Phase I/II clinical trial of temsirolimus and lenalidomide in patients with relapsed and refractory lymphomas

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Patient Selection and Eligibility

Eligibility Criteria

1.1. Histology: Bone marrow biopsies (with the exception of lymphoplasmacytic lymphoma) as the sole means of diagnosis are not acceptable. Fine needle aspirates are not acceptable.

1.2. Phase I: Previously treated, histologically confirmed Hodgkin and non-Hodgkin lymphomas. The only exception to a requirement for a lymph node biopsy is lymphoplasmacytic lymphoma, which can be diagnosed based on morphologic evidence in the bone marrow plus the appropriate paraprotein.

1.3. Phase II: Previously treated, histologically confirmed mature NHL stratified by histology:

- 1.3.1. Group A: Diffuse large B-cell lymphoma (All patients with DLBCL must have germinal center vs. non-germinal center phenotype established via immunohistochemistry)
- 1.3.2. Group B: Follicular lymphoma
- 1.3.3. Group C: Lymphoma, NOS (including Hodgkin lymphoma, T-cell non-Hodgkin lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, and mantle cell lymphoma)

1.4. No limit to number of prior therapies. Prior autologous transplantation is allowed.

1.5. Age $\geq$18 years.

1.6. ECOG performance status $\leq$2.

1.7. Patients must have normal organ and marrow function as defined below:

- 1.7.1. absolute neutrophil count $\geq$ 1000/µl
- 1.7.2. platelets $\geq$ 75,000/µl
- 1.7.3. total bilirubin $\leq$ 1.5 X ULN (unless due to Gilbert's)
- 1.7.4. AST(SGOT)/ALT(SGPT) $\leq$ 2.5 X ULN
- 1.7.5. creatinine clearance $\geq$ 60 mL/min as determined by calculated Cockcroft-Gault equation
- 1.7.6. fasting serum cholesterol $\leq$ 350 mg/dL
- 1.7.7. fasting serum triglycerides $\leq$ 2.5 X ULN

1.8. All patients are required to have measurable disease. Non-measurable disease alone is not acceptable. Any tumor mass > 1 cm is acceptable. Lesions that are considered non-measurable include the following:

- 1.8.1. Bone lesions (lesions if present should be noted)

1.8.2. Ascites
1.8.3. Pleural/pericardial effusion
1.8.4. Lymphangitis cutis/pulmonis
1.8.5. Bone marrow (involvement by lymphoma should be noted)
1.8.6. For Waldenstrom's macroglobulinemia, Measurable disease is defined as at least one lesion with a single diameter of greater than 2 cm by computed tomography **or** bone marrow involvement with greater than 10% malignant cells and quantitative monoclonal protein (IgM, IgG, IgA) greater than 1,000 mg/dL.

1.9. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. Further, they 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 starting lenalidomide. 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. A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

1.10. Ability to understand and the willingness to sign a written informed consent document.

1.11. Patients who are HIV positive are allowed to participate BUT must meet the following criteria (see also Appendix D):

1.11.1. No AIDS-defining illness, AND
(see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm)
1.11.2. CD4 count $\geq$ 400 cells/mm3, AND
1.11.3. No anti-retroviral therapy (including HAART) within 7 days of starting protocol therapy, AND
1.11.4. Patient may not take concurrent anti-retroviral therapy (including HAART) while on protocol
1.11.5. Note: It is not generally recommended to suspend anti-retroviral therapy (including HAART). The medical team enrolling a patient who suspends anti-retroviral therapy for the purpose of study participation must have a documented note reviewing the potential risks/benefits with the patient in the medical chart.

Exclusion Criteria

1.1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.Patients who are receiving any other investigational agents.

1.2. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

1.3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to temsirolimus or lenalidomide used in study.

1.4. Because of the high potential for drug-drug interaction, patients requiring active anti-retroviral therapy for HIV are excluded.

1.5. No “currently active” second malignancy, other than non-melanoma skin cancers. Patients are not considered to have a “currently active” second malignancy if they have completed anti-cancer therapy and are considered by their physicians to be at less than 30% risk of relapse.

1.6. No history (within 3 months of study entry) of DVT/PE. Patients with a distant history (greater than 3 months before study entry) of DVT/PE are eligible, but should receive prophylactic aspirin or low molecular weight heparin.

1.7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

1.8. Patients with relapsed/refractory DLBCL or HL who are eligible and willing to undergo potentially curative stem cell transplant.

