barrier contraception. In addition, partners of these men who could become pregnant should also utilize a highly effective method of birth control. See Appendix 10 for highly effective methods of birth control and the definition of sterile.
12. Life expectancy ≥ 6 months
13. Able to comply with the requirements of the study
14. Ongoing toxicities from prior anticancer therapies should have resolved or decreased to ≤ Grade 1 in severity (except for alopecia)

Exclusion Criteria

1. Participant has any of the following conditions:
   a. Non secretory MM (Serum free light chains < 10 mg/dL)
   b. Solitary plasmacytoma
   c. Active plasma cell leukemia (5% of peripheral white blood cells)
   d. Waldenström macroglobulinemia
   e. Amyloidosis
   f. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome
2. Chronic respiratory disease that requires continuous oxygen and/or respiratory failure requiring assisted ventilation
3. Significant cardiovascular disease, including but not limited to:
   a. Myocardial infarction ≤ 6 months before screening
   b. Ejection fraction ≤ 50%
   c. Unstable angina ≤ 3 months before screening
   d. New York Heart Association Class III or IV congestive heart failure (see Appendix 5)
   e. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
   f. Heart rate-corrected QT interval > 480 milliseconds based on Fridericia's formula
   g. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
   h. Uncontrolled hypertension at screening, defined as systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg by ≥ 2 consecutive measurements
4. Prior therapy with BGB-11417 or other agents inhibiting Bcl-2 activity (eg, venetoclax)
5. Known infection with human immunodeficiency virus (HIV).
6. Serologic status reflecting active viral hepatitis B (HBV) or viral hepatitis C (HCV) infection as follows:
   a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if HBV DNA is undetectable (limitation of sensitivity < 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
   b. Presence of HCV antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (limitation of sensitivity < 15 IU/mL).
7. Major surgery within 4 weeks prior to enrollment.
   Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, or meninges), the surgery is considered major.
8. Acute infections requiring antimicrobial therapy (antibiotic, antifungal, or antiviral) that have not been resolved for > 14 days prior to Cycle 1 Day 1.
9. Need for chronic corticosteroid therapy (> 10 mg prednisone or equivalent daily).
10. Any other medical condition that, in the opinion of the investigator, would adversely affect the participant's participation in the study or will render the administration of study drug(s) hazardous or obscure the interpretation of safety or efficacy results.
11. Psychiatric or cognitive dysfunction precluding active participation with the study protocol.
12. Radiation therapy that could affect bone marrow (eg, encompassing ≥ 5% of total bone marrow).
13. Use of the following substances prior to the first dose of study drug(s):
    a. ≤ 30 days prior to the first dose of study drug(s)
       − Any biologic and/or anti-CD38-based therapy
    b. ≤ 14 days prior to the first dose of study drug(s)
       − Systemic chemotherapy or therapeutic radiation therapy (palliative radiation therapy for bone lesions is acceptable)
    c. ≤ 7 days prior to the first dose of study drug(s)
       − Corticosteroid given with antineoplastic intent
       − Dexamethasone for any indication
       − BTK inhibitor, tyrosine kinase inhibitor, or other targeted small molecule (with 5 half-lives ≥ 7 days) given with antineoplastic intent
14. A history of other active malignancies, including myelodysplastic syndrome, within the past 2 years prior to study entry, with the following exceptions
    a. Adequately treated in situ carcinoma
    b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    c. Prostate cancer ≤ Gleason Grade 6 and with stable prostate-specific antigen levels off treatment
    d. Previous malignancy, > 2 years with no evidence of disease, confined and surgically resected (or treated with other modalities) with curative intent, and unlikely to impact survival during the duration of the study
15. If patient had prior allogeneic stem cell transplant, there is evidence of ongoing graft-versus host disease.
16. Pregnant or lactating women.
17. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedure, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
18. Receiving any treatment with a moderate or strong CYP3A4 inhibitor (≤ 7 days or 5 half-lives) or moderate or strong CYP3A4 inducer (≤ 14 days or 5 half-lives) before first dose of sonrotoclax. See Appendix 6 for guidance on CYP3A inhibitors and inducers.

Note: For patients in the pomalidomide cohort, a mandatory washout period of 7 days must be completed for patients on strong CYP1A2 inhibitors prior to Cycle 1 Day 1.

19. History of hypersensitivity to excipient(s) of sonrotoclax, dexamethasone, carfilzomib, daratumumab, or pomalidomide.
20. Vaccination with a live vaccine ≤ 35 days before first dose of study drug(s).

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed. A non-live COVID-19 vaccine may be administered if recommended per local practice.

A PHASE 1 STUDY OF KTX-1001, AN ORAL, FIRST-IN-CLASS, SELECTIVE, AND POTENT MMSET CATALYTIC INHIBITOR THAT SUPPRESSES H3K36ME2 IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Protocol Number: K36MMSET-001

