

**Clinical Trials in Myeloma and Related Disorders at PMH**  
***(Version: November 2017)***

**NEWLY DIAGNOSED MULTIPLE MYELOMA**

**Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation (Protocol Number: C16021)**

***Inclusion Criteria***

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

1. Adult male or female patients aged 18 years or older with a confirmed diagnosis of symptomatic NDMM according to standard criteria.
  2. Completed 6 to 12 months (+/- 2 weeks) of initial therapy, during which the patient was treated to best response, defined as the best response maintained for 2 cycles after the M-protein nadir is reached.
  3. Documented major response (PR, VGPR, and CR) according to the IMWG uniform response criteria, version 2011, after this initial therapy.
  4. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)
- Male patients, even if surgically sterilized (ie, status postvasectomy), who:
- Agree to practice effective barrier contraception during the entire study
  - Treatment period and through 90 days after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
5. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
  6. Complete documentation of the details of the initial therapy before randomization including cytogenetics and ISS is available.
  7. Eastern Cooperative Oncology Group Performance Status of 0 to 2.

8. Suitable venous access for the study-required blood sampling and consent for the specific amounts that will be taken.
9. Patient is willing and able to adhere to the study visit schedule and other protocol requirements including blood sampling and bone marrow aspiration.
10. Patients must meet the following clinical laboratory criteria at study entry:
  - Absolute neutrophil count (ANC)  $\geq 1,000/\text{mm}^3$  without growth factor support and platelet count  $\geq 75,000/\text{mm}^3$ . Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before randomization.
  - Total bilirubin  $\leq 1.5 \times$  the upper limit of the normal range (ULN).
  - Alanine aminotransferase and aspartate amino transferase  $\leq 3 \times$  ULN.
  - Calculated creatinine clearance  $\geq 30 \text{ mL/min}$  (using the Cockcroft-Gault equation)

### ***Exclusion Criteria***

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

1. Multiple myeloma that has relapsed after, or was not responsive to, initial therapy.
2. Prior SCT.
3. Radiotherapy within 14 days before randomization.
4. Diagnosed or treated for another malignancy within 5 years before randomization or previous diagnosis with another malignancy. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
5. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.
6. Major surgery within 14 days before randomization.
7. Central nervous system involvement.
8. Infection requiring IV antibiotic therapy or other serious infection within 14 days before randomization.
9. Diagnosis of Waldenstrom's Macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, uncontrolled congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
11. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, Voriconazole, ketoconazole, nefazodone, posaconazole), or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use of Ginkgo biloba or St. John's wort within 14 days before randomization.
12. Ongoing or active infection, known human immunodeficiency virus positive, active hepatitis B or C infection.

## **Clinical-grade Molecular Profiling of Patients with Multiple Myeloma and Related Plasma Cell Malignancies (Protocol MMRF-002)**

### ***Inclusion Criteria:***

1. Patients must have a diagnosis of multiple myeloma or related plasma cells malignancies
2. Patients are undergoing standard of care bone marrow aspirates.
3. Patients (male or female) from any race or ethnicity must be 18 years of age at the time of registration
4. Procedure-specific signed informed consent form (ICF) prior to initiation of any study-related procedures.

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

1. It is the enrolling study physician's discretion to decide if a patient is not fit enough to undergo tissue biopsy.
2. Patients who are incarcerated are not eligible to participate.
3. Women who are pregnant.
4. Patients who have had another malignancy within the last five (5) years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)

## **Health-related quality of life and caregiver burden assessment in multiple myeloma and lymphoma patients and their caregivers undergoing outpatient autologous stem cell transplantation as compared to inpatient transplantations: a needs assessment (Non-Interventional)**

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

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

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

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

# **Phase 1/2 Multicenter, Open-Label Study to Determine the Recommended Dose and Regimen of Durvalumab (Medi4736) In Combination with Lenalidomide (Len) With and Without Dexamethasone (Dex) In Subjects with Newly Diagnosed Multiple Myeloma (Protocol: MEDI4736-MM-002)**

## ***Inclusion criteria***

1. Subjects must satisfy the following criteria to be enrolled into the study:
  - Subject is  $\geq 18$  years of age at the time of signing the informed consent form (ICF)
  - Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
  - Subject is willing and able to adhere to the study visit schedule and other protocol requirements
  - Subject must have documented diagnosis with previously untreated (for cohort C, the induction and consolidation treatment along with the first ASCT are allowed), symptomatic MM as defined by the criteria below (Rajkumar, 2014; NCCN-MM, 2015):
2. MM diagnostic criteria (all 3 required);
  - Monoclonal protein present in the serum and/or urine
  - Clonal bone marrow plasma cells  $\geq 10\%$  or biopsy-proven bony or extramedullary plasmacytoma\*
  - Any one or more of the following myeloma defining events:
    - i. One or more of the following Myeloma-related organ dysfunction (at least one)
      - [C] Calcium elevation (serum calcium  $>11.5$  mg/dl) [ $> 2.65$  mmol/L]
      - [R] Renal insufficiency (serum creatinine  $>2$  mg/dl) [ $177 \mu\text{mol/L}$  or more] or creatinine clearance  $< 40$  ml/min
      - [A] Anemia (hemoglobin  $<10$  g/dl or  $>2$  g/dL below the lower limit of laboratory normal)
      - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, CT, or PET-CT
    - ii. One or more of the following biomarkers of malignancy:
      - Clonal bone marrow plasma cell percentage\*  $\geq 60\%$
      - Abnormal serum free light-chain ratio  $\geq 100$  (involved kappa) or  $< 0.01$  (involved lambda)
      - $>1$  focal lesions detected by functional imaging including PET/CT and/or whole body magnetic resonance imaging (MRI)

**AND have measurable disease by protein electrophoresis analyses as defined by the following:**

  - IgG MM: Serum monoclonal paraprotein (M-protein) level  $\geq 1.0$  g/dl or urine M protein level  $\geq 200$  mg/24 hours
  - IgA MM: Serum M-protein level  $\geq 0.5$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - IgM MM (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level  $\geq 1.0$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - IgD MM: Serum M-protein level  $\geq 0.05$  g/dl or urine M-protein level  $\geq 200$  mg/24 hours
  - Light chain MM: Serum M-protein level  $\geq 1.0$  g/dl or urine M-protein level  $\geq 200$ mg/24 hours
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
4. Females of childbearing potential (FCBP1) must:
  - Have two negative pregnancy tests as verified by the investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence<sup>2</sup> from heterosexual contact.
  - She must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and be source documented) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study treatment, during the study therapy (including dose interruptions), and for 90 days after discontinuation of study treatment.
  - Refrain from egg cell and blood donation for 90 days after the final dose of Durvalumab.

5. Male subjects must:
  - Practice true abstinence (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions and for at least 90 days following study treatment discontinuation, even if he has undergone a successful vasectomy.
  - Refrain from sperm and blood donation for at least 90 days after the final dose of Durvalumab
6. For Cohort A subject must be transplant non-eligible (TNE) and meet at least one of the following high risk factors:
  - Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q rearrangement; and / or t(14;16); or
  - ISS Stage III; or
  - Serum LDH > 2 x ULN;
7. For Cohort B subject must be ≥ 65 years of age at the time of signing the informed consent form (ICF) and transplant non-eligible (TNE); excluding the subjects who meet the Cohort A criteria
8. For Cohort C subject must be after first autologous stem cell transplantation (ASCT) for NDMM and meet the following criteria:
  - Have a post-transplant response as PR or better at the time of enrollment to this study;
  - Have one of the following high risk factors at the time of NDMM diagnosis;
    - i. Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q rearrangement; and / or t(14; 16); or
    - ii. ISS stage III; or
    - iii. Serum LDH > 2 x ULN;
9. MRD positive (defined as more than 1 malignant cell in 105 cells) measured by ClonoSIGHT™ NGS assay of a BMA sample) at the time of enrollment to this study; BMA sample collected at the time of multiple myeloma diagnosis, prior to induction therapy available for central MRD assessment by ClonoSIGHT™ NGS assay

