Protocol Title: Open-Label, Multicenter, Phase II Study of CLR 131 in Patients with Relapsed or Refractory (R/R) Select B-Cell Malignancies

Target Population:
- Multiple Myeloma
- Small Lymphocytic Lymphoma
- Marginal Zone Lymphoma
- Diffuse Large B Cell Lymphoma
- Chronic Lymphocytic Leukemia
- Lymphoplasmacytic Lymphoma
- Mantle-Cell Lymphoma

Summary: This study evaluates CLR 131 in patients with select B Cell Malignancies, including Multiple Myeloma (MM), Indolent Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL), Lymphoplasmacytic Lymphoma (LPL), Marginal Zone Lymphoma (MZL), Mantle Cell Lymphoma (MCL), and Diffuse Large B Cell Lymphoma (DLBCL) who have been previously treated with standard therapy for underlying malignancy.

Key Inclusion Criteria:
- Histologically or cytologically confirmed MM; CLL/SLL, LPL, MZL; or MCL OR histologically proven, de novo, DLBCL.
- ECOG Performance Status of 0 to 2.
- 18 Years of age or older.
- Life expectancy of at least 6 Months.
- If patient is on full-dose anticoagulation therapy, the anticoagulation therapy must be reversible and reversal of the anticoagulation therapy must not be life-threatening, as judged by the Investigator.
- Patients who have undergone stem cell transplant must be at least 100 Days from transplant.
- Patients with Multiple Myeloma:
  - At least 2 prior regimens and no more than 5, which must include at least 1 approved Proteasome Inhibitor (Bortezomib or Carfilzomib) and at least 1 approved immunomodulatory agent (Thalidomide, Lenalidomide, or Pomalidomide), with or without maintenance therapy, unless patients are ineligible to receive such agents.
  - Bone marrow biopsy within 28 Days of CLR 131 infusion demonstrating at least 5% plasma cell involvement.
  - Progressive disease defined by any of the following:
    - 25% increase in serum M-protein from the lowest response value during (or after) last therapy and/or absolute increase in serum M-protein of ≥ 0.5 g/dL.
    - 25% increase in urine M-protein from the lowest response value during (or after) last therapy and/or absolute increase in urine M-protein of ≥ 200 mg/24 h.
    - 25% increase in bone marrow plasma cell percentage from the lowest response value during (or after) last therapy.
    - Absolute bone marrow plasma cell percentage must be ≥ 10% unless prior CR when absolute bone marrow plasma cell percentage must be ≥ 5%.
    - New onset hypercalcemia > 11.5 mg/dL.
  - Measurable disease defined by any of the following:
    - Serum M-protein > 0.5 g/dL.
    - Urine M-protein > 200 mg/24 h.
    - Serum FLC assay: Involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.
    - Measurable Plasmacytoma.
- Patients who are non-secretors will be considered for accrual on a case-by-case basis by the Sponsor and will require an Investigator plan to define PD prior to enrollment and to assess clinical benefit after treatment.
Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, or Marginal Zone Lymphoma:

- Prior treatment with at least 2 and no more than 4 prior regimens, which may include chemotherapy, an approved anti-CD20 antibody with or without maintenance therapy, and an approved targeted agent, unless patients are ineligible to receive such agents.
- Patients with Helicobacter pylori+ mucosa-associated lymphoid tissue lymphoma must have received 1 prior antibiotic regimen for H pylori.
- At least 1 measurable nodal lesion with longest diameter > 15 mm or 1 measurable extranodal lesion (e.g., hepatic nodule) with longest diameter > 10 mm.

Patients with Helicobacter pylori+ mucosa-associated lymphoid tissue lymphoma must have received 1 prior antibiotic regimen for H pylori.

Patients with Mantle Cell Lymphoma:

- Prior treatment with at least 1 and no more than 2 prior regimens.
- At least 1 measurable nodal lesion with longest diameter > 15 mm or 1 measurable extranodal lesion (e.g., hepatic nodule) with longest diameter > 10 mm.

Patients with Diffuse Large B Cell Lymphoma:

- Relapsed or refractory to combination chemotherapy for DLBCL that contains Rituximab and an Anthracycline.
  - Relapsed disease is defined as either recurrence of disease after a CR or PD after achieving a partial response (PR) or SD.
  - Refractory disease is defined as failure to achieve at least SD with any 1 line of therapy or with PD ≤ 3 Months of the most recent chemotherapy regimen.
- One additional therapy or stem cell transplant for DLBCL is allowed.
- At least 1 measurable nodal lesion with longest diameter > 15 mm or 1 measurable extranodal lesion (e.g., hepatic nodule) with longest diameter > 10 mm.

Key Exclusion Criteria:

- Ongoing Grade 2 or greater toxicities due to previous therapies.
- Prior external-beam RT resulting in greater than 20% of total bone marrow receiving greater than 20 Gy.
- Prior total body or hemi-body irradiation.
- Extradural tumor in contact with the spinal cord or tumor located where swelling in response to therapy may impinge upon the spinal cord.
- Central nervous system involvement unless previously treated with surgery or radiotherapy with the patient neurologically stable and off corticosteroids.
- For patients with CLL/SLL, LPL, or MZL, transformation to a more aggressive form of NHL.
- Ongoing chronic immunosuppressive therapy.
- Clinically significant bleeding event within prior 6 Months.
- Ongoing anti-platelet therapy (except low-dose aspirin [e.g., 81 mg daily] for cardioprotection).
- Radiation therapy, chemotherapy, immunotherapy, or investigational therapy within 2 Weeks of eligibility-defining bone marrow biopsy.
- History of hypersensitivity to Iodine.

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For additional information: [https://clinicaltrials.gov/ct2/show/NCT02952508](https://clinicaltrials.gov/ct2/show/NCT02952508)