

**Clinical Trials in Myeloma and Related Disorders at  
Princess Margaret Hospital  
May 2012**

**MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED #1**

**An Open-label, Pharmacokinetic Study of Lenalidomide (Revlimid®) and High-dose Dexamethasone induction therapy in previously untreated multiple myeloma (MM) patients with Various Degrees of Renal Dysfunction – Validation of Official Dosing Guidelines for Renal Failure.**

**Protocol RV-MM-PI-0505**

**Inclusion criteria**

1. Previously untreated, symptomatic multiple myeloma
2. Eligible for autologous stem cell transplantation as per Princess Margaret Hospital criteria.
3. Disease measurable by serum or urine M protein, free light chain assay, bone marrow plasmacytosis or plasmacytoma.
4. No prior myeloma therapy (Exception: up to 480 mg of dexamethasone is allowed within the past 28 days, as well as palliative, localized radiation therapy, without the requirement of a washout period prior enrollment)
5. Laboratory test results within these ranges:
  - Absolute neutrophil count  $\geq 1,000/\text{mm}^3$
  - Platelet count  $\geq 50,000/\text{mm}^3$  (untransfused)
  - Total bilirubin  $\leq 22 \text{ umol/L}$
  - AST (SGOT) and ALT (SGPT)  $\leq 2 \times \text{ULN}$  or  $\leq 5 \times \text{ULN}$  if hepatic metastases are present.
  - Renal function must be measured by 24hour urine for creatinine clearance (CrCl) – any level of CrCl is allowed for eligibility.
6. Able to take aspirin 81mg daily as prophylactic anticoagulation (patients intolerant to ASA may use low molecular weight heparin).

## **Exclusion criteria**

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

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
2. Use of any other experimental drug or therapy, except for up to 480 mg of dexamethasone or palliative, localized radiation therapy, without the requirement of a washout period prior enrollment.
3. Known hypersensitivity to thalidomide.
4. Any prior use of lenalidomide.
5. Concurrent use of other anti-cancer agents or treatments.
6. Known positive for HIV or infectious hepatitis, type B or C.
7. Evidence of AL amyloidosis

Contact: Dr. Christine Chen/Olga Levina Open for enrollment ONLY for subjects with renal impairment

## **MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED #2**

**Protocol: An Open-Label, Dose-Escalation, Phase 1/2 Study of the Oral Form of MLN9708, a Next-Generation Proteasome Inhibitor, Administered in Combination With a Standard Care Regimen of Melphalan and Prednisone in Patients With Newly Diagnosed Multiple Myeloma Requiring Systemic Treatment**

### **Inclusion criteria:**

1. Patient for whom standard MP treatment is indicated and who is not a candidate for HDT-SCT for 1 of the following reasons:
  - a. The patient is 65 years of age or older.
  - b. The patient is less than 65 years of age but has significant comorbid condition(s) that are likely to have a negative impact on tolerability of HDT-SCT
2. Patients must have measurable disease. Patients must have measurable disease defined by at least 1 of the following 3 measurements:
  - Serum M-protein: 1 g/dL ( $\geq$  10 g/L), Urine M-protein: 200 mg/24 hours

- Serum free light chain assay: involved free light chain level  $\geq 10$  mg/dL ( $\geq 100$  mg/L), provided that the serum free light chain ratio is abnormal
- 3. Counts requires as follows; ANC: 1,000/mm<sup>3</sup> and platelet count: 75,000/mm<sup>3</sup>.
- 4. Calculated creatinine clearance  $\geq 30$  mL/min
- 5. ECOG performance status of 0 to 2

**Exclusion Criteria:**

1. Peripheral neuropathy of Grade 2
2. Diarrhea: Grade 1, based on the NCI CTCAE grading, in the absence of antidiarrheals
3. Prior systemic therapy for MM, including investigational drugs. Prior treatment with corticosteroids or localized radiation therapy does not disqualify the patient (the maximum dose of corticosteroids should not exceed the equivalent of 160 mg of dexamethasone, a total of which can be given in a 2-week period).
4. Systemic treatment with strong inhibitors of CYP1A2 Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
5. QTc > 470 msec on a 12-lead ECG obtained during the Screening period.
6. Known or suspected human immunodeficiency virus (HIV) positive,
7. Known or suspected hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection

Contact: Dr. Christine Chen/Diana Arones Open for enrollment

**MULTIPLE MYELOMA TRIALS – NEWLY DIAGNOSED #3**

**A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone with or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma. Protocol CA204006**

**Inclusion Criteria**

- 1) Target Population
  - a) Age  $\geq 18$  years or legal age of consent per local regulations.
  - b) ECOG performance status  $\leq 2$ .
  - c) Life-expectancy > 3 months.
  - d) Newly diagnosed, untreated, symptomatic, documented myeloma AND;
    - i) Who are not candidates for high-dose therapy plus SCT because of age ( $\geq 65$  years) or coexisting conditions AND;
    - ii) Measureable disease: serum IgG, IgA, IgM M-protein  $\geq 0.5$  g/dL or serum IgD M-protein  $\geq 0.05$  g/dL or  $\geq 200$  mg urinary M-protein excretion /24-hour.

## Exclusion Criteria

### 1) Target Disease Exceptions

- a) Subjects with non-secretory or oligo-secretory or serum free light-chain only myeloma.
- b) Smoldering MM, defined as asymptomatic MM with absence of lytic bone lesions.
- c) Monoclonal Gammopathy of Undetermined Significance (MGUS) defined by all of the following: serum M protein < 3 g/dL, absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency related to monoclonal protein and (if determined) proportion of plasma cells in the bone marrow of 10% or less.
- d) Diagnosis of Waldenstrom's disease or other conditions in which IgM M protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.
- e) Plasma cell leukemia (defined as either 20% of peripheral WBC comprised of plasma/CD138+ cells or an absolute count of  $2 \times 10^9/L$ ).

### 2) Medical History and Concurrent Diseases

- a) Known or suspected cardiac amyloidosis; POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
- b) Significant cardiac disease as determined by the investigator including:
  - i) Known or suspected cardiac amyloidosis;
  - ii) Congestive heart failure of Class III or IV of the NYHA classification;
  - iii) Uncontrolled angina, hypertension or arrhythmia;
  - iv) Myocardial infarction in past 6 months;
  - v) Any uncontrolled or severe cardiovascular disease.
- c) Prior cerebrovascular event with persistent neurologic deficit.
- d) Known history of, or documented positive hepatitis B or C or HIV infection.
- e) Any medical conditions that, in the investigator's opinion, would impose excessive risk to the subject. Examples of such conditions include:
  - i) Any uncontrolled disease, such as pulmonary disease, infection, seizure disorder;
  - ii) Active infection of Hepatitis A or that requires parenteral anti-infective treatment;
  - iii) Any altered mental status or any psychiatric condition that would interfere with the understanding of the informed consent.
- f) Prior or concurrent malignancy, except for the following:
  - i) Adequately treated basal cell or squamous cell skin cancer;
  - ii) Cervical carcinoma in situ;
  - iii) Adequately treated Stage I or II cancer from which the subject is currently in complete remission;
  - iv) Or any other cancer from which the subject has been disease-free for

≤ 3 years.

g) Uncontrolled diabetes (defined as Hgb A1C ≥ 8.0% and fasting glucose ≥ 160 mg/dl).

h) Unable to tolerate thromboembolic prophylaxis including, aspirin, Coumadin (warfarin) or low-molecular weight heparin as clinically indicated.

### 3) Physical and Laboratory Test Findings

a) Corrected serum calcium ≥ 14 mg/dl within 2 weeks of randomization (despite appropriate measure such as a short course of steroids, bisphosphonates, hydration, calcitonin).

b) Absolute neutrophil count < 1000 cells/mm<sup>3</sup>. No growth factors allowed within 1 week of randomization.

c) Platelets < 75,000 cell/mm<sup>3</sup> (75 x 10<sup>9</sup>/L). Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

d) Hemoglobin < 8 g/dL. Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

e) Total bilirubin ≥ 2 x ULN, and direct bilirubin ≥ 2.0 mg/dL.

f) AST or ALT ≥ 3 x ULN.

g) Creatinine clearance (CrCl) < 30 mL/min measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula:

Female CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 0.85$   
72 x serum creatinine in mg/dl

Male CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 1.00$   
72 x serum creatinine in mg/dl

### 4) Prior Therapy or Surgery

a) Administration of systemic chemotherapy, biological, immunotherapy, clarithromycin or any investigational agent (therapeutic or diagnostic) for multiple myeloma except bisphosphonate therapy.