Contact: Dr. Suzanne Trudel /Trina Wang – Enrollment on hold by Sponsor

Inclusion Criteria

1. Voluntarily provide informed consent prior to initiation of study specific activities
2. ≥18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) score ≤ 1
4. Patients must have a confirmed diagnosis of RRMM (as per IMWG).
   - Patients must have received at least 3 prior lines of therapy as defined by IMWG, including a PI, an IMiD, and an anti-CD38 antibody
   - Patients must have exhausted available therapeutic options that are expected to provide a meaningful clinical benefit, either through disease relapse, treatment refractory disease, intolerance, or refusal of the therapy
   - *For expansion cohorts in Part B only:* Have t(4;14) confirmed by standard of care fluorescence in situ hybridization (FISH) testing or GOF mutation in MMSET confirmed by local sequencing test.
5. Measurable disease, including at least 1 of the following criteria:
   - Serum M protein (detected by serum protein electrophoresis [SPEP]) ≥ 0.50 g/dL
   - For patients with immunoglobulin class A (IgA) myeloma whose disease can only be reliably measured by quantitative immunoglobulin measurement, a serum IgA ≥ 0.50 g/dL (IgA will similarly be used for response)
   - Urine M protein (detected by urine protein electrophoresis [UPEP]) ≥ 200 mg/24 h
   - Serum free light chain (sFLC) involved light chain ≥ 10 mg/dL (100 mg/L) provided sFLC ratio is abnormal
   - ≥ 1 extramedullary lesion on imaging, including ≥ 1 lesion that is ≥ 1 cm in size and able to be followed by imaging assessments (Dose Escalation Only)
   - Bone marrow plasma cells ≥ 10% (Dose Escalation Only)
6. Recovery to Grade ≤ 1 for any nonhematologic toxicities due to prior therapy, excluding alopecia or Grade 2 neuropathy
7. Ability and willingness to adhere to study visit schedule and protocol requirements

Exclusion Criteria

1. Treatment with the following therapies in the specified time period:
   - Radiation, chemotherapy, immunotherapy, or any other anticancer therapy ≤ 2 weeks prior to Cycle 1 Day 1 (C1D1)
   - Cellular therapies (eg, chimeric antigen receptor T cell) ≤ 8 weeks prior to C1D1
   - < 100 days post autologous transplant (prior to first dose)
   - ≤ 6 months post allogenic transplant prior to C1D1 or if > than 6 months from allogenic transplant, no active graft-versus-host disease requiring treatment
   - Major surgery ≤ 4 weeks from C1D1
2. History of or current plasma cell leukemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, and skin changes) syndrome, solitary bone lesion or bone lesions as the only evidence for plasma cell dyscrasia, myelodysplastic syndrome, or a myeloproliferative neoplasm or light chain amyloidosis.
3. Active central nervous system (CNS) disease: patients with previously treated stable CNS disease are eligible
4. Inadequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) < 1000 cells/mm3
   - Platelets (PLT) < 75,000 cells/mm3
   - Hemoglobin < 8 g/dL (may be transfused provided no evidence of active bleeding)
5. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN)
6. Total bilirubin > 1.5 × ULN, > 2 × ULN for patients with documented Gilbert's syndrome
7. Prothrombin time (PT) or partial thromboplastin time (PTT) international normalized ratio (INR) > 1.5 × ULN, OR INR > 1.5 × ULN or within target range if on prophylactic anticoagulation
8. Creatinine clearance < 50 mL/min by Cockcroft-Gault formula
9. Active, ongoing, or uncontrolled systemic viral, bacterial, or fungal infection. Prophylactic medications, antimicrobials or antiretroviral therapies are permitted provided the agents are not prohibited
   - HIV-positive patients with CD4+ T-cell counts < 350 cells/µL or not on a stable antiretroviral regimen for > 4 weeks with a viral load > 400 copies/mL prior to enrollment may not be enrolled
   - Hepatitis C virus (HCV)-positive patients who have not completed curative antiviral treatment and have a quantifiable viral load may not be enrolled
   - Hepatitis B surface antigen (HBs-AG)-positive and hepatitis B core antigen (anti-HBc)-positive patients may be enrolled following a discussion with the Medical Monitor to discuss anti-hepatitis B virus (HBV) prophylaxis. Patients with chronic HBV infection should complete an anti-HBV therapy regimen with follow-up assessment for response and tolerability prior to initiating study medication
10. Use of prohibited medications, including acid reducing agents and strong inhibitors or inducers of CYP3A4, within 14 days or 5 half-lives prior

to starting KTX-1001

11. Uncontrolled thromboembolic events or recent severe hemorrhage that, in the opinion of the Investigator or Medical Monitor would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion
12. Any history of pulmonary embolism or deep vein thrombosis (DVT) within 1 month of enrollment. Therapeutic dosing of anticoagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) is allowed for history of DVT if > 3 months from time of enrollment.
13. Active, unstable cardiovascular function; presence of any of the following:
    - Symptomatic ischemia
    - Uncontrolled clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on antiarrhythmics are excluded; patients with first degree atrioventricular or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded)
    - Congestive heart failure or New York Heart Association Class ≥ 3
    - Myocardial infarction within 3 months prior to C1D1
    - Uncontrolled hypertension
    - QTc > 470 ms
14. Active malignancy not related to myeloma that has required therapy in the last 2 years prior to enrollment or is not in complete remission. Exceptions to these criteria include successfully treated nonmetastatic basal cell or squamous cell skin carcinoma, or prostate cancer that does not require therapy. Other similar malignant conditions may be discussed with and permitted by the Medical Monitor
15. Malabsorption syndrome or other condition affecting oral absorption
16. Men and women of reproductive potential who are unwilling to practice acceptable methods of effective birth control while on study through 6 months (women) or 3 months (men) after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (refraining from heterosexual intercourse; men, women); vasectomy; tubal ligation; or a condom with spermicide (men) in combination with barrier methods, hormonal birth control or intrauterine device (women)
    - Pregnancy, or females planning on becoming pregnant while on study or through 6 months after last study drug administration; or females who are lactating/breast feeding or who plan to breastfeed while on study through 6 months after last study drug administration
    - Male patients must refrain from sperm donation, or attempt to conceive from study drug administration until 3 months after last dose of study drug
17. History or evidence of any other clinically significant disorder, condition, or disease (except for those outlined above) that, in the opinion of the Investigator or Medical Monitor would pose a risk to patient safety or interfere with the study evaluation, procedures or completion, including inability to find alternative concomitant medications that may be potential risk for drug-drug interaction (DDI)