### ***Exclusion criteria***

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

1. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of Cycle 1 Day 1], for Cohort C, the induction and consolidation treatment along with the first ASCT are allowed)
2. Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) < 1,000/μL
  - Untransfused platelet count < 75,000 cells/μL
  - Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 2.5 × upper limit of normal (ULN)
  - Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
  - Corrected serum calcium >13.5 mg/dL (> 3.4 mmol/L)
3. Renal failure requiring hemodialysis or peritoneal dialysis
4. Any serious medical condition that places the subject at an unacceptable risk if he or she participates in this study. Examples of such a medical condition are, but are not limited to, subject with unstable cardiac disease as defined by: cardiac events such as myocardial infarction (MI) within the past 6 months, NYHA (New York Heart Association) heart failure class III-IV, uncontrolled atrial fibrillation or hypertension; subjects with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis and lupus, that likely need additional steroid or immunosuppressive treatments in addition to the study treatment
5. Peripheral neuropathy ≥ Grade 2
6. Primary AL (immunoglobulin light-chain) amyloidosis and myeloma complicated by amyloidosis
7. Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies:

- Basal cell carcinoma of the skin
  - Squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix
  - Carcinoma in situ of the breast
  - Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
8. Subject is positive for human immunodeficiency virus (HIV); chronic or active hepatitis B or active hepatitis A, or C
  9. Subject had prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibody or inhibitor, cell-based therapies, or cancer vaccines
  10. Subject has history of organ or allogeneic stem cell transplantation
  11. Subject who has had clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS multiple myeloma, or plasma cell leukemia
  12. Known or suspected hypersensitivity to the excipients contained in the formulation of
  13. Durvalumab, lenalidomide, or dexamethasone
  14. Major surgery (as defined by the investigator) within the 28 days prior to the first dose of study treatment
  15. Received prior treatment (for any reason) with a monoclonal antibody within 5 half-lives of initiating study treatment
  16. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment.

# RELAPSED OR REFRACTORY MULTIPLE MYELOMA

## Phase 1/2 trial of Idasanutlin in combination with Ixazomib and dexamethasone in patients with 17p deleted, relapsed multiple myeloma (MC1582/MMRC-061; Protocol: MC1582/MMRC-061)

### ***Inclusion Criteria***

1. Diagnosis of MM with deletion 17p (del17p) or monosomy 17 by FISH who have received at least one line of therapy.
2. The following laboratory values obtained  $\leq 14$  days prior to registration.
  - Calculated creatinine clearance  $\geq 30$  mL/min
  - AST (SGOT) and ALT (SGPT)  $\leq 3.0$  x upper limit of normal (ULN)
  - Total bilirubin  $\leq 1.5$  x the upper limit of the normal range (ULN)
  - Absolute neutrophil count (ANC)  $\geq 1500$ /mm<sup>3</sup>
  - Platelet count  $\geq 75,000$ /mm<sup>3</sup>
  - Hemoglobin  $\geq 8.0$  g/dL

NOTE: White blood count and platelet count criteria must be met without any transfusion or growth factor support.

3. Patients with measurable disease defined as at least one of the following:
  - Serum monoclonal protein  $\geq 1.0$  g/dL by protein electrophoresis
  - $>200$  mg of monoclonal protein in the urine on 24-hour electrophoresis
  - Serum immunoglobulin free light chain  $\geq 10$  mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
4. ECOG performance status 0, 1 or 2

### ***Exclusion Criteria***

1. Other malignancy requiring active therapy.
  - EXCEPTIONS: Non-melanoma skin cancer, DCIS or carcinoma-in-situ of the cervix.
  - NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer
2. Other concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational.
  - NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment
3. Patient has  $>$ Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.
4. All CYP2C8 inhibitors, inducers, and substrates should be discontinued  $\geq 7$  days prior to registration. Systemic treatment with CYP2C8 inhibitors (anastrozole, montelukast, quercetin, trimethoprim, gemfibrozil, rosiglitazone, pioglitazone), inducers (carbamazepine, phenytoin, rifabutin, rifampin), or substrates (amiodarone, repaglinide, rosiglitazone, sorafenib, torsemide) should be discontinued  $\geq 7$  days prior to registration.
5. Systemic treatment with strong inhibitors of CYP3A4 (clarithromycin, telithromycin, itraconazole, Voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A4 inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, Gingko biloba, St. John's wort) are not allowed  $\leq 14$  days before registration.
6. Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within the past 6 months. Note: Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
7. QTc  $>470$  milliseconds (msec) on a 12-lead ECG obtained during the Screening period.
8. Known human immunodeficiency virus (HIV) positive.
9. Known hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection

10. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib or idasanutlin including difficulty swallowing
11. Diarrhea >Grade 1, based on the NCI CTCAE grading, or currently taking antidiarrheals
12. Need for ongoing therapeutic anticoagulation.
13. Patients that have previously been treated with ixazomib, or who participated in a blinded study with ixazomib (whether treated with ixazomib or not).

## **A Randomized, Open-label, Phase 3 Study Comparing Carfilzomib, Dexamethasone, and Daratumumab to Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Protocol: Amgen 20160275)**

### ***Inclusion Criteria***

1. Relapsed **or progressive** multiple myeloma **after** last treatment
2. Received at least 1 but not more than 3 prior lines of therapy for multiple myeloma
3. Prior therapy with carfilzomib is allowed as long as the patient had at least a PR to **most recent therapy with carfilzomib**, was not removed due to toxicity, did not relapse within 60 days from discontinuation of carfilzomib, and will have at least a 6-month carfilzomib treatment-free interval from last dose received until first study treatment.
4. Left ventricular ejection fraction  $\geq 40\%$  as assessed by transthoracic echocardiogram (TTE)
5. Prior therapy with anti-CD38 antibodies is allowed as long as the patient had at least a PR to **most recent therapy with CD38 antibody**, was not removed due to toxicity, did not relapse within 60 days from intensive treatment (at least every other week) of CD38 antibody therapy, and will have at least a 6-month CD38 antibody treatment-free interval from last dose received until first study treatment.
6. Absolute neutrophil count (ANC)  $\geq 1 \times 10^9/L$  within 21 days prior to randomization. Screening ANC should be independent of granulocyte- and granulocyte macrophage-colony stimulating factor support for at least 1 week and of pegylated granulocyte stimulating factor for  $\geq 2$  weeks.
7. Hemoglobin  $\geq 80$  g/L within 21 days prior to randomization. **Patients should not have received red blood cell (RBC) transfusions for at least 7 days prior to obtaining the screening hemoglobin**
8. Platelet count  $\geq 75 \times 10^9/L$  ( $\geq 50 \times 10^9/L$  if myeloma involvement in the bone marrow is  $\geq 50\%$ ) within 21 days prior to randomization. Patients should not have received platelet transfusions for at least 7 days prior to obtaining the screening platelet count.
9. Calculated or measured creatinine clearance (CrCl) of  $\geq 20$  mL/min within 21 days prior to randomization based on standard formula such as the Cockcroft and Gault. (Subjects on dialysis are excluded)

### ***Exclusion Criteria***

14. Contraindication to use daratumumab or any of its components: allergies, hypersensitivity, or intolerance to mannitol, monoclonal antibodies or human proteins or excipients (refer to Daratumumab's IB), or known sensitivity to mammalian-derived products.
15. Known moderate or severe persistent asthma within the past 2 years
16. Known chronic obstructive pulmonary disease (COPD) with a **FEV1 < 50%** of predicted normal
17. Active congestive heart failure (New York Heart Association [NYHA] Class III to IV), symptomatic ischemia, uncontrolled arrhythmias, clinically significant electrocardiogram (ECG) abnormalities, screening ECG with corrected QT interval (QTc) of  $> 470$  msec, pericardial disease, or myocardial infarction within 4 months prior to randomization
18. Known human immunodeficiency virus (HIV) infection, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed), or hepatitis B infection (subjects with hepatitis B surface antigen [SAg] or core antibody **that achieve sustained virologic response with** antiviral therapy directed at hepatitis B are allowed)
19. Subjects with grade 3 or worse neuropathy within 14 days prior to randomization

