

**TYPE OF CANCER:** Chronic Lymphocytic Leukemia /  
Non-Hodgkin's Lymphoma  
**TYPE OF TRIAL:** Phase I/II  
**TRIAL SPONSOR:** Gilead  
  
**PRINCIPAL INVESTIGATOR:** NAM DANG, M.D., Ph.D.  
**CONTACT PERSON:** Christine Zades  
(702) 822-5456

### **STUDY SUMMARY**

Multi-center, Open-label, Dose-escalating Phase I/II Trial of GS 9219 Administered Once Every Three Weeks Intravenously to Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Non-Hodgkin's Lymphoma. GS-9219 is a novel inhibitor of DNA replication and has potent antiproliferative activity against activated Peripheral Blood Mononuclear Cells and various cell lines of hematopoietic origin.

### **TREATMENT OVERVIEW**

- Each cycle is 21 days long
- Patient should be seen by the physician at least every week
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression for up to 6 cycles

### **PRETREATMENT ASSESMENT**

- Written informed consent
- Medical history and complete physical examination
- Vital signs: height, weight, ECOG performance status
- Rai staging for CLL
- Ann Arbor staging for NHL and ISS staging for MM
- Serum pregnancy test (for females of childbearing potential only)
- 12-lead ECG
- Hematology
- Biochemistry
- Urinalysis
- Bone marrow
- Aspirate and biopsy (recommended, not required for CLL/NHL)
- Beta-2-microglobulin
- Radiologic evaluation by x-ray or CT as indicated
- Concomitant medications
- Chest x-ray (if no radiologic chest evaluation was performed within 4 weeks of dosing)
- Pulmonary function testing (spirometry with total lung volume and diffusion evaluation)

- Adverse event assessment

***For MM subjects, in addition to the above mentioned procedures:***

- Quantitative immunoglobulins
- Serum protein electrophoresis (SPEP)
- Immunofixation
- 24-hour urine collection for total protein and electrophoresis (UPEP) and immunofixation Serum free light chain assay
- C-reactive protein.
- Skeletal survey (MRI or CT scan are also acceptable if appropriate) including evaluation of plasmacytoma within 4 weeks of dosing is required.
- Bone marrow aspirate and biopsy (within 4 weeks of dosing) is required.

**ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL**

*Inclusion Criteria:*

- Age  $\geq$  18 years
- Subjects with relapsed or refractory CLL, NHL, or MM:  
Patients are considered relapsed or refractory when showing evidence of disease progression after having received at least two types of prior chemotherapy, i.e., primary treatment and at least one salvage therapy. The therapies must include a single drug or multiple combination chemotherapy regimen with well documented activity in NHL, CLL, or MM to ensure that only patients with no known effective alternative therapy are included.

Antibodies such as rituximab, when given alone will not count as a primary or salvage therapy. Antibody therapy, given in combination with a single drug or a combination chemotherapy regimen will be considered one prior chemotherapy.

Subjects with prior stem cell transplant (autologous or allogeneic) are eligible. Pre-induction chemotherapy with autologous or allogeneic transplant will be considered one prior chemotherapy.

– Subjects with CLL will be staged according to the Rai staging criteria (see Appendix 6). All patients in the Rai high-risk groups (i.e., Rai stages 3 and 4 based on the original five-stage system) are eligible. Intermediate risk patients (i.e., Rai stages 1 and 2 based on the original five-stage system) with one or more signs of active disease (such as progressive lymphocytosis, lymphadenopathy, splenomegaly, weight loss  $>$  10% within six months, extreme fatigue, fever and/or night sweats without evidence of infection) are also eligible.

– Subjects with NHL will be staged according to the Ann Arbor Classification (Appendix 7) and must present with bidimensionally measurable disease either on physical examination or on imaging studies. Any tumor mass measurable in two dimensions and  $\geq 2$  cm in its longest transverse diameter is acceptable (or  $\geq 1.5$  cm in its longest transverse diameter if 0.5 cm slices are used as in spiral CT scans).

– Subjects with MM will be staged according to the International Staging System (see Appendix 10). All patients with Stage II or III diseases are eligible. Subjects must have secretory and measurable disease [measurable defined as one or more of the following: serum M-protein  $\geq 1$  g/dL by serum protein electrophoresis, urine M-protein  $\geq 200$  mg/24 hours, serum free light chain (FLC) measurement  $\geq 10$  mg/dL provided serum FLC ratio is abnormal.]

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (see Appendix 5).

- Subjects must demonstrate adequate organ function during the Screening Period and at the Cycle 1 Pre-Dose assessment as defined below:

- Hematology:

Absolute neutrophil count (ANC)  $\geq 1,500$  cells/mm<sup>3</sup>,

Platelets  $\geq 100,000$ /mm<sup>3</sup>, and

Hemoglobin  $\geq 8.5$  mg/dL

- Liver Function:

Total serum bilirubin within normal range,

Aspartate transaminase (AST)  $\leq 3$  times ULN, and

Alanine transaminase (ALT)  $\leq 3$  times ULN

- Renal Function:

Serum creatinine  $\leq 1.5$  mg/dL

- Electrocardiogram (ECG) without evidence of clinically significant ventricular arrhythmias, conduction abnormalities, or active ischemia as determined by the Investigator.

- Women of childbearing potential and male partners of women of childbearing potential must agree to use a highly effective method of contraception.

- Ability to understand and willingness to sign a written informed

*Exclusion Criteria:*

- Subjects with AIDS-related lymphoma.

- Subjects with NHL who present exclusively with non-measurable lesions. Lesions that are considered intrinsically non-measurable

include the following: bone lesions; leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed by imaging techniques; cystic lesions; and lesions that are situated in a previously irradiated area.

- Subjects with MM who have non-secretory and/or non-measurable disease.
- Recent anticancer therapy: Patients who underwent chemotherapy, radiotherapy, any major surgery, and/or biotherapy within four weeks (at least 12 weeks for stem cell transplantation) prior to starting treatment with GS-9219 are excluded.
- Use of any investigational agents within four weeks prior to starting treatment with GS-9219.
- Other concurrent malignancy. Patients with a history of basal or squamous cell skin cancer and/or in situ cervical cancer within the previous three years who were treated adequately and with curative intent may be enrolled. Patients with a history of any other cancer who have been disease-free for at least five years must be carefully assessed at the time of study entry to rule out recurrent disease.
- Women who are pregnant or breast-feeding.
- Uncontrolled concurrent illness including, but not limited to, human immunodeficiency virus (HIV)-positive subjects receiving antiretroviral therapy, ongoing or active infection requiring systemic antibiotic, New York Heart Association class III or IV heart disease, unstable angina pectoris, ventricular arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients on chronic, systemically administered steroids, with the exception of inhaled steroids.
- Known hypersensitivity to nucleoside analogues in general, the study drug, the metabolites or formulation excipients