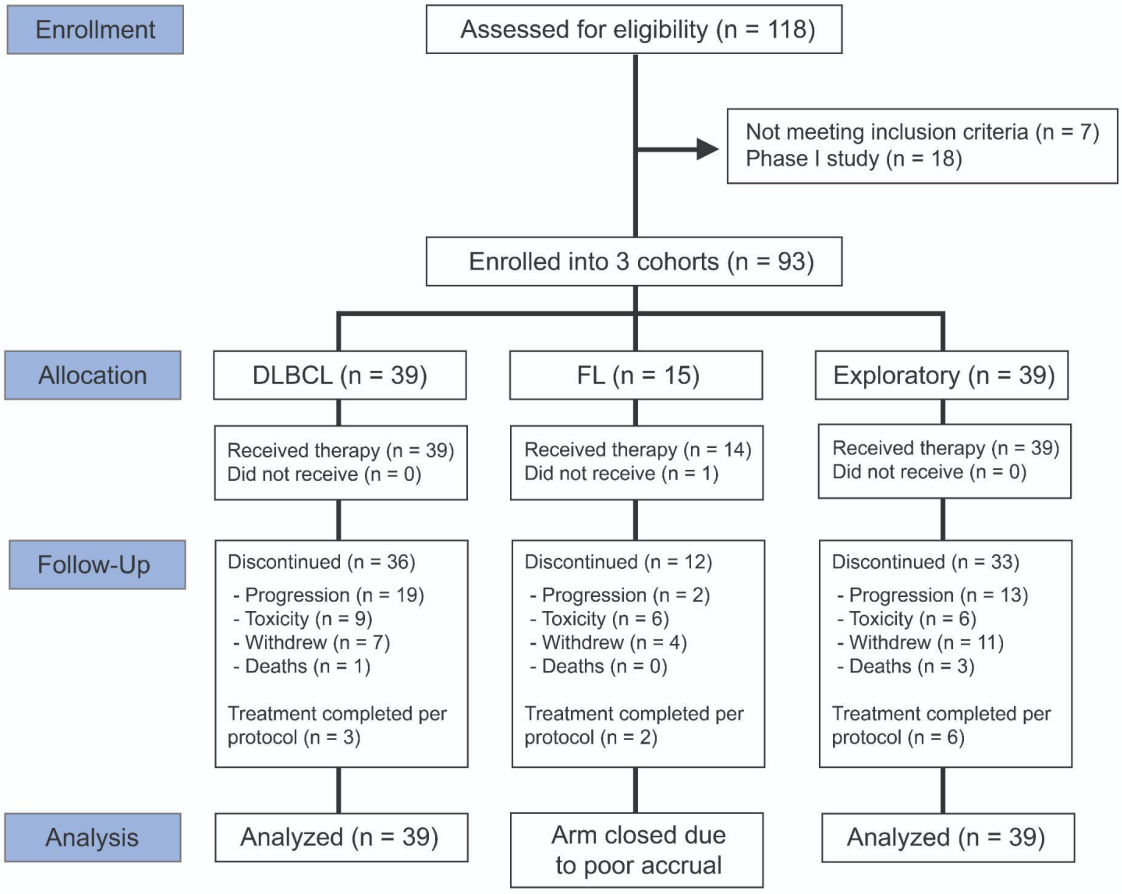
1.9. Patients with CLL/SLL are excluded.

1.10. No corticosteroids within 14 days prior to study, except for maintenance therapy for a non-malignant disease. Maintenance therapy dose may not exceed 10 mg/day prednisone or equivalent. Any patient on steroid therapy must receive thromboembolic prophylaxis.

Study Endpoints and Statistical Analysis

For the DLBCL and exploratory cohorts, we tested the null hypothesis that the response rate was ≤30% versus the alternative hypothesis that it was ≥50%, using the minimax design. Seven or fewer responses in the first 28 patients would result in early termination. Otherwise, an additional 11 patients were to be enrolled and, if there were 16 or more responders, the treatment would be deemed sufficiently active to warrant further study. For the FL cohort, we tested the null hypothesis that the response rate was ≤50% versus the alternative hypothesis that it was ≥70%. Eleven or fewer responses in the first 23 patients would lead to early termination of the trial. Otherwise, an additional 16 patients would be enrolled and, if there were 24 or more responders, the treatment would be considered worthy of further study. The designs provided 90% power under a one-sided alpha level of 0.10.

Supplementary Figure 1. CONSORT diagram for the phase II study.



Supplementary Table 1. Summary of reported toxicities in the phase I study occurring in either greater than 10% of patients or grade ≥3 in severity. There were no grade 5 toxicities in the phase I study.

Toxicity	All grades	Grade 3-4
Non-hematologic toxicity		
Abdominal pain	2 (11%)	0
ALT increased	7 (39%)	1 (6%)
Alk phos increased	4 (22%)	0
Allergic rhinitis	3 (17%)	0
Anorexia	8 (44%)	0
AST increased	6 (33%)	0
Bleeding	2 (11%)	0
Bilirubin increased	2 (11%)	0
Blurred vision	2 (11%)	0
Chills	3 (17%)	0
High cholesterol	6 (33%)	0
Constipation	3 (17%)	0
Cough	5 (28%)	0
Diarrhea	4 (22%)	0
Dizziness	4 (22%)	0
Dry eye	2 (11%)	0
Dry mouth	4 (22%)	0
Dysgeusia	5 (28%)	0
Dyspnea	3 (17%)	0
Edema	2 (11%)	0
Fatigue	10 (56%)	1 (6%)
Febrile neutropenia	1 (6%)	1 (6%)
Flushing	2 (11%)	0
Hyperglycemia	11 (61%)	3 (17%)

Hypermagnesemia	4 (22%)	0
Hypernatremia	2 (11%)	0
Hypertriglyceridemia	6 (33%)	2 (11%)
Hypoalbuminemia	8 (44%)	0
Hypocalcemia	6 (33%)	0
Hypokalemia	8 (44%)	2 (11%)
Hypomagnesemia	3 (17%)	0
Infection	2 (11%)	1 (6%)
Insomnia	3 (17%)	0
Myalgia	2 (11%)	0
Nausea	4 (22%)	0
Pneumonitis	1 (6%)	1 (6%)
Pruritus	4 (22%)	0
Rash	7 (39%)	0
Sinus disorder	2 (11%)	0
Skin infection	1 (6%)	1 (6%)
Vomiting	2 (11%)	1 (6%)
Hematologic toxicity		
Anemia	13 (72%)	4 (22%)
Lymphopenia	10 (56%)	8 (44%)
Neutropenia	10 (56%)	8 (44%)
Thrombocytopenia	14 (78%)	11 (61%)