20. Allogeneic stem cell transplant less than 100 days prior to randomization
21. Patients on any immunosuppressive therapy for graft versus host disease, even if it has resolved

## **A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of Oprozomib in Combination with Pomalidomide and Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma (Protocol: 20160104)**

### ***Inclusion Criteria***

1. Subject must have a pathologically documented, definitively diagnosed, multiple myeloma relapse, or refractory progressive disease after at least 2 lines of therapy for multiple myeloma. Prior therapeutic treatment or regimens must include a proteasome inhibitor and lenalidomide
2. Measurable disease (assessed within 28 days prior to day 1), as indicated by one or more of the following:
  - Serum M-protein  $\geq 0.5$  g/dL
  - Urine M-protein  $\geq 200$  mg/24 hours
  - In subjects without detectable serum or urine M-protein: serum Free Light Chain (sFLC)  $\geq 10$  mg/dL ( $\geq 100$  mg/L) and an abnormal sFLC ratio
3. Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 2$
4. Hematological function, as follows, without transfusion support:
  - Absolute neutrophil count  $\geq 1.0 \times 10^9$ /L
  - Platelet count  $\geq 75 \times 10^9$ /L (in patients with  $< 50\%$  of bone marrow nucleated cells were plasma cells) or  $\geq 50 \times 10^9$ /L (in patients with  $\geq 50\%$  of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support
  - Hemoglobin  $> 8$  g/dL ( $> 80$  g/L) Use of erythropoietic stimulating factors and red blood cell (RBC) transfusions per institutional guidelines is allowed, however most recent RBC transfusion must not be within 7 days prior to obtaining screening hemoglobin
5. Coagulation function as follows: PT/INR and PTT  $< 1.5 \times$  Institutional Upper Limit of Normal (ULN)
6. Renal function as follows: estimated glomerular filtration rate based on Modification of Diet in Renal Disease calculation (MDRD)  $> 30$  mL/min/1.73 m<sup>2</sup>
7. Hepatic function, as follows: AST and ALT  $< 3 \times$  ULN, Total bilirubin  $< 1.5 \times$  ULN (except subjects with Gilbert's syndrome)

### ***Exclusion Criteria***

1. Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study(s)
2. Previously received an allogeneic stem cell transplant and the occurrence of one or more of the following:
  - Received the transplant within 6 months prior to study day 1
  - Received immunosuppressive therapy within the last 3 months prior to study day
  - Having signs or symptoms of acute or chronic graft-versus-host disease
3. Autologous stem cell transplant  $< 90$  days prior to study day 1
4. Multiple myeloma with IgM subtype
5. POEM syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
6. Plasma cell leukemia ( $> 2.0 \times 10^9$ /L circulating plasma cells by standard differential)
7. Waldenstrom's macroglobulinemia, Amyloidosis
8. Requirement for plasmapheresis during the screening period

9. Dexamethasone at cumulative doses of greater than 160 mg or equivalent within 21 days prior to study day 1 is not allowed. Use of topical or inhaled steroids is Acceptable
10. History of other malignancy, except:
  - Current use of therapeutic doses of anticoagulation unless agreed upon by the investigator and the Amgen Medical Monitor. Please note: thromboprophylaxis is recommended with pomalidomide treatment
11. History of clinically significant GI hemorrhage (Grade  $\geq 2$ ) in the 6 months prior to study day 1, unless agreed upon by the investigator and the Amgen Medical Monitor
12. Known positive results for Human Immunodeficiency Virus (HIV)
13. Prior systemic radiation therapy must have been completed at least 28 days before study day 1. Prior focal radiotherapy completed at least 14 days before study day 1
14. Prior use of pomalidomide if subjects required pomalidomide dose reduction or pomalidomide discontinuation due to toxicity

**Autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug. A Phase II Open Label, Multicenter, Trial of JNJ-42756493 in Combination with Dexamethasone for the Treatment of FGFR3 Wild-type or Mutation Positive Relapsed and/or Refractory Multiple Myeloma (Protocol: PM-MM003)**

***Inclusion Criteria***

**Patients must meet all of the following inclusion criteria to be eligible for participation in this study.**

1. A diagnosis of MM and documentation of at least 1 prior line of therapy including proteasome and immunomodulatory agents (in separate regimens or in combination).
2. Documented lab results confirming FGFR3 expression and mutational status determined by a clinical grade, next generation sequencing platform (e.g. Michigan Center for Translational Pathology, Foundation Medicine, Inc.) approved by the Sponsor-Investigator, the results of which must be obtained prior to registration.
3. Patients with measurable disease defined as at least one of the following (these baseline laboratory studies for determining eligibility must be obtained within 28 days prior to start of study drug):
  - Serum M-protein  $\geq 0.5$  g/dl ( $\geq 5$  g/l)
  - Urine M-protein  $\geq 200$  mg/24 h
  - Serum free light chains (FLC) assay: Involved FLC level  $\geq 10$  mg/dl ( $\geq 100$  mg/l) and an abnormal serum free light chain ratio ( $< 0.26$  or  $> 1.65$ )
4. The following laboratory results must be met within 7 days of first study drug administration:
  - Absolute neutrophil count (ANC)  $\geq 1,000$  cells/dL ( $1.0 \times 10^9$ /L). Growth factors cannot be given within 7 days of study drug administration.
  - Serum AST and ALT  $\leq 2.5$  x upper limit of normal (ULN).
  - Creatinine clearance  $\geq 40$  mL/min either directly measured via 24-hour urine collection or calculated using Cockcroft-Gault.
  - Platelet count  $\geq 50,000$  cells/dL ( $50 \times 10^9$ /L). Platelet transfusions to help patients meet eligibility criteria are not allowed within 7 days before study enrollment.
  - Hemoglobin  $\geq 8.0$  g/dL.
  - Total bilirubin  $\leq 1.5$  x ULN, unless known to have Gilbert's disease.
  - Albumin  $\geq 2.0$  g/dL (20 g/L).
  - Electrolytes: Magnesium within 0.85 to 1.25 x institutional ULN; Sodium  $\geq 130$  mEq/L; and potassium within institutional normal limits (correction with supplementation and re-testing is permitted).

## ***Exclusion Criteria***

**Patients who meet any of the following exclusion criteria are not eligible for enrollment.**

1. Patients in whom FGFR3 expression or mutational status cannot be determined.
2. Chemotherapy, limited palliative radiotherapy or other anti-myeloma therapy within 14 days prior to the first dose of study drug. In addition, any treatment-related toxicity should have recovered < Grade 1 unless deemed to be irreversible (an example of an irreversible toxicity would include steroid induced cataracts or peripheral neuropathy).
3. Patients who are receiving any other investigational agent.
4. Patients with known CNS involvement, plasma cell leukemia or amyloidosis.
5. Use of an investigational drug within 21 days or five-half-lives, whichever is shorter but not less than 14 days, preceding the first dose of study drug.
6. History of allogeneic stem cell transplant.
7. Autologous, peripheral stem cell transplant within 12 weeks of the first dose of study drug.

## **A Phase 2, Multicenter, Multi-Cohort, Open label Study of Pomalidomide in Combination with Low-Dose Dexamethasone or Pomalidomide in Combination with Low Dose Dexamethasone and Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma Following Lenalidomide-Based Therapy in The First or Second Line Setting (Protocol number: CC-4047-MM-014)**

### ***Key Inclusion Criteria***

1. Subjects must have documented diagnosis of multiple myeloma and have measurable disease by serum or urine protein electrophoresis (sPEP or uPEP): sPEP  $\geq$  0.5 g/dL or uPEP  $\geq$  200 mg/24 hours.
2. Subjects enrolling in Cohort A (Pom+LD-dex) must have received 2 prior treatment lines of anti-myeloma therapy. Subjects enrolling in Cohort B (Pom+Dara+LD-dex) must have received 1 or 2 prior treatment lines of anti-myeloma therapy.
3. All subjects must have received prior treatment with LEN or a LEN-containing regimen for at least 2 consecutive cycles as the most recent treatment regimen.
4. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
5. All subjects must have documented disease progression during or after their last antimyeloma therapy
6. All subjects must provide an adequate bone marrow sample at screening that definitively evaluates the presence or absence of myelodysplastic changes.