A PHASE 3 RANDOMIZED STUDY COMPARING JNJ-79635322 AND AN ANTI-BCMAXCD3 BISPECIFIC ANTIBODY IN PARTICIPANTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST 3 PRIOR LINES OF THERAPY INCLUDING A PI, AN IMID, AND AN ANTI-CD38 ANTIBODY

Protocol Number: 79635322MMY3001

Contact: Dr. Guido Lancman /Elim Chen – **Open Enrollment**

Inclusion Criteria

1. ≥18 years of age.
2. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
3. Received at least 3 prior lines of antimyeloma therapy including a PI, an IMiD, and an anti-CD38 antibody.
4. Documented evidence of PD or failure to achieve a response (i.e., PR or better) to the last line of therapy based on investigator's determination of response by the IMWG criteria.
5. Have discontinued concurrent use of any other anticancer treatment (including nonpalliative radiotherapy) or investigational agent. Toxicity related to previous anticancer therapy must have resolved to resolved to Grade 1 or better (except alopecia, skin fibrosis or discoloration, dry mouth, endocrinopathy managed with replacement therapy, peripheral neuropathy, and dysgeusia, which must be Grade 2 or better).
6. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 to 2 at screening and Treatment
7. Renal function: Have an eGFR, calculated with the CKD-epi creatinine formula (Section 10.12), of >30 mL/min during the screening period.
8. Hepatic function: Participants are eligible if they have the following laboratory values during the screening period and within 1 day of the start of administration of study treatment:
    - AST and ALT<2.5×ULN
    - Total bilirubin <1.5×ULN
    - Bilirubin in case of known congenital nonhemolytic hyperbilirubinemias such as Gilbert's Syndrome, isolated total bilirubin ≥1.5×ULN with direct bilirubin <1.5×ULN
9. Clinical laboratory values:
    - **Hemoglobin** ≥7.5 g/dL, without use of transfusion or growth factors within 7 days **Platelets** ≥50×109/L (without transfusion support in the prior 7 days)
    - **Absolute Neutrophil Count (ANC)** 1≥0.75×103/µL (prior growth factor support is permitted but must be without support for 7 days for G-CSF or GM-CSF and for 14 days for pegylated G-CSF prior to the laboratory test
    - **Platelets** ≥50×103/µL, without use of transfusion or growth factors within 7 day

Exclusion Criteria

1. Serious underlying medical conditions, such as:
    a. Evidence of active systemic viral, fungal, or bacterial infection requiring systemic antiviral, antifungal, or antimicrobial therapy
    b. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment
    c. Overt clinical evidence of dementia or altered mental status
    d. Any of the following within 6 months prior to first dose of study treatment: severe or unstable angina, myocardial infarction, seizure, major thromboembolic events (eg, pulmonary embolism, cerebrovascular accident [including TIA and stroke]), clinically significant ventricular arrhythmias or heart failure New York Heart Association functional classification Class III to IV
2. Active hepatitis of infectious origin.
    - Seropositive for hepatitis B:
    - Known hepatitis C infection or positive serologic testing for hepatitis C virus (anti-HCV) antibody.
    - Other clinically active liver disease of infectious origin.
3. Participants who are HIV-positive and meet any of the following
    - Detectable viral load (i.e., ≥50 copies/mL) at screening
    - CD4+ count ≤300 cells/mm3 at screening
    - Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of screening
    - Receive treatment other than continued HAART.
4. Plasma cell leukemia at the time of screening (≥5% circulating PCs in peripheral blood smear), Waldenstrom's macroglobulinemia, POEMS syndrome
5. Presence of any of the following:
    - Any ongoing myelodysplastic syndrome or B-cell malignancy
    - Any history of malignancy, other than MM, that is considered at high risk of recurrence requiring systemic therapy.
6. Suspected or known allergies, hypersensitivity, or intolerance to the excipients of JNJ- 79635322
7. Major surgery, (e.g., requiring general anesthesia) within 2 weeks before first dose, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study
8. Suspected or known allergies, hypersensitivity, or intolerance to teclistamab or its excipients (TECVAYLI USPI 2024).
9. Prior or concurrent exposure to any of the following, in the specified time frame prior to randomization:
    - T-cell redirection therapy (eg, CAR-T, bispecific antibody) within 6 months.
    - History of receiving both BCMA and GPRC5D-directed therapy
    - History of receiving a BCMA-directed bispecific antibody
    - An allogenic stem cell transplant within 6 months before first dose of study drug.
    - Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14 days prior to first dose of study drug.
10. Received or plans to receive any live, attenuated vaccine within 4 weeks before the first dose of study treatment, during, or within 90 days after the last dose of study treatment.