b) Treatment with plasmapheresis within 4 weeks prior to randomization.

c) No steroids within 3 weeks of randomization, except:

i) short course (of ≤ 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);

ii) ≤ 5 mg prednisone or equivalent per day;

iii) Steroid with little to no systemic absorption (ie, topical or inhaled steroids).

d) Major surgery within 4 weeks prior to randomization (kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities.

e) Radiation therapy within 2 weeks prior to randomization

Contact: Dr. Donna Reece/Luisa Del Rizzo Open for enrollment

## **MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY #1**

### **A PHASE II STUDY OF AT9283 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA**

**NCIC CTG Protocol Number: IND.191**

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria must be addressed PRIOR to registration.

#### **Eligibility criteria:**

1. A confirmed diagnosis of multiple myeloma, according to the internationally accepted criteria for myeloma, must have been made prior to initial treatment.
2. Patients must have measurable disease, according to the internationally accepted criteria for myeloma [Durie 2006].
3. Age > 18 years.
4. ECOG performance status of 0, 1 or 2.
5. Life expectancy > 3 months.
6. Patients must have received prior treatment for multiple myeloma and have relapsed or progressed on prior therapy. (There is no limit on number of prior treatment regimens, but patients must have completed prior treatment at least 4 weeks prior to registration. Patient must have recovered from any treatment related adverse events.)
7. Prior radiation is permitted, but must have been completed at least 4 weeks prior to registration.
8. Laboratory Requirements: (must be within 7 days prior to registration)  
Hematology:
  - Absolute granulocytes (AGC) >  $1.0 \times 10^9/L$
  - Platelets >  $70 \times 10^9/L$
  - Hemoglobin > 100 g/LBiochemistry:
  - Serum creatinine < 1.5 x ULN
  - Bilirubin normal
  - AST and ALT < 2 x upper normal limit
  - Calcium normal

9. In patients with significant cardiac history or prior anthracycline exposure, Left Ventricular Ejection Fraction (LVEF) must be  $\geq 50\%$ .
10. Patients must be accessible for treatment and follow-up.
11. In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient registration.

**Ineligibility criteria:**

1. Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, prostate cancer with stable PSA for  $> 3$  years, or other solid tumours curatively treated with no evidence of disease for  $> 5$  years.
2. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test within 7 days prior to registration and must be using effective contraception throughout the study.
3. Patients receiving concurrent treatment with other anti-cancer therapy.
4. Patients with active or uncontrolled infections, or with serious illnesses or medical conditions which would not permit that patient to be managed according to the protocol.
5. Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects) are not eligible.
6. Patients with uncontrolled hypertension (resting BP consistently higher than systolic  $> 140$  mmHg and/or diastolic  $> 90$  mmHg).

Contact: Dr. Donna Reece/Trina Wang – Open for enrollment

<b>MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY #2</b>
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**A Phase 3, Randomized, Open Label Trial of Lenalidomide/Dexamethasone with or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma**

**Inclusion Criteria**

Target Population

- a) Age  $\geq 18$  years or legal age of consent per local regulations
- b) ECOG performance status  $\leq 2$
- c) Life-expectancy  $> 3$  months
- d) Documented evidence of multiple myeloma and
- i) Received between 1 to 3 prior lines of therapy with documented progression

by EBMT criteria after the most recent therapy AND

- ii) Measureable disease: serum IgG, IgA, IgM M-protein  $\geq 0.5$  g/dL or serum IgD M-protein  $\geq 0.05$  g/dL or  $\geq 200$  mg urinary M-protein excretion /24-hour.
- e) Prior lenalidomide exposure is permitted only if they fulfill all of the following:
  - i) Best response achieved was  $\geq$  PR
  - ii) Were not refractory to prior lenalidomide defined as no progression while receiving lenalidomide or within 9 months of last dose of lenalidomide
  - iii) Subject did not discontinue lenalidomide due to a Grade  $\geq 3$  related AE
  - iv) Subject did not receive more than 9 cycles of lenalidomide and had at least 9 months between the last dose of lenalidomide and progression
  - f) Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG). The first should be performed within 10 - 14 days and the second within 24 hours prior to the start of the investigational product. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.
  - g) Women must not be breastfeeding.