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

1. Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) < 1,000/ $\mu$ L
  - Hemoglobin < 8 g/dL (< 4.9 mmol/L)
  - Platelet count < 75,000/ $\mu$ L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/ $\mu$ L for subjects in whom  $\geq$  50% of bone marrow nucleated cells are plasma cells
  - Corrected serum calcium > 11.5 mg/dL (> 2.8 mmol/L)
  - Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN)
  - Serum total bilirubin > 2.0 x ULN
  - Severe renal impairment (creatinine clearance < 30mL/min) requiring dialysis
2. Previous therapy with pomalidomide or daratumumab
3. Hypersensitivity to thalidomide, LEN, or dex (this includes  $\geq$  Grade 3 rash during prior thalidomide or LEN therapy)

4. Clinically significant abnormal ECG finding at screening.
5. Prior history of malignancies, other than MM, unless the subject has been free of the disease for  $\geq 5$  years. Allowed exceptions include the following:
  - Basal or squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix or breast
  - Incidental histological finding of prostate cancer (TNM [tumor, nodes, metastasis] stage of T1a or T1b)
6. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment and are currently dependent on such treatment.
7. Subjects with any one of the following:
  - Congestive heart failure (NY Heart Association Class III or IV)
  - Myocardial infarction within 12 months prior to starting study treatment
  - Unstable or poorly controlled angina pectoris, including Prinzmetal's variant angina pectoris
8. Known human immunodeficiency virus (HIV) positivity; active infectious hepatitis A, B, or C; or chronic hepatitis B or C.

**A PHASE 3 RANDOMIZED, CONTROLLED, OPEN-LABEL STUDY OF SELINEXOR, BORTEZOMIB, AND DEXAMETHASONE (SVD) VERSUS BORTEZOMIB AND DEXAMETHASONE (VD) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM) - Protocol number: KCP-330-023 (BOSTON)**

***Key Inclusion Criteria***

1. Documented evidence of progressive MM (based on the Investigator's determination according to the modified IMWG response criteria) on or after their most recent regimen.
2. Prior treatment with bortezomib or other PI is allowed. Must have had at least a 6-month PI-treatment-free interval prior to C1D1 of study treatment.
3. Resolution of any clinically significant non-hematological toxicities (if any) from previous treatments to  $\leq$  Grade 1 by C1D1.
4. Adequate hepatic function within 28 days prior to C1D1:
  - Total bilirubin  $< 1.5 \times$  upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of  $< 3 \times$  ULN), and
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) normal to  $< 2 \times$  ULN.
5. Adequate renal function within 28 days prior to C1D1 (estimated creatinine clearance [CrCl] of  $\geq 20$  mL/min)
6. Adequate hematopoietic function within 7 days prior to C1D1: total white blood cell (WBC) count  $\geq 1500/\text{mm}^3$ , absolute neutrophil count  $\geq 1000/\text{mm}^3$ , hemoglobin  $\geq 8.5$  g/dL and platelet count  $\geq 75,000/\text{mm}^3$  (patients for whom  $< 50\%$  of bone marrow nucleated cells are plasma cells) or  $\geq 50,000/\text{mm}^3$  (patients for whom  $\geq 50\%$  of bone marrow nucleated cells are plasma cells).
  - Patients receiving hematopoietic growth factor support must have a 2-week interval between growth factor support and the Screening assessments, but they may receive growth factor support during the study.
  - Patients must have at least a 2-week interval from the last red blood cell (RBC) transfusion and 1-week interval prior to the Screening

***Key Exclusion Criteria***

1. Has received Selinexor or another XPO1 inhibitor previously.
2. Prior malignancy that required treatment, or has shown evidence of recurrence
3. Has any concurrent medical condition or disease (e.g., uncontrolled active hypertension, uncontrolled active diabetes, active systemic infection, active, unstable cardiovascular function).

4. Active plasma cell leukemia, systemic light chain amyloidosis, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, MM involving the central nervous system or Spinal cord compression.
5. Greater than Grade 2 neuropathy or  $\geq$  Grade 2 neuropathy with pain at baseline, regardless of whether or not the patient is currently receiving medication.
6. Intolerance, hypersensitivity, or contraindication to glucocorticoids.
7. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy  $\leq$  2 weeks prior to C1D1.
8. Prior autologous stem cell transplantation < 1 month or allogeneic stem cell transplantation < 4 months prior to C1D1.
9. Active graft versus host disease (after allogeneic stem cell transplantation) at C1D1.
10. BSA < 1.4 m<sup>2</sup> at baseline.
11. Life expectancy of < 4 months.

**An Open-Label, Randomized Phase 3 Study of Combinations of Nivolumab, Elotuzumab, Pomalidomide and Dexamethasone in Relapsed and Refractory Multiple Myeloma (Protocol number: CA209-602) - Enrollment on Hold by Sponsor**

***Inclusion Criteria***

1. Signed Written Informed Consent
2. Target Population
  - Must have received 2 prior lines of therapy which must have included at least 2 consecutive cycles of each immune modulatory drug (IMiD) and a proteasome inhibitor alone or in combination
  - Documented refractory or relapsed and refractory (R/R) multiple myeloma
  - Refractory (progressed on or within 60 days of treatment) to their last treatment
  - Subjects must have failed treatment with a proteasome inhibitor and an IMiD in one of the following ways
    - i. “Double Refractory” = Refractory to a proteasome inhibitor and an IMiD, and to their last treatment
    - ii. “Relapsed and refractory” = patients had achieved at least a partial response to previous treatment with proteasome inhibitor or IMiD, or both, but progressed within 6 months, and were refractory to their last treatment
  - Measurable disease at screening, based on central lab results within 28 days of randomization.
  - Eastern Cooperative Oncology Group (ECOG) performance status  $\leq$ 2
3. Age and Reproductive Status
  - Males and Females at least 18 years or legal age of consent per local regulations
  - Women of childbearing potential (WOCBP) must have two negative serum or urine pregnancy tests.
    - i. Men who are sexually active with WOCBP must agree for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks (except the Pd arm -where only 4 weeks is required) post-treatment completion
  - Women must not be breastfeeding
  - Male patients must not donate sperm, for up to 180 days (4 weeks only for Pd arm) post treatment completion
  - Azoospermic males and WOCBP who are not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section
  - All subjects must not donate blood for 90 days post treatment completion
  - All subjects must be willing and able to comply with Pomalyst® REMS program, where applicable
  - All subjects must agree not to share study medication

## Exclusion Criteria

1. Target Disease Exceptions
  - Subjects with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
  - Subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), amyloidosis, Waldenström's Macroglobulinemia, or POEMS syndrome (plasma cell dyscrasia with poly neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
  - Subjects with active plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of plasma/CD138+ cells or an absolute plasma cell count of  $2 \times 10^9/L$ )
2. Medical History and Concurrent Diseases
  - Women who are of childbearing potential not complying to the above described contraceptive measures or are breastfeeding, and sexually active fertile men whose partners are WOCBP if they are not complying to the above described contraceptive measures
  - Any uncontrolled or severe cardiovascular or pulmonary disease determined by the investigator, including:
    - i. NYHA functional classification III or IV, congestive heart failure, unstable or poorly controlled angina, uncontrolled hypertension, arrhythmia, or myocardial infarction in the past 12 months
    - ii. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
  - Active infection
  - Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
  - Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of initiation of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
  - Unable to tolerate thromboembolic prophylaxis while on the study
  - Hypersensitivity reaction to prior IMiD (thalidomide or lenalidomide)
  - Grade  $\geq 2$  peripheral neuropathy (per NCI CTCAE v4.0)
  - Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
  - Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation
  - Gastrointestinal disease that may significantly alter the absorption of pomalidomide
  - Prior or concurrent invasive malignancy, except for the following:
    - i. Adequately treated basal cell or squamous cell skin cancer
    - ii. Adequately treated in-situ cancer
    - iii. Any cancer (other than those noted above) from which the subject has been disease free for > 3 years prior to study entry
3. Prior Therapy or Surgery
  - Prior treatment with pomalidomide, Nivolumab (or any PD-1 or PD-L1 inhibitor) or Elotuzumab
  - Use of any anti-myeloma drug therapy, within 14 days of the initiation of study drug treatment or use of any experimental drug therapy or plasmapheresis within 28 days (or 5 half-lives of the experimental drug; whichever is longer) of the initiation of study drug treatment (includes dexamethasone). Bisphosphonate use permitted if initiated prior to first dose of study medication
  - Treatment with melphalan or monoclonal antibodies within 4 weeks (or 5 half-lives of the monoclonal antibody; whichever is longer) of the first dose of study drug
  - Prior autologous stem cell transplant within 12 weeks of the first dose of study drug
  - Prior allogeneic stem cell transplant except subjects who have completed the stem cell transplant > 12 months prior to first dose of study drug, have no current or history of graft versus host disease, and are not on topical or systemic immunosuppressive therapy