A PHASE ½ STUDY OF ETENTAMIG IN COMBINATION WITH A CELMOD AGENT FOR THE TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Protocol Number: M24-555

Contact: Dr. Guido Lancman / Trina Wang And Trisha Ramanan **– Open Enrollment**

Inclusion Criteria

1. ≥18 years of age.
2. Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria
3. Must have the following:
    - Phase 1 Dose Escalation: subjects with 3-5 prior lines of therapies.
    - Phase 2 Dose Expansion and Selection: subjects with 1-3 prior lines of therapies, subjects with BCMA-targeted CAR-T-cell (completed at least 6 months prior to the first dose of study treatment) or BCMA-targeted ADCs (completed at least 30 days prior to the first dose of study treatment) are allowed. Additionally any subjects who received CD3-directed T cell engager therapy as the last line and subjects with prior BCMA directed T cell engager therapy are excluded
4. Measurable disease at screening defined as per central laboratory with at least 1 of the following assessed within 28days prior to enrollment:
    - Serum monoclonal para protein (M-protein) level ≥ 0.5 g/dL (≥5 g/dL);
    - or Urine M-protein level ≥200 mg/24 hours;
    - or Serum Ig free light chain (FLC) ≥10 mg/dL (involved light chain) and an abnormal serum kappa lambda ratio only for subjects without measurable serum or urine M-protein.
5. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1.
6 Clinical laboratory values:
    - Hemoglobin ≥8.0 g/dL; subject may receive red blood cell (RBC) transfusions in accordance with institutional guidelines to meet this criterion. Subjects may not have received a red blood cell (RBC) transfusion within 7 days prior to the hemoglobin result used for eligibility.
    - Platelets ≥ 75,000/mm3 . For subjects with >50% myeloma involvement in the marrow, a platelet count of ≥ 50,000 mm3 is allowed. Subjects may not have received a platelet transfusion within 7 days

prior to the platelet count used for eligibility.
- Absolute Neutrophil Count (ANC) ≥ 1,000/µL; subject may use growth factor support to achieve ANC eligibility criteria. Subjects may not have received a GCSF within 7 days prior to the ANC result used for eligibility.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)≤3 ×ULN
- Creatinine clearance ≥ 30 mL/min, measured by 24 hour urine collection or calculated using the MDRD formula
- Total bilirubin ≤ 2.0 × ULN (except for subjects with documented Gilbert's syndrome, in which case direct bilirubin ≤ 1.5 × ULN is required)
- Serum calcium corrected for albumin ≤14 mg/dL (≤3.5 mmol/L)

7. Subjects must have a fresh pretreatment bone marrow tumor aspirate and core biopsy (if the bone marrow biopsy is collected as part of standard of care). If a bone marrow core biopsy is not collected as part of standard of care, then a fresh bone marrow aspirate clot must be provided. If available, an archival bone marrow tumor tissue (core block/slides or aspirate clot block/slides) that was collected within 12 weeks prior to the first dose and without intervening treatment should also be provided.

Exclusion Criteria:

Subject History:

1.Subject who has received prior etentamig treatment

2. Subject who has received prior CELMoD (iberdomide or mezigdomide)

3. Subject who has received a peripheral ASCT within 12 weeks, or an allogeneic SCT within ≤6 months of the first dose of study treatment. Subjects with allogenic stem cell transplant should not have any symptoms of acute or chronic graft versus host disease.

4. Subjects who has unresolved AEs ≥Grade 1 (NCI CTCAE version 5.0) from prior anticancer therapy, except for alopecia or fatigue. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (e.g., hearing loss)

5. Subjects who has known active central nervous system involvement MM.

6. Subject who has history of clinically significant renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, pulmonary, or hepatic disease within the last 6 months that in Investigator's opinion, would adversely affect the subject's participation in the study.

7. Subject who has history of significant cardiovascular or pericardial disease, including uncontrolled angina, arrhythmia, recent myocardial infarction within 6 months of first dose, congestive heart failure cardiovascular disability status of New York Heart Association Class ≥3, severe cardiac insufficiency, or persistent QT interval corrected for heart rate (QTc) prolongation (>480 msec, QTc Fridericia)

8. Subject who has known history of other active malignancies, including myelodysplastic syndrome within the past 3 years with the following exceptions:
- Adequately treated in situ carcinoma of the cervix uteri or the breast;
- Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
- Prostate cancer Gleason grade 6 or lower AND with stable Prostate Specific Antigen levels
- Previous malignancy with no evidence of disease confined and surgically resected (or treated with other modalitities) with curative intent and unlikely to impact survival during the duration of the study.

9. Subject who has evidence of active hepatitis B (HBsAg positive) infection based on screening blood testing. Hepatitis B testing must include HBsAg, antiHBc, and antiHBs.

10. Subject who has evidence of active hepatitis C infection based on screening blood testing; Subject may not be seropositive for hepatitis C (except in the setting of a sustained virologic response, defined as aviremia at least 12 weeks after completion of antiviral therapy)

11. Subject who has known active SARS-CoV-2 infection.

12. Subject who has known active infection with HIV.

13. Subject who has the following conditions:
- Non-secretory MM;
- Active Plasma cell leukemia, i.e., either 5% of peripheral white blood cells or >5.0 X 108/L circulating plasma cells by standard differential;
- Waldenstrom's macroglobulinemai;
- Light chain amyloidosis;
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes);
- Major surgery within 21 days prior to first dose or planned study participation;
- Acute infections within 14 days prior to the first dose of study treatment requiring therapy (antibiotic, antifungal or antiviral)

14. Subject who has known or suspected hypersensitivity to the excipients contained in the formulation of etentamig, iberdomide. Subject who had known allergies, significant sensitivity, or intolerance to constituents of the required pre-medications

15. Subject who has known history of clinically significant (per investigator's judgement) alcohol abuse

16. Subjects unable (due to known contraindication) or unwilling to take antithrombotic prophylaxis for Iberdomide. Antithrombotic prophylaxis includes low-dose aspirin, low molecular weight heparin, or other equivalent.