## **Exclusion Criteria**

### 1) Target Disease Exceptions

- a) Subjects with non-secretory or oligo-secretory or free light-chain only myeloma
- b) Active plasma cell leukemia (defined as either 20% of peripheral WBC comprised of plasma/CD138+ cells or an absolute count of  $2 \times 10^9/L$ ).

### 2) Medical History and Concurrent Diseases

- a) All Adverse Events of any prior chemotherapy, surgery, or radiotherapy not resolved to NCI CTCAE (v. 3.0) Grade  $\leq 2$
- b) Known or suspected cardiac amyloidosis; POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
- c) Significant cardiac disease as determined by the investigator including:
  - i) Known or suspected cardiac amyloidosis
  - ii) Congestive heart failure of Class III or IV of the NYHA classification;
  - iii) Uncontrolled angina, hypertension or arrhythmia
  - iv) Myocardial infarction in past 6 months
  - v) Any uncontrolled or severe cardiovascular disease
- d) Prior cerebrovascular event with persistent neurologic deficit
- e) Known history of, or documented positive hepatitis B or C or HIV infection
- f) Any medical conditions that, in the investigator's opinion, would impose excessive risk to the subject. Examples of such conditions include:
  - i) Any uncontrolled disease, such as pulmonary disease, infection, seizure disorder
  - ii) Active infection of Hepatitis A or that requires parenteral anti-infective

treatment

iii) Any altered mental status or any psychiatric condition that would interfere with the understanding of the informed consent

g) Prior or concurrent malignancy, except for the following:

h) Uncontrolled diabetes (defined as Hgb A1C  $\geq$  8.0% and fasting glucose  $\geq$  160 mg/dl).

i) Unable to tolerate thromboembolic prophylaxis including, as clinically indicated, aspirin, Coumadin (warfarin) or low-molecular weight heparin.

### 3) Physical and Laboratory Test Findings

a) Corrected serum calcium  $\geq$  14 mg/dl within 2 weeks of randomization (despite appropriate measure such a short course of steroids, bisphosphonates, hydration, calcitonin)

b) Absolute neutrophil count  $<$  1000 cells/mm<sup>3</sup>. No growth factors allowed within 1 week of randomization.

c) Platelets  $<$  75,000 cell/mm<sup>3</sup> (75 x 10<sup>9</sup>/L). Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

d) Hemoglobin  $<$  8 g/dL. Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

e) Total bilirubin  $\geq$  2 x ULN , and direct bilirubin  $\geq$  2.0 mg/dL

f) AST or ALT  $\geq$  3 x ULN

g) Creatinine clearance (CrCl)  $<$  30 mL/min measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula:

Female CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 0.85$   
72 x serum creatinine in mg/dl

Male CrCl =  $(140 - \text{age in years}) \times \text{weight in kg} \times 1.00$   
72 x serum creatinine in mg/dl

### 4) Prior Therapy or Surgery

a) No major surgery within 4 weeks or radiation therapy within 2 weeks prior to randomization

b) Administration of chemotherapy, biological, immunotherapy, or investigational agent (therapeutic or diagnostic) within 3 weeks prior to randomization (14 days for non-myelosuppressive therapy). Subjects should be 6 weeks from last dose of nitrosourea, nitrogen mustards or monoclonal antibody, 12 weeks from autologous SCT, and 16 weeks from allogeneic SCT.

c) If prior allogeneic stem cell transplant, history of moderate to severe chronic graft versus host disease (GvHD)

d) Treatment with plasmapheresis within 4 weeks prior to randomization.

e) Prior therapy with elotuzumab or any IMiD (including pomalidomide), except for prior thalidomide or lenalidomide (as defined in inclusion criteria).

f) Refractory to prior lenalidomide

g) No steroids within 3 weeks of randomization, except:

i)  $\leq 5$  mg prednisone or equivalent per day

ii) Steroid with little to no systemic absorption (ie, topical or inhaled steroids)

5) Allergies and Adverse Drug Reaction

a) Known hypersensitivity to lenalidomide, dexamethasone, any excipients in the elotuzumab formulation or recombinant protein

b) History of Grade 4 rash associated with thalidomide treatment

6) Sex and Reproductive Status

a) Sexually active fertile men not using 2 forms of effective birth control if their partners are WOCBP.