- Treatment with corticosteroids within 2 weeks of the first dose of study drug, except for the equivalent of 10 mg prednisone per day or corticosteroids with minimal to no systemic absorption (ie, topical or inhaled steroids) or for short course (4 days) of 40 mg dexamethasone or equivalent for emergency use (baseline M proteins must be drawn after this short course and prior to randomization). Adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
  - Major cardiac surgery within 8 weeks prior to the first dose of study drug; all other major surgery within 4 weeks prior to the first dose of study drug. (Kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities
4. Physical and Laboratory Test Findings
- Screening Laboratory evaluations within the following parameters:
- Absolute neutrophil count (ANC) < 1,000 cells/ $\mu$ L ( $1.0 \times 10^9$ /L) (Growth factors cannot be used within 1 week of first drug administration. No pegylated growth factors within 3 weeks of first drug administration)
  - Platelet count < 75,000 cells/ $\mu$ L ( $75 \times 10^9$ /L) (<  $30 \times 10^9$ /L if  $\geq 50\%$  of bone marrow nucleated cells were plasma cells). Qualifying laboratory value must occur at most recent measurement prior to study entry. No transfusions are allowed within 72 hours prior to qualifying laboratory value
  - Hemoglobin < 8 g/dl (No transfusions are allowed within 72 hours prior to qualifying laboratory value)
  - Total Bilirubin > 1.5 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin up to 3.0 X ULN)
  - AST (SGOT) and ALT (SGPT) > 3.0x ULN
  - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula < 30 mL/min
  - Corrected serum calcium  $\geq 11.5$  mg/dl within 2 weeks of initiation of study drug (despite appropriate measures such a short course of steroids, bisphosphonates, hydration, calcitonin)
5. Allergies and Adverse Drug Reaction a) History of allergy or hypersensitivity to study drug components

**A Phase 2, Multicenter, Open-label, Study to Determine the Safety and Efficacy for the Combination of Durvalumab (DURVA) and Daratumumab (DARA) (D2) in Subjects with Relapsed and Refractory Multiple Myeloma (Protocol Number: MEDI4736-MM-003) – Enrollment on Hold by Sponsor**

***Inclusion Criteria***

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

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

4. Subject has evidence of PD on or within 60 days of the most recent prior treatment regimen
5. Subject received an alkylating agent alone or in combination with other myeloma treatment
6. Subject has an Eastern Cooperative Oncology Group performance-status score of 2 or less
7. Subject's toxicities resulting from previous therapy (including peripheral neuropathy) have resolved or stabilized to  $\leq$  Grade 1.

**Exclusion Criteria:**

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

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

- Basal cell carcinoma of the skin
- Squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Carcinoma in situ of the breast
- Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative

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

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

## **A single arm phase II study of high-dose weekly Carfilzomib plus Cyclophosphamide and Dexamethasone in the Treatment of Relapsed Multiple Myeloma after 1-3 prior therapies (Protocol Number: MYX.1/MCRN-003) - Enrollment Temporarily on Hold**

### **Eligibility Criteria**

**Patients must fulfil all of the following criteria to be eligible for admission to the study:**

#### **Disease-Related**

1. Relapsed symptomatic multiple myeloma as per the International Myeloma Working group criteria [Palumbo 2009].
2. Measurable disease, as defined by one or more of the following (assessed within 21 days prior to registration):
  - Serum M-protein  $\geq$  5 g/L (0.5g/dL)
  - Urine Bence-Jones protein  $\geq$  200 mg/24 hours
  - Involved serum free light chain (FLC) measurement  $\geq$  100 mg/L (10 mg/dL), provided serum FLC ratio is abnormal (abnormal if FLC ratio is  $<$ 0.26 or  $>$ 1.65)
  - Biopsy proven plasmacytoma
  - For IgA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA)  $\geq$  750 mg/dL (0.75 g/dL)
3. Prior treatments with at least one, but no more than three, regimens for multiple myeloma.
4. Documented relapse or progressive disease on or after any regimen (subject's refractory to the most recent line of therapy are eligible except those who are refractory to bortezomib as described in exclusion criteria 1).
5. Achieved a response to at least one prior regimen (defined as  $\geq$  25% decrease in M-protein).

#### **Demographic**

1. Age  $\geq$  18 years.
2. Life expectancy  $\geq$  3 months.
3. ECOG performance status 0–2. Laboratory Requirements (must be done within 21 days of registration):
  - Hematology:
    - i. Absolute neutrophil count (ANC)  $\geq$   $1.0 \times 10^9/L$
    - ii. Hemoglobin  $\geq$  8 g/dL (80 g/L) (subjects may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines)
    - iii. Platelet count  $\geq$   $50 \times 10^9/L$  ( $\geq$   $30 \times 10^9/L$  if myeloma involvement in the bone marrow is  $\geq$  50%)
  - Biochemistry:
    - i. ALT  $\leq$  3.5 x UNL

- ii. Serum direct bilirubin  $\leq$  2 mg/dL (34  $\mu$ mol/L)
  - iii. Creatinine clearance (CrCl)  $\geq$  30 mL/minute (Cockcroft and Gault formula)
4. Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.
  5. Patients must be accessible for treatment and follow up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 1 ½ hour's driving distance) placed on patients being considered for this trial. (Call the CRO office at 613-533-6430 if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.
  6. In accordance with CRO policy, protocol treatment is to begin within 2 working days of patient registration.
  7. Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. Contraception must continue during study drug dose interruption intervals until 30 days after the last study drug administration. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

### ***Ineligibility Criteria***

**Patients who fulfill any of the following criteria are not eligible for admission to the study:**

#### **Disease-Related**

1. Bortezomib (alone or in combination) refractory disease defined as patients who do not respond to bortezomib, who initially respond and then progress while on bortezomib, or patients who relapse within 60 days of stopping bortezomib.
2. Prior carfilzomib treatment.
3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Waldenstrom's Macroglobulinemia or IgM myeloma
5. Plasma cell leukemia ( $> 2.0 \times 10^9$ /L circulating plasma cells by standard differential)

#### **Concurrent Treatments**

1. Chemotherapy or investigational agent within 3 weeks prior to registration or antibody therapy within 6 weeks prior to registration
2. Radiotherapy to multiple sites within 28 days prior to registration; localized radiotherapy to a single site within 7 days prior to registration
3. Plasmapheresis within 14 days of registration.

#### **Concurrent Conditions**

1. Pregnant or lactating females.
2. Major surgery within 21 days prior to registration.
3. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to registration.
4. Known human immunodeficiency virus infection.
5. Active hepatitis B or C infection.
6. Myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or

electrocardiographic evidence of acute ischemia or grade 3 conduction system abnormalities unless subject has a pacemaker.

7. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to registration.
8. Other malignancy, including MDS, within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels; or cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumours of the adrenal or pancreas.
9. Significant neuropathy ( $\geq$  grade 3, or grade 2 with pain) within 14 days prior to registration.
10. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
11. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity antiviral drugs, or intolerance to hydration due to pre-existing pulmonary or cardiac impairment.
12. Ongoing graft-versus-host disease.
13. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to registration.
14. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

## **A Phase I Trial of MK-3475 in Combination with Lenalidomide and Dexamethasone in Subjects with Multiple Myeloma (Protocol: Merck 023) - Enrollment on Hold by Sponsor**

### ***Inclusion Criteria***

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical research.
2. Be 18 years of age on day of signing informed consent.
3. Has a confirmed diagnosis of multiple myeloma based on standard criteria (see Durie 1986 for criteria [55]).
4. Currently has MM with measurable disease, defined as:
  - A monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL and/or
  - Urine monoclonal protein levels of at least 200 mg/24 hours
  - For subjects without measurable serum and urine M-protein levels, an abnormal free light chain ratio (normal value: 0.26 - 1.65) with involved FLC level  $\geq$ 10 mg/dL ( $\geq$ 100 mg/L).
5. Has relapsed/refractory MM who has failed at least two lines of prior therapy, including bortezomib and an IMiD (thalidomide, pomalidomide, lenalidomide).

**Relapsed MM** defined as disease progression following stabilization or a response to at least one anti-myeloma regimen.

**Refractory MM** defined as meeting one or more of the following:

  - Nonresponsive to most recent therapy (e.g., stable disease only, or progressive disease while on treatment)
  - Disease progression within 60 days of discontinuation from most recent Therapy
6. Be able to provide archival (if available) and newly obtained bone marrow aspirate/biopsy material for biomarker analysis and disease assessment.
7. Has a performance status of 0 or 1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function. All screening labs should be performed within 7 days of treatment initiation.
9. All subjects must agree to follow the regional requirements for lenalidomide counseling, pregnancy testing, and birth control; and be willing and able to comply with the regional requirements (for example, periodic pregnancy tests, safety labs, etc.).

## **Exclusion Criteria**

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has myeloma and a history of repeated infections, primary amyloidosis, hyperviscosity, plasma cell leukemia, POEMS syndrome, Waldenström's Macroglobulinemia or IgM myeloma.
3. Has a diagnosis of immunosuppressive disorder or is on any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
4. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e.  $\leq$  Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has had prior chemotherapy (including dexamethasone), targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e.  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.
  - Note: Subjects with  $\leq$  Grade 2 neuropathy are an exception to this criterion and may qualify for the trial.
  - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
  - Note: Toxicity that has not recovered to  $\leq$  Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 1.
6. Has been free of additional malignancy for at least 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
7. Has known clinically active CNS involvement.
8. Has an active autoimmune disease or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the trial.
9. Has evidence of active, non-infectious pneumonitis.
10. Has an active infection requiring intravenous systemic therapy.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) infection.
15. Has a clinically significant coagulopathy per investigator's assessment.
16. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
17. Has received an allogenic stem cell transplant.
18. Has received autologous stem cell transplant within 12 weeks before the first infusion.
19. Has received bortezomib, pomalidomide or thalidomide within 2 weeks before the first infusion.
20. Subjects with a prior history of Grade 4 rash associated with thalidomide treatment.
21. Has known hypersensitivity to thalidomide or pomalidomide.
22. Is planning for or is eligible for allogenic hematopoietic stem cell transplant.
23. Has known gastrointestinal disease that may significantly alter the absorption of lenalidomide.
24. Is unable or unwilling to undergo antithrombotic prophylactic treatment.

25. Has received a live vaccine within 30 days prior to first dose.

## **A Phase 1b/2 Study of Selinexor (KPT-330) in Combination with Backbone Treatments for Resistant/Refractory Multiple Myeloma (Protocol: KCP-330-017)**

### ***Inclusion Criteria***

1. Written informed consent
2. Age  $\geq$  18 years.
3. Histologically confirmed diagnosis, measurable disease and evidence of disease Progression of MM, based on IMWG guidelines.
4. Patients must have measurable disease as Defined by at least one of the following:
5. Serum M-protein  $\geq$  0.5 g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or
6. Urinary M-protein excretion at least 200 mg/24 hours; or FLC  $\geq$  100 mg/L, provided that FLC ratio is abnormal
7. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement (e.g., for IgA MM), then quantitative Ig levels by nephelometry or turbidometry are acceptable.
8. No evidence of prior drug-related toxicities to  $\geq$  Grade 2

### **SdP (Selinexor Dexamethasone Pomalidomide) Only:**

1. Relapsed and refractory MM with:
  - Documented evidence of PD after achieving at least SD for  $\geq$  1 cycle during previous MM treatment (i.e., relapsed MM).
  - Disease progression during or within 60 days from the end of the most recent MM treatment (i.e., refractory MM).
  - Previously undergone  $\geq$  2 cycles of lenalidomide and a proteasome inhibitor (in separate regimens or in combination).

### **SdB (Selinexor Dexamethasone Bortezomib) Only:**

1. Relapsed or refractory MM with
  - Documented evidence of relapse after  $\geq$  1 previous line of therapy.
  - Not refractory to bortezomib in their most recent line of therapy.

### **Both SdP and SdB:**

1. Eastern Cooperative Oncology Group (ECOG) Performance Status of  $\leq$  2.
2. Adequate hepatic function within 21 days prior to Cycle 1 Day 1 (i.e., Day -21 to Day -1): Total bilirubin  $<$  2x ULN, AST  $<$  2.5x ULN and ALT  $<$  2.5x ULN.
3. Adequate renal function within 21 days prior to Cycle 1 Day 1: estimated creatinine clearance of  $\geq$  45 mL/min, calculated using the formula of Cockcroft and Gault:  $(140 - \text{Age}) \cdot \text{Mass (kg)} / (72 \cdot \text{creatinine mg/dL})$  multiply times 0.85 if the patient is female.
4. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.
5. Adequate hematopoietic function within 21 days prior to Cycle 1 Day 1: total WBC count  $\geq$  1,500/mm<sup>3</sup>, ANC  $\geq$  1000/mm<sup>3</sup>, hemoglobin (Hb)  $\geq$  8.0 gm/dL, and platelet count  $\geq$  75,000/mm<sup>3</sup> for patients with plasma cells of  $<$  50% of bone marrow nucleated cells; or  $\geq$  30,000/mm<sup>3</sup> for patients with plasma cells of  $\geq$  50% of bone marrow nucleated cells.

6. Patients receiving hematopoietic growth factor support, including erythropoietin (EPO), darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophagecolony stimulating factor (GM-CSF), and platelet stimulators (e.g., eltrombopag or romiplostim or IL-11) may continue to do so.

### **Exclusion Criteria**

26. Smoldering MM.
27. Multiple myeloma that does not express M-protein or FLC (i.e., non-secretory MM is excluded), and quantitative Ig levels cannot be used instead.
28. Documented systemic amyloid light chain amyloidosis.
29. Active MM involving the central nervous system (CNS).
30. Plasma cell leukemia.
31. Pregnant or breastfeeding.
32. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy  $\leq$  2 weeks prior to Cycle 1 Day 1, and radio-immunotherapy within 6 weeks prior to Cycle 1 Day 1. However, dexamethasone, up to 40 mg per week, is allowed as monotherapy up to the start of study treatment on Cycle 1 Day 1.
33. Treatment with an investigational anti-cancer therapy within 3 weeks prior to receiving first dose of study drug on Cycle 1 Day 1.

### **SdB arm only:**

1. Prior history of neuropathy Grade  $> 2$ , or Grade 2 neuropathy with pain at screening (within 21 days prior to Cycle 1 Day 1).
2. Prior autologous stem cell transplantation  $< 1$  month, or allogeneic stem cell transplantation  $< 3$  months prior to Cycle 1 Day 1.
3. Active graft versus host disease after allogeneic stem cell transplantation. A life expectancy of  $< 3$  months.
4. Major surgery within four weeks prior to Cycle 1 Day 1.
5. Unstable cardiovascular function:
  - Symptomatic ischemia, Or
  - Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on anti arrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
  - Congestive heart failure (CHF) of New York Heart Association (NYHA) Class  $\geq 3$ , or
  - Myocardial infarction (MI) within 3 months prior to Cycle 1 Day 1. Ejection fraction (EF)  $< 40\%$  at screening.
  - Uncontrolled hypertension.
6. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to first dose.
7. Known active hepatitis A, B or C.
8. Known HIV infection or HIV seropositivity.
9. Prior malignancies except treated cervical carcinoma in situ. Cancer treated with curative intent  $> 5$  years before study enrollment and without evidence of recurrence will be allowed. Cancer treated with curative intent  $< 5$  years previously will not be allowed unless approved by the medical monitor.
10. Any GI dysfunction that prevents the patient from swallowing tablets, or interferes with absorption of study treatment.
11. A serious psychiatric or medical condition that, in the opinion of the investigator, could interfere with treatment.