Concomitant Medications:

17. Subject treated with any investigational drug within 21 days or 5 half-lives (whichever is longer), of the drug (contact TA MD if half-life is unknown) prior to the first dose of study treatment or is currently enrolled in another interventional clinical study or was previously enrolled in this study.

18. Subject requires chemotherapy with an antineoplastic intent for other malignancies.

19. Subject received any live vaccine within 30 days prior to the first dose of the study treatment.

20. Subject received treatment with anti-cancer therapy including chemotherapy, radiotherapy, biologics, immunotherapy, cellular therapies anticancer hormonal therapy (except androgen deprivation therapy for prostate cancer started prior to enrollment on study or ongoing endocrine therapy post-breast cancer treated with curative intent < 3 years prior to study
enrollment), and/or steroids at doses >20mg dexamethasone or equivalent or undergone a major surgical procedure within 21 days or within 5 half-lives of an anticancer therapy, prior to the first dose of study treatment, whichever is shorter.

21. For subjects receiving iberdomide, subject systemically used known strong inhibitors or strong inducers of CYP3A4/5 within 2 weeks or 5 half-lives of the drug, whichever is longer (2 weeks if half-life is unknown) prior to the first dose of the study treatment.

AMYLOIDOSIS TRIALS:

A PHASE 1B/2 STUDY OF AZD0120 (ALSO KNOWN AS GC012F), A CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY TARGETING CD19 AND B CELL MATURATION ANTIGEN IN PARTICIPANTS WITH RELAPSED OR REFRACTORY AL AMYLOIDOSIS.
Protocol Number: AZD0120-AL-201 - D831AC00001
Contact: Dr. Vishal Kukreti/Trina Wang – **Enrollment on hold by sponsor-release of new slots in November**

Inclusion Criteria

Age

1. Must be ≥18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Confirmed histopathological diagnosis of AL amyloidosis based on polarizing light microscopy of green bi-refringent material in Congo red stained tissue specimens and confirmation of AL derived amyloid deposits by at least one of the following: immunohistochemistry, immunofluorescence, mass spectrometry, characteristic electron microscopy appearance/immunoelectron microscopy. Confirmed diagnosis on historic biopsy is acceptable, with no requirement for repetition.
3. One or more organs currently or historically impacted by AL amyloidosis according to consensus guidelines
4. Measurable hematologic disease: dFLC > 20 mg/L or serum M-protein > 5g/L
5. Relapsed disease or refractory disease defined as a need for additional therapy after at least 1 line of anti-plasma cell-directed therapy. Prior therapies must include at least one CD38 monoclonal antibody and at least one proteasome inhibitor. Participants should not be in a CR at the time of inclusion. Participants who did not reach VGPR after at least 2 cycles of initial therapy can be included, as well as participants who initially attained a CR or VGPR with initial therapy with evidence of rising dFLC or rising M-protein, that the Investigator deems as requiring further anti-plasma cell directed treatment.
6. ECOG performance status of 0 to 1

Sex and Contraceptive/Barrier Requirements

7. Male or female
   Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

   a. Male Participants:
      - Use of a condom plus an additional contraceptive method from the time of signing the ICF and throughout the study, until 12 months after receiving AZD0120 infusion or until CAR T cell DNA is no longer detectable by PCR (whichever is later) or 6 months after receiving the last dose of fludarabine or cyclophosphamide, whichever occurs last. In addition, male participants must refrain from sperm donation while on-study and for 12 months after receiving AZD0120 infusion or until CAR T cell DNA is no longer detectable by PCR, whichever is later.
      - NOTE: Non-pregnant female partners of male participants enrolled in this study should use acceptable contraception (Section 10.5) during their partner's participation in the study and until at least the same timeframe for their male partners.

   b. Female Participants:
      - FONCBP
      - Females receiving HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for FOCBP if they wish to continue using HRT during the study. Otherwise, HRT must be discontinued to allow confirmation of post-menopausal status prior to enrollment.
      - FOCBP must use one highly effective form of birth control from the time of signing the ICF, throughout the study and until 12 months after receiving AZD0120 infusion or until CAR T cell DNA is no longer detectable by PCR (whichever is later) or 12 months after receiving the last dose of fludarabine or cyclophosphamide, whichever occurs last. Cessation of contraception after this point should be discussed with the treating physician.
      - All FOCBP must have a negative serum and/or urine pregnancy test result at screening and thereafter as defined in SoA.
      - NOTE: Non-sterilized partners of FOCBP participants enrolled in this study should use acceptable contraception during their partner's participation in the study and until at least the same timeframe specified for their female partners.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
9. Must be able and willing to adhere to the study visit schedule and other protocol requirements.