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Contact: Dr. Donna Reece/Trina Wang– Open for enrollment

## **MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY #3**

**A Phase Ib Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the Oral AKT Inhibitor GSK2110183 Administered in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed/Refractory Multiple Myeloma**

### **Inclusion Criteria**

1. Performance status score of 0 - 2 according to the ECOG scale.

2. Able to swallow and retain oral medication.

3. Histologically confirmed diagnosis of secretory Multiple Myeloma (must have measurable M protein in serum or urine) with at least one of the following:

a. Serum M-protein  $\geq 1$  g/dl ( $\geq 10$ gm/l)

b. Urine M-protein  $\geq 200$  mg/24h

c. Serum FLC assay: Involved FLC level  $\geq 10$ mg/dl ( $\geq 100$ mg/l) and an abnormal serum free light chain ratio ( $<0.26$  or  $>1.65$ )

d. Biopsy proven plasmacytoma (should be measured within 28 days of Screening Visit)

4. Failed at least 1 line of systemic therapy containing proteasome inhibitor. The preparative regimen (with or without total body irradiation) and subsequent autologous stem cell rescue used for an autologous stem cell transplant are considered as one line of therapy.

5. Subjects with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:

- transplant was  $> 100$  days prior to study enrolment

- no active infection
6. Fasting serum glucose <126 mg/dL (<7 mmol/L). Subjects diagnosed previously with Type 2 diabetes must also meet the additional following criteria:
- Diagnosis of diabetes ≥6 months prior to enrolment
  - HbA1c ≤8% at Screening visit
7. Adequate organ system function as defined : ANC ≥ 1.0 X 10<sup>9</sup>/L, Hb ≥ 8.0 g/dL, Platelets ≥ 70 X 10<sup>9</sup>/L, serum creatinine <2.5mg/dL, creatinine clearance ≥ 30 mL/min

### **Exclusion Criteria**

1. Chemotherapy, radiotherapy, immunotherapy, or other anti-multiple myeloma therapy within 14 days prior to the first dose of any one of the drugs in the combination regimen. In addition, any drug-related toxicity should have recovered to Grade 1 or less.
2. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of any one of the drugs in the combination regimen.
3. History of an allogeneic stem cell transplant. Subjects with a history of an autologous stem cell transplant are NOT excluded if they meet Inclusion Criteria
4. Current use of prohibited medication (See protocol Section 9.2) during treatment with GSK2110183.
5. Current use of oral corticosteroids, with the exception of inhaled or topical steroids. Dexamethasone will be given only in combination with bortezomib on this study.
6. Anticoagulants are permitted only if the subject meets PTT and INR entry criteria. Their use must be monitored in accordance with local institutional practice.
7. Presence of active gastrointestinal disease or other condition that could affect gastrointestinal absorption (e.g. malabsorption syndrome) or predispose subject to gastrointestinal ulceration.
8. Evidence of mucosal or internal bleeding.
9. Presence of > Grade 1 peripheral neuropathy at screening.
10. Unresolved toxicity (except alopecia) ≥ Grade 2 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 4.0 [NCI-CTCAE, 2009] from previous anti-cancer therapy.
11. Any major surgery within the last four weeks.
12. Type 1 diabetes mellitus.
13. Any serious or unstable pre-existing medical, psychiatric, or other condition (including lab abnormalities) that could interfere with subject's safety or providing informed consent.
14. Known active infection requiring parenteral or oral anti-infective treatment.
15. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal or cardiac disease, unstable hypertension).
16. Primary or metastatic malignancy of the central nervous system.
17. Diagnosis of or treatment for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after

curative therapy.

18. QTc interval  $\geq$  470 msec.

19. Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3<sup>rd</sup> degree atrioventricular (AV) block.

20. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.

21. Class III or IV heart failure as defined by the New York Heart Association [NYHA, 1994] functional classification system.

22. Known hypersensitivity to any of the components of the study treatment.

23. Pregnant or lactating female.

24. History of known HIV infection.

25. Subjects with a positive test for Hepatitis B surface antigen (HBsAg) or a positive test for Hepatitis C (HCV) antibody are excluded.

Contact: Dr. Donna Reece/Diana Arones– Open for enrollment

## **MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY #4**

**A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma (and companion trial)**

### **Inclusion Criteria**

1. Subjects must have documented diagnosis of multiple myeloma and have measurable disease (serum M-protein  $\geq$  0.5 g/dL or urine M-protein  $\geq$  200 mg/24 hours).