## **An Open Label Continuation Study of the Oral AKT Inhibitor GSK2110183 in Subjects with Hematologic or Solid Tumor Malignancy (PROTOCOL No. PKB115131 [Rollover])**

### ***Inclusion Criteria***

**A subject will be eligible for inclusion in this study only if all of the following criteria apply:**

- 1. Is currently participating in a GSK2110183 study (monotherapy or in combination with an approved anti-cancer agent) sponsored by GSK or by another research organization working on behalf of GSK.**
- Currently benefitting from continued treatment and have an acceptable safety profile with GSK2110183 as determined by the investigator following previous treatment with GSK2110183 either as monotherapy or as part of a combination treatment regimen.
- Continued ability to swallow and retain orally administered study treatment(s) and does not have any clinically significant GI abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
- Has adequate organ function:
  - Absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/L$
  - Hemoglobin  $\geq 8.0$  g/dL
  - Platelets  $\geq 50 \times 10^9/L$
  - PT/INR and PTT  $\leq 1.5 \times$  ULN
  - Total bilirubin  $\leq 1.5 \times$  ULN (isolated bilirubin  $> 1.5 \times$  ULN is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ )
  - AST and ALT  $\leq 3 \times$  ULN. If liver involvement is present and ALT and AST levels are  $> 3 \times$  ULN and  $< 5 \times$  ULN, enrollment into PKB115131 can occur as long as there is no concurrent bilirubin or INR elevation
  - Serum creatinine OR Calculated creatinine clearance  $\leq$  ULN  $\geq 30$  mL/min
  - Ejection Fraction (LVEF)  $\geq 50\%$  by TTE or MUGA

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

**A subject will not be eligible for inclusion in this study if any of the following criteria apply:**

- Permanent discontinuation of GSK2110183 in the parent study due to toxicity or disease progression.
- Concomitant use of any type of anti-cancer treatment other than studied in the parent protocol.
- Local access to commercially available GSK2110183.
- Current use of a prohibitive medication(s) as listed in Section 7.2 of the protocol
- Current use of anticoagulants is only allowed if PTT/INR values fulfill entry criteria.
- Any unresolved toxicity  $>$  Grade 2, except for alopecia, (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.0) from parent study treatment at the time of transition to this study.
- History of HIV infection.
- Peripheral neuropathy Gr $>1$
- History of hepatitis B or C infection (subjects with evidence of cleared hepatitis B are permitted).
- Evidence of severe or uncontrolled systemic diseases (e.g., unstable, or uncompensated respiratory, hepatic, renal, metabolic or cardiac disease).
- QTcF interval  $>$  500 msec at the time of transition to this study.
- Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
- Evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association [NYHA, 1994] functional classification system at the time of transition to this study.
- Symptomatic or untreated leptomeningeal, CNS or brain metastases or spinal cord compression at the time of transition to this study.

**NOTE:** Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs (EIAEDs). Continued stability of brain metastases must be confirmed with imaging.

**Multicenter, Open-label, Single-arm, Phase 1b/2 Study of the Safety and Efficacy of Combination Treatment with Pomalidomide, Dexamethasone, and Carfilzomib (PdC) in Subjects with Relapsed and Relapsed/ Refractory Multiple Myeloma (Protocol: MMRC-048) - Enrollment Temporarily on Hold**

***Inclusion Criteria***

1. Relapsed and relapsed/refractory multiple myeloma requiring systemic therapy.
2. All subjects must have failed 1+ prior treatment, one of which must include lenalidomide therapy and have been determined to be refractory to it.
  - Refractory to lenalidomide will be defined as a history of progression on or within
  - 60 days of completion of a regimen of a minimum of 2 cycles containing full or maximally tolerated dose of lenalidomide.
  - Patients progressing on lenalidomide maintenance in the first line of therapy will be eligible provided that they have received at least 2 cycles of lenalidomide at best tolerated dose or at least 2 cycles of treatment which included lenalidomide at 25 mg per dose, or at equivalent renally-adjusted doses respectively. For patients requiring 3rd or higher line of therapy, lenalidomide-refractory status is not required.
  - In addition to lenalidomide refractory, subject's refractory to (1) pomalidomide (2) Carfilzomib, or (3) RVD are permitted limited to separate enrollment during Phase II
3. Measurable disease, as indicated by one or more of the following:
  - Serum M-protein  $\geq 0.5$  g/dL
  - Urine M-protein  $\geq 200$  mg/24 hours
  - If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement, then quantitative immunoglobulin levels are acceptable
  - Involved serum free light chains  $\geq 10$  mg/dL provided that free light chain ratio is abnormal
4. Males and females  $\geq 18$  years of age
5. Life expectancy of more than 3 months
6. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
7. Adequate hepatic function, with bilirubin  $< 1.5$  times the upper limit of normal (ULN), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $< 2.5$  times ULN
8. Absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/L$ , hemoglobin  $\geq 8$  g/dL, platelet count  $\geq 75 \times 10^9/L$ . Subjects may receive RBC transfusions or platelet transfusions, if clinically indicated in accordance with institutional guidelines. However, screening platelet count should be independent of platelet transfusions for at least 2 weeks.
9. Calculated or measured creatinine clearance of  $\geq 30$  mL/minute, calculated using the following formula of Cockcroft and Gault:
  - $(140 - \text{age}) \times \text{mass (kg)} \times 0.85$  (if female)  $72 \times \text{creatinine (mg/dL)}$
10. Written informed consent in accordance with federal, local, and institutional guidelines
11. Females of childbearing potential (FCBP)<sup>†</sup> must have a negative serum or urine pregnancy test with a sensitivity of at least 25mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation about pregnancy precautions and risks of fetal exposure.
12. Subjects must agree to adhere to all study requirements, visit schedule, outpatient treatment, required concomitant medications, and laboratory monitoring.

### **Exclusion criteria**

1. Non-secretory or hyposecretory multiple myeloma, defined as <0.5 g/dL M-protein in serum, <200 mg/24 hr urine M-protein, or disease only measured by serum free light chain
2. Subjects for whom there is the prospect of stem cell transplantation in the next 6 months in the treatment plan are excluded (including subjects for whom the PdC regimen is being considered as pre-transplant cytoreduction).
3. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
4. Plasma cell leukemia
5. Waldenström's macroglobulinemia or IgM myeloma
6. Radiotherapy to multiple sites or immunotherapy within 4 weeks before start of protocol treatment (localized radiotherapy to a single site at least 1 week before start is permissible)
7. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives ( $t_{1/2}$ ) prior to first dose, whichever time is greater
8. Refractory to bortezomib, except if meeting criteria for RVD-refractory group (during Phase II)

### **Concurrent Conditions**

9. Pregnant or lactating females
10. History of allergy to mannitol or prior hypersensitivity to thalidomide, lenalidomide or pomalidomide
11. Major surgery within 3 weeks prior to first dose, prior peripheral stem cell transplant within 12 weeks of study enrollment, Subject has received any anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal (with the exception of hormones for thyroid conditions or estrogen replacement therapy [ERT]), or any investigational therapy) within 21 days of enrollment.
12. Myocardial infarction within 6 months prior to enrollment, NYHA Class III or IV heart failure (Appendix B), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities
13. Uncontrolled hypertension or diabetes
14. Acute active infection requiring systemic antibiotics, antivirals, or antifungals within two weeks prior to first dose
15. Known or suspected HIV infection, known HIV seropositivity
16. Active hepatitis A, B, or C infection
17. Non-hematologic malignancy within the past 3 years except adequately treated basal cell, squamous cell skin cancer, thyroid cancer, carcinoma in situ of the cervix or breast, prostate cancer < Gleason Grade 6 with stable prostate specific antigen levels or cancer considered cured by surgical resection alone
18. Any clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent
19. Significant neuropathy (Grades 3-4, or Grade 2 with pain) at the time of the first dose and/or within 14 days before enrollment
20. Contraindication to any of the required concomitant drugs, including proton-pump inhibitor (eg, lansoprazole), enteric-coated aspirin, allopurinol or if a history of prior thrombotic disease, warfarin or low molecular weight heparin
21. Subjects in whom the required program of PO and IV fluid hydration is contraindicated, eg, due to pre-existing pulmonary, cardiac, or renal impairment
22. Subjects with known or suspected amyloidosis of any organ
23. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis.