Exclusion Criteria

Any potential participant who meets any of the following criteria up until apheresis will be excluded from participating in the study:

Medical Conditions

1. Have any other form of amyloidosis other than AL amyloidosis
2. Have any other form of amyloidosis other than AL amyloidosis
   a. Mayo Stage IIIb AL amyloidosis (Wechalekar, 2013)
   b. NT-proBNP levels as follows:
      - NT-proBNP ≥ 2000 ng/L (Phase 1b dose escalation portion and Phase 2 lower NT-proBNP group)
      - NT-proBNP < 2000 and > 5000 ng/L (Phase 1b dose extension portion and Phase 2 higher NT-proBNP group).
   c. High-sensitivity cardiac troponin T > 75 ng/L
   d. NYHA Class III – IV
   e. LVEF < 45% by echocardiogram
   f. Medically refractory atrial or ventricular arrhythmias as determined by Investigator
   g. Symptomatic or medically refractory pleural effusions as determined by Investigator
   h. Decompensated heart failure
   i. Unexplained syncope, not believed to be vasovagal
   j. Standing systolic BP < 100 mm Hg or symptomatic orthostatic hypotension, defined as a decrease in systolic BP upon standing of > 30 mmHg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion
   k. Myocardial infarction, coronary revascularization or CABG ≤ 6 months prior to screening
   l. Pacemaker/ICD/CRT-D implantation within ≤ 6 months prior to screening
3. Severe Factor X deficiency (Factor X < 10%) or Factor X deficiency with significant risk of bleeding as determined by Investigator
4. Extensive GI involvement with evidence of active GI bleeding/risk of bleeding as determined by Investigator.
5. Oxygen saturation < 95% on room air
6. Prior therapies:
   a. CAR T cell therapy directed at any target
   b. Prior BCMA-targeting therapy
   c. Prior treatment with any FDA approved or investigational T cell engaging therapies (including T cell-directed bispecific or trispecific therapies) at any target within the last 6 months.
   d. An allogenic stem cell transplant within 6 months before apheresis. Participants who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks before apheresis without signs of GVHD.
   e. An autologous stem cell transplant ≤ 12 weeks before apheresis
   f. Prior therapy as follows, prior to apheresis:
      - Investigational product within 5 half-lives or ≤ 21 days (whichever is the shorter).
      - Monoclonal antibody treatment for AL within 21 days.
      - Cytotoxic/alkylating therapy within 21 days
      - Proteasome inhibitor therapy within 14 days.
      - Immunomodulatory agent therapy within 14 days.
      - Received a cumulative dose of systemic corticosteroids, equivalent to ≥ 70 mg of prednisone, within 7 days prior to apheresis.
7. Toxicity from previous anti-cancer or anti-PC-directed therapy did not resolve to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy. For eligibility criteria related to hemoglobin, lymphocyte, platelet and neutrophil thresholds, refer to Exclusion Criteria 16 to 19.
8. Active plasma cell leukemia at the time of screening, Waldenstrom's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). IgM associated AL amyloidosis is permitted, as long as participant meets other eligibility criteria including requisite prior therapies.
9. Multiple myeloma defined as clonal bone marrow plasma cells ≥10% and any one or more of the following myeloma defining events (deemed as attributable to multiple myeloma by Investigator)
   a. Hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the ULN or > 2.75 mmol/L (> 11 mg/dL) OR
   b. Renal insufficiency: creatinine clearance < 40 mL per minute or serum creatinine > 177 µmol/L (> 2 mg/dL) OR
   c. Anemia: hemoglobin value of > 20 g/L below the lowest limit of normal, or a hemoglobin value < 100 g/L OR
   d. Bone lesions: one or more lesions on imaging tests (performed ≤ 3 months prior to signing the ICF or during Screening): skeletal radiography, CT, or PET/CT, or MRI.
   e. 60% or greater clonal plasma cells on bone marrow biopsy in screening

Note: a multiple myeloma diagnosis with a serum FLC ratio >100, as the only myeloma-defining event, does not constitute an exclusion.

10. Have history of any HLH and/or history of Grade 3 or higher CRS and/or neurotoxicities during prior T cell engaging therapy.
11. Have history of a prior malignancy, unless the participant has been disease-free with no evidence of recurrence for ≥ 2 years. The following are exceptions:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin in situ (Stage 0)
    - 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

12. Exclusion criteria relating to neurological conditions:
    a. History of neurodegenerative disorders or significant neurological condition including but not limited to stroke, intracranial hemorrhage, severe brain injury, dementia, cerebellar disease, Parkinson's disease, organic brain syndrome or seizure within 6 months prior to apheresis.
    b. History of Guillain-Barre syndrome or its variants, or history of any Grade 3 or higher peripheral motor polyneuropathy.
13. Seropositive for HIV.
14. Vaccinated with live, attenuated vaccine within 4 weeks prior to apheresis.
15. Serologic status reflecting active hepatitis B or C:
    a. Patients who are anti-HBc antibody positive and who are surface antigen negative will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded.
    b. Patients who are hepatitis C antibody positive will need to have a negative PCR result before enrollment.
    c. Those who are hepatitis C PCR positive will be excluded. For participants with known history of HCV infection, confirmation of sustained virologic response is required for study eligibility, defined as ≥ 12 weeks after completion of antiviral therapy.
16. Hemoglobin < 8 g/dL (without prior red blood cell transfusion within 7 days before the laboratory test. For participants who meet the exclusion criteria at Screening, transfusion of red blood cells is permitted after Screening as needed to maintain a hemoglobin level ≥ 8.0 g/dL).
17. Platelets < 50,000/µL (participants above this threshold must not have received platelet transfusion support within 7 days before the laboratory test).
18. Absolute lymphocyte count < 300/µL
19. ANC < 1000/uL (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test
20. AST or ALT >2.5×ULN
21. Total bilirubin >1.5×ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin <1.5×ULN is required)
22. Calculated creatinine clearance < 30mL/min (per Cockcroft-Gault formula)
23. Known life threatening allergies, hypersensitivity, or intolerance to AZD0120 or its excipients, including DMSO, or to fludarabine and cyclophosphamide.
24. Serious underlying medical condition, such as:
    a. Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection
    b. Active autoimmune disease or a history of autoimmune disease requiring treatment within 3 years
    c. Overt clinical evidence of dementia or altered mental status.
    d. IBD requiring treatment within the past 5 years
25. Any issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the Investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
26. Pregnant or breast-feeding, or planning to become pregnant while enrolled in this study and within 12 months post-AZD0120 infusion or until CAR T cell DNA is no longer detectable by ddPCR, whichever occurs last.
27. Plans to father a child while enrolled in this study and within at least one-year post- AZD0120 infusion or until CAR T cell DNA is no longer detectable by ddPCR, whichever occurs last.
28. Major surgery within 4 weeks prior to apheresis, or has major surgery planned between apheresis and infusion of AZD0120, or within 4 weeks after study drug infusion with AZD0120.