2. Subjects must have undergone prior treatment with  $\geq$  2 treatment lines of anti-myeloma

therapy. Induction therapy followed by ASCT and consolidation/maintenance will be considered as one line.

3. Subjects must have either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy.

- Primary refractory: Subjects who have never achieved any response better than PD to any previous line of anti-myeloma therapy.

- Relapsed and refractory: Subjects who have relapsed after having achieved at least stable disease for at least two cycles of treatment to at least one prior regimen and then developed PD on or within 60 days of completing their last myeloma therapy.

4. All subjects must have received at least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib, either alone or in combination regimens.

5. Subjects must have received adequate prior alkylator therapy either as part of a stem cell transplant or a minimum of 6 consecutive cycles of an alkylator based therapy.

6. All subjects must have failed both lenalidomide and bortezomib and medical records must be available that provide documentation of the following criteria for refractoriness that make the subject eligible for the study:

a. All subjects must have failed treatment with the last lenalidomide-containing regimen in one of the following ways:

- Documented PD during or within 60 days of completing treatment with lenalidomide, or

- In case of prior response ( $\geq$  PR) to lenalidomide, subjects must have relapsed within 6 months after stopping treatment with lenalidomide-containing regimens

b. All subjects must have failed treatment with the last bortezomib-containing regimen in one of the following ways:

- Documented PD during or within 60 days of completing treatment with bortezomib, or

- In case of prior response ( $\geq$  PR) to bortezomib, subjects must have relapsed within 6 months after stopping treatment with bortezomib-containing regimens, or

- Subjects who have not had a  $\geq$  MR response and have developed intolerance/toxicity after a minimum of two cycles of a bortezomib-containing regimen. For example, a toxicity such as  $>$  grade 2 peripheral neuropathy or  $\geq$  grade 2 painful neuropathy. Peripheral neuropathy must resolve to grade 1 prior to study entry.

7. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

### **Exclusion criteria:**

1. Any of the following laboratory abnormalities:

· Absolute neutrophil count (ANC)  $<$  1,000/ $\mu$ 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

· Creatinine Clearance  $<$  45 mL/min according to Cockcroft-Gault formula

· Corrected serum calcium  $>$  14 mg/dL ( $>$  3.5 mmol/L)

· Hemoglobin  $<$  8 g/dL ( $<$  4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted)

· Serum SGOT/AST or SGPT/ALT  $>$  3.0 x upper limit of normal (ULN)

· Serum total bilirubin  $>$  2.0 mg/dL (34.2  $\mu$ mol/L); or  $\geq$  3.0 x ULN for subjects with hereditary benign hyperbilirubinaemia

2. Prior history of malignancies, other than MM, unless the subject has been free of the disease for  $\geq 3$  years. Exceptions include the following:
  - Basal or Squamous cell carcinoma of the skin
  - Carcinoma in situ of the cervix or breast
  - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
3. Previous therapy with Pomalidomide.
4. Hypersensitivity to thalidomide, lenalidomide, or dexamethasone. (This includes  $\geq$  Grade 3 rash during prior thalidomide or lenalidomide therapy.)
5. Resistance to high-dose dexamethasone used in the last line of therapy: Defined as disease progression on or within 60 days of receiving the last dose of high-dose dexamethasone used in the last line of therapy, either as single agent or in combination. Subjects who progressed on low-dose dexamethasone will qualify for the trial.
6. Peripheral neuropathy  $\geq$  Grade 2.
7. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant  $\leq 12$  months prior to initiation of study treatment or subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant  $> 12$  months prior to initiation of study treatment and are currently on immunosuppressive medications related to the transplant.
8. Subjects who are planning for or who are eligible for stem cell transplant.
9. 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 variant angina pectoris
10. Subjects who received any of the following within the last 14 days of initiation of study treatment:
  - Plasmapheresis
  - Major surgery (kyphoplasty is not considered major surgery)
  - Radiation therapy
  - Use of any anti-myeloma drug therapy
11. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment.
12. 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. Subjects receiving corticosteroids ( $> 10$  mg/day of prednisone or equivalent) within 3 weeks prior to enrollment.
13. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
14. Incidence of gastrointestinal disease that may significantly alter the absorption of pomalidomide.

15. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment will not be eligible to participate in this study.
16. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the informed consent form.
17. Pregnant or breastfeeding females.
18. Known HIV positivity or active infectious hepatitis A, B or C

Contact: Dr. Christine Chen/Trina Wang– Open for enrollment

## **MULTIPLE MYELOMA TRIALS – RELAPSED OR REFRACTORY #5**

### **An Open Label Continuation Study of the Oral AKT Inhibitor GSK2110183 in Subjects with Hematologic or Solid Tumor Malignancy. PROTOCOL NO.: PKB115131**

#### **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.
2. 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.
3. 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.
4. 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  $> 3 \times$ UNL 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:

1. Permanent discontinuation of GSK2110183 in the parent study due to toxicity or disease progression.
2. Concomitant use of any type of anti-cancer treatment other than studied in the parent protocol.
3. Local access to commercially available GSK2110183.
4. Current use of a prohibitive medication(s) as listed in Section 7.2 of the protocol
5. Current use of anticoagulants is only allowed if PTT/INR values fulfill entry criteria.
6. 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.
7. History of HIV infection.
8. Peripheral neuropathy Gr>1
9. History of hepatitis B or C infection (subjects with evidence of cleared hepatitis B are permitted).
10. Evidence of severe or uncontrolled systemic diseases (e.g., unstable, or uncompensated respiratory, hepatic, renal, metabolic or cardiac disease).
11. QTcF interval > 500 msec at the time of transition to this study.
12. Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
13. 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.
14. 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.

Contact: Dr. Christine Chen/Diana Arones– Open for enrollment

## AMYLOIDOSIS TRIAL

**Title: An Open label, Dose escalation phase 1 study of the oral formulation of MLN9708 administered weekly in adult patients with relapsed or refractory Light Chain (AL) Amyloidosis who require further treatment.**

### Inclusion Criteria:

1. Histologic diagnosis of AL amyloidosis confirmed by positive Congo red stain.
2. Measurable disease as defined by serum differential FLC concentration  $\geq 40$  mg/L (difference between amyloid forming and non amyloid forming FLC)
3. Less than 30% plasma cells in the bone marrow.
4. Must have measurable Heart or Kidney involvement (may have other organ involvement as well but either heart or kidneys involvement is a must): Renal involvement is defined as albuminuria  $> 0.5$  g/day in 24 hr urine analysis and Heart involvement is defined as presence of mean left ventricular wall thickness on echo of  $> 12$ mm in the absence of a h/o of HTN or valvular heart disease or unexplained low voltage ( $< 0.5$  mV) on ECG or NT-proBNP  $> 332$  ng/L in the absence of renal failure.
5. Relapsed or refractory after at least 1 prior line of therapy and should require further treatment
6. ECOG of 2 or less
7. Ejection fraction of  $\geq 40\%$  on echo
8. Plt.  $\geq 75$
9. Neutrophils  $\geq 1.0$
10. Total bilirubin  $\leq 1.5 \times$  ULN
11. ALP  $\leq 5 \times$  ULN
12. ALT and AST  $\leq 3 \times$  ULN

### Exclusion Criteria

1. Washout of 28 days for any investigational drugs
2. Failure to fully recover from the side effects of prior chemo
3. QTc  $> 470$  ms on a 12 lead ECG
4. NYHA class III or above
5. MI within last 6 months.
6. Chronic atrial fibrillation
7. Grade II or III AV block (Mobitz, Type I permitted)
8. Supine systolic BP  $< 90$  or symptomatic orthostatic HTN or a decrease of systolic BP  $> 20$  despite treatment for orthostatic HTN
9. H/o bleeding diathesis or currently on warfarin (pts. are allowed aspirin)
10. Severe diarrhoea ( $\geq$  grade 3) not controlled with meds or requires administration of TPN

11. Known GI disease which could interfere with GI absorption of the drug.
12. Grade 2 or above neuropathy
13. Known HIV, Hep b surface antigen positive or Hep C infection
14. Clinically overt multiple myeloma
15. Other active malignancy except nonmelanoma skin cancer, cervical cancer, treated early stage prostate cancer with PSA within normal limits or any completely resected carcinoma in situ.

Contact: Dr. Vishal Kukreti/Olga Levina – Open for enrollment

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