## CHRONIC LYMPHOCYTIC LEUKEMIA TRIALS:

### A Randomized, Multicenter, Open-Label, Phase 3 Study of Acalabrutinib (ACP-196) Versus Investigator's Choice of Either Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia (PROTOCOL NUMBER: ACE-CL-309)

#### **Key Inclusion Criteria:**

1. Diagnosis of CLL that meets published diagnostic criteria (Hallek 2008):
  - Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing  $\geq 1$  B-cell marker (CD19, CD20, or CD23) and CD5.
  - Prolymphocytes may comprise  $\leq 55\%$  of blood lymphocytes.
  - Presence of  $\geq 5 \times 10^9$  B lymphocytes/L (5000/ $\mu\text{L}$ ) in the peripheral blood (at any point since diagnosis).
2. Must have documented CD20-positive CLL.
3. Active disease meeting  $\geq 1$  of the following IWCLL 2008 criteria for requiring treatment.
4. Meet the following laboratory parameters.
  - ANC  $\geq 750$  cells/ $\mu\text{L}$  ( $0.75 \times 10^9/\text{L}$ ), or  $\geq 500$  cells/ $\mu\text{L}$  ( $0.50 \times 10^9/\text{L}$ ) in subjects with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.
  - Platelet count  $\geq 50,000$  cells/ $\mu\text{L}$  ( $50 \times 10^9/\text{L}$ ), or  $\geq 30,000$  cells/ $\mu\text{L}$  ( $30 \times 10^9/\text{L}$ ) in subjects with documented bone marrow involvement, and without transfusion support 7 days before assessment. Subjects with transfusion-dependent thrombocytopenia are excluded. If an investigator has chosen Bendamustine/rituximab as the Arm B treatment, platelets must be  $\geq 75,000$  cells/ $\mu\text{L}$ .
  - Serum AST and ALT  $\leq 2.0 \times \text{ULN}$ .
  - Total bilirubin  $\leq 1.5 \times \text{ULN}$ .
  - Estimated creatinine clearance of  $\geq 30$  mL/min
5. Must have received  $\geq 1$  prior systemic therapy for CLL. If a single-agent anti-CD20 antibody was previously administered; subjects must have received  $\geq 2$  doses.

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

**Subjects will be ineligible for this study if they meet any of the following criteria**

1. Known CNS lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's Syndrome.
3. Uncontrolled AIHA or ITP defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids.
4. Prior exposure to a BCL-2 inhibitor (eg, venetoclax/ABT-199) or a BCR inhibitor.
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug.
6. Corticosteroid use  $> 20$  mg within 1 week before first dose of study drug, except as indicated for other medical conditions.
7. Prior radio- or toxin-conjugated antibody therapy.
8. Prior allogeneic stem cell transplant or prior autologous transplant within 6 months of first dose of study drug(s) or presence of graft-vs-host
9. Known history of infection with HIV or any uncontrolled active systemic infection (eg, bacterial, viral or fungal. Active CMV infection, active hepatitis B or C infection, ongoing drug-induced pneumonitis, history of bleeding diathesis.

10. Requires or receiving anticoagulation, requires treatment with a strong CYP3A inhibitor/inducer, requires treatment with proton-pump inhibitors.
11. Prothrombin time/INR or aPTT (in the absence of a Lupus anticoagulant) > 2.0 x ULN.

## **AMYLOIDOSIS TRIALS:**

### **A Phase 3, Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients with Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis (Protocol C16011)**

#### ***Inclusion Criteria:***

1. Male or female patients 18 years or older.
2. Biopsy-proven diagnosis of AL amyloidosis according to the following standard criteria:
  - Histochemical diagnosis of amyloidosis, as based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence
  - If clinical and laboratory parameters insufficient to establish AL amyloidosis or in cases of doubt, amyloid typing may be necessary
3. Measurable disease as defined by serum differential free light chain concentration (dFLC, difference between amyloid forming [involved] and nonamyloid forming [uninvolved] free light chain [FLC])  $\geq 50$  mg/L).
4. Objective, measurable major (cardiac or renal) organ amyloid involvement as defined as follows (amyloid involvement of at least 1 required):
  - Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram greater than 12 mm in the absence of a history of hypertension or valvular heart disease, or in the presence of unexplained low voltage (< 0.5 mV) on the electrocardiogram
  - Renal involvement is defined as proteinuria (predominantly albumin) > 0.5 g/day in a 24- hour urine collection
  - Note: Amyloid involvement of other organ systems is allowed, but not required.
5. Must be relapsed or refractory after 1 or 2 prior therapies.

For this protocol, relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy.

- Patient may not be refractory to proteasome inhibitor therapy
  - Given that the physician may select from an offered list of regimens to treat a specific patient, the patient may be refractory to an agent/s listed within the list of offered treatment choices
  - Must have recovered (ie,  $\leq$  Grade 1 toxicity or patient's baseline status) from the reversible effects of prior therapy
  - If a patient has received a transplant as his/her first-line therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant
6. Patient must meet criteria for 1 of the following AL Amyloidosis Risk Stages (as defined by NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds):
    - Stage 1: both NT-proBNP and troponin T under threshold
    - Stage 2: either NT-proBNP or troponin T [but not both] over threshold;
    - Stage 3: both NT-proBNP and troponin T over threshold (but NT-proBNP < 8000 pg/mL)
  7. ECOG Performance Status  $\leq 2$
  8. Clinical laboratory values:

- Absolute neutrophil count  $\geq 1000/\mu\text{L}$
  - Platelet count  $\geq 75,000/\mu\text{L}$
  - Total bilirubin  $\leq 1.5 \times \text{ULN}$
  - Alkaline phosphatase  $\leq 5 \times \text{ULN}$ ,
  - ALT or AST  $\leq 3 \times \text{ULN}$
  - Calculated creatinine clearance  $\geq 30 \text{ mL/min}$
9. Female patients who:
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study treatment, AND
  - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
  - Agree to completely abstain from heterosexual intercourse
- Male patients, even if surgically sterilized (ie, status post vasectomy), who:
- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, AND
  - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
  - Agree to completely abstain from heterosexual intercourse
10. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

### **Exclusion Criteria**

1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis.
2. Female patients who are lactating, breastfeeding, or pregnant.
3. Medically documented cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure (Section 15.6), myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically important autonomic disease.
4. Clinically overt multiple myeloma, including monoclonal BM plasma cells  $\geq 10\%$  to  $\geq 30\%$ , and at least 1 of the following:
  - Bone lesions
  - Hypercalcemia, defined as a calcium of  $> 11 \text{ g/dL}$
5. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements or GI procedure that could interfere with the oral absorption or tolerance of treatment.
6. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational or which would be considered as a treatment of AL amyloidosis. However, patients may be on chronic steroids (maximum dose 20 mg/day prednisone or equivalent [Section 15.7]) if they are being given for disorders other than amyloidosis (eg, adrenal insufficiency, rheumatoid arthritis, etc.).
7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
8. Ongoing or active infection, known HIV positive, known to be hepatitis B surface antigen-positive or has known or suspected active hepatitis C infection.
9. Psychiatric illness/social situations that would limit compliance with study requirements.
10. Known allergy to boron, MLN9708, any of the study treatments, their analogues, or excipients.
11. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, Voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.