(Note: participants with planned surgical procedures to be conducted under local anesthesia may participate).

CHRONIC LYMPHOCYTIC LEUKEMIA & WALDESTROM'S TRIALS

THE USE OF PERIPHERAL BLOOD CELL-FREE DNA (CFDNA) FOR GENETIC PROFILING IN PATIENTS WITH LYMPHOPLASMACYTIC LYMPHOMA (LPL) AND WALDENSTROM'S MACROGLOBULINEMIA (WM)
Protocol Number: PM-WM001
Non-Interventional
Contact: Dr. Christine Chen/Harjot Vohra -**Open Enrollment**

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

A PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF MK-1026 IN PARTICIPANTS WITH HEMATOLOGIC MALIGNANCIES.
Protocol Number: MK-1026-003-09
Contact: Dr. Christine Chen/ Olga Levina **– Open Enrollment only for Part 2, Cohort J (WM patients)**

Inclusion Criteria

The criteria listed below pertain to Cohort J in Part 2, which is currently open for enrollment. The relevant information has been extracted in accordance with protocol Amendment 9.0 (PA9.0) dated 21 August 2025, and incorporated into the key eligibility criteria below.

Participants eligible for inclusion in this study must be relapsed or refractory to existing treatment. The definition of relapsed/refractory disease is as follows:

The following disease-specific criteria must be met according to the WHO classification of hematological malignancies

1. Part 2 (Cohort J) has a confirmed diagnosis of CLL/SLL with:

- Part 2 Cohort J: CLL/SLL participants whose disease relapsed or was refractory to prior therapy with a covalent/irreversible BTKi and BCL2i (both classes of therapies are required). Additional use of noncovalent/reversible BTKi is permitted provided participant's disease relapsed/was refractory to such therapy. CLL participants must have received and failed, been intolerant to, or determined by their treating physician to be a poor PI3Ki candidate or ineligible for a PI3Ki per local (institution) guidelines. The participant is not eligible if response cannot be assessed after stopping BTKi and BCL2i. The participant will be eligible once disease progression or refractory status is determined.

NOTE: As of Protocol Amendment 09, at least 10 CLL/SLL participants whose disease relapsed or was refractory to prior therapy with a covalent/irreversible BTKi, BCL2i and noncovalent/reversible BTKi (all three classes of therapies are required) will be enrolled into Cohort J.

- Active disease for CLL/SLL clearly documented to initiate therapy. At least 1 of the following criteria should be met:
- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cut-off levels of Hb <10 g/dL or platelet counts <100 × 109/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 × 109/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
- Massive (i.e., >+6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or LDT <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; participants with initial blood lymphocyte counts ≥30 × 109/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
- Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extra nodal involvement (e.g., skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
    - Unintentional weight loss ≥10% within the previous 6 months
    - Significant fatigue (i.e., ECOG performance score 2 or worse; cannot work or unable to perform usual activities).
    - Fever of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
    - Night sweats for ≥1 month without evidence of infection.

NOTE: CLL participants must have at least one parameter that can be objectively measured for response per iwCLL.
SLL participants must have measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan. A minimum measurement must be >15 mm in the longest diameter.

- For SLL participants in Part 2: Participants with lymphoma must provide a lymph node biopsy for biomarker analysis from an archival (within 1 year relative to the date of sample submission to the central laboratory provided there was no intervening therapy) or newly obtained lymph node biopsy or bone marrow aspirate at Screening. If a lymph node biopsy is considered medically unsafe to perform, Sponsor consultation/approval is required for enrollment. CLL participants in Part 2 will only provide Cycle 1 Day 1 blood sample.

2. Have an ECOG performance status of 0 to 2 within 7 days before allocation.
3. Have a life expectancy of at least 3 months, based on the investigator assessment.
4. Have the ability to swallow and retain oral medication.
5. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.

NOTE: Participant should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

Hepatitis B screening tests are not required unless:
- Known history of HCV infection

- As mandated by local health authority

6. Participant with history of HCV infection are eligible if HCV viral load is undetectable at screening

NOTE: Participant must have completed curative antiviral therapy at least 4 weeks before randomization.

Hepatitis C Screening tests are not required unless:

- Known history of HCV infection
- As mandated by the local health authority

7. Have adequate organ function as defined in Table 7. Specimens must be collected within 7 days before the start of study intervention.

Table 7 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥750/µL
Platelets	≥50 000/µL [a]
Hemoglobin	≥8.0 g/dL [a, b]
Renal	
Measured or calculated c CrCl (GFR can also be used in place of creatinine or CrCl)	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN In participants with documented liver metastases and/or Gilbert's syndrome, total bilirubin of ≤3 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase).
ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CLL=chronic lymphocytic leukemia; CrCl=Creatinine clearance; GFR=glomerular filtration rate; INR=International normalized ratio; pRBC=packed red blood cell; PT=prothrombin time; SLL=small lymphocytic leukemia; ULN=upper limit of normal.
[a] No requirement in participants with significant bone marrow involvement.
[b] Criteria must be stable for ≥1 week
[c] CrCl should be calculated per institutional standard.

Demographics

8. Is individual of any sex/gender, 18 years of age or older at the time of providing documented informed consent.

Male Participants

9. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is:
    - MK-1026: 12 days

- Uses a penile/external condom when having penile-vaginal intercourse with nonparticipant of childbearing potential who is not currently pregnant.
- Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

NOTE: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required.

Female Participants

10. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and at least 30 days after the last dose of study intervention (MK-1026). The number of days should be after 5 half-lives.

- A POCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.

Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

- A POCBP is eligible to participate if they use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or if they adhere to penile-vaginal intercourse abstinence as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5, during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is:
  - MK-1026: 30 days

NOTE: The investigator should evaluate the potential for contraceptive method failure (i.e., noncompliance, recent initiation) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the local contraception requirements for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of POCP with an early undetected pregnancy.

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Refer to Appendix 7 for country-specific requirements.

Other Inclusions

12. Participants with HIV are eligible if they meet ALL of the following criteria:

- The CD4 count is >350 cells/µL at Screening
- The HIV viral load is below the detectable level as per locally available testing
- Are on a stable ART regimen for at least 4 weeks before study entry.

NOTE: ART includes drugs which are NOT strong CYP3A4 inducers (participants receiving ART that are strong CYP3A4 inducers are not eligible to be included in the study).

- Are compliant with their ART

NOTE: If the participant has had an AIDS defining opportunistic infection in the past 12 months before Screening, they are not eligible to be included in the study.

- No HIV testing is required unless per local health guidelines.

Refer to Appendix 7 for additional country-specific requirements.

<u>Exclusion Criteria</u>

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Part 2 participants: active HBV/HCV infection. See Inclusion Criteria 7 (HBV) and 8 (HCV) for requirements.
2. Has a history of malignancy ≤3 years before providing documented informed consent.

NOTE: participants with basal cell carcinoma of skin, squamous cell carcinoma o skin, or carcinoma in situ (e.g., Breast carcinoma, cervical cancer in situ) that have undergone potential curative therapy are not excluded. Participants with low-risk, early-stage prostate cancer (T1-T2a, Gleason score <6, and prostaticspecific antigen<10 ng/mL) either treated with definitive intent or untreated in active surveillance with SD are not excluded.

3. Has active CNS disease.
4. Has an active infection requiring systemic therapy.
5. Exclusion criterion removed.
6. Has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstance that might confound the results of the study, or interfere with the participant's ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
7. Has QTc prolongation (defined as a QTcF >470 msec) or other significant ECG abnormalities including second degree AV block type II, third degree AV block, or bradycardia (ventricular rate less than 50 beats/min).

NOTE: If triplicate ECG were performed, QTc prolongation is defined as a QTcF >470 msec on 2 out of 3 consecutive ECGs, and mean QTcF> 470 msec on all 3 ECG.

a) QTcF is calculated using Fridericia's Formula (QTcF = QT/ (RR^0.33).
b) Correction of suspected drug-induced QTcF prolongation or prolongation due to electrolyte abnormalities can be attempted at the Investigator's discretion, and only if clinically safe to do so with either discontinuation of the offending drug or switch to another drug not known to be associated with QTcF prolongation or electrolyte supplementation.

Prior/Concomitant Therapy

8. Has received prior systemic anticancer therapy within 5 half-lives or 4 weeks (if prior therapy was a monoclonal antibody) before C1D1.

NOTE: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

NOTE: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention before starting study intervention.

9. Currently being treated with the following drugs:

- P-gp substrates with a narrow therapeutic index

- CYP3A strong inducers
- CYP3A strong inhibitors

NOTE: A washout period of at least 5 times the half-life after the last dose of any of the above treatments is required for a participant to be eligible for study enrollment.

Prior/Concurrent Clinical Study Experience

10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.

NOTE: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

11. Prior exposure to noncovalent, reversible BTK inhibitors.

NOTE: For Part 2 Cohort J, prior exposure to nemtabrutinib is not permitted. Additional prior use of noncovalent, reversible BTK inhibitor(s) other than nemtabrutinib is (are) permitted.

Diagnostic Assessments

12. Exclusion criterion removed

Other Exclusions

13. Has any clinically significant gastrointestinal abnormalities that might alter absorption.
14. Has a known severe hypersensitivity (≥Grade 3) to nemtabrutinib, its active substance and/or any of its excipients. Refer to the IB for a list of excipients.
15. History of severe bleeding disorders.

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