

TYPE OF CANCER: Diffuse Large B-cell Lymphoma
TYPE OF TRIAL: Phase I
TRIAL SPONSOR: Seattle Genetics

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STUDY SUMMARY

A Phase Ib Study of SGN-40 (anti-huCD40 mAb) in Combination with Rituximab and Gemcitabine for the Treatment of Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

TREATMENT OVERVIEW

- Each cycle is 28 days long
- Patient should be seen by the physician at least every 2 weeks
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression for up to 8 cycles

PRETREATMENT ASSESMENT

- Informed consent
- Inclusion/exclusion criteria
- Demographics/ Medical history
- Physical Examination
- Vital signs (height, weight, ECOG)
- International Prognostic Index
- Archive or fresh tumor sample for CD40 expression
- Archive or fresh tumor sample molecular profiling and genomic analysis
- Tumor Evaluation [CT scan, PET scan]
- Lymphocyte subset analysis
- FcyR polymorphism analysis
- EKG/ECG
- Quantitative immunoglobulins
- Hematology
- Serum chemistry
- Lactate Dehydrogenase
- Phosphorus
- Urinalysis
- Coagulation Panel
- Pregnancy test

- Concomitant medications

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Patients must have a histologic diagnosis of DLBCL, including transformed histology and follicular grade 3 disease.
2. Patients must have at least one site of biopsy-proven disease defined as demonstrating both of the following:
 - bidimensional measurable disease with the longest axis >1.5 cm by radiographic imaging.
 - positive FDG-PET scan at baseline
3. Patients must have relapsed, refractory, or progressive disease following intensive salvage therapy, OR must have relapsed, refractory, or progressive disease following initial therapy and be medically unfit to receive intensive therapy (defined as combination chemotherapy +/- autologous SCT).
4. If applicable, patients must have completed auto SCT at least 8 weeks prior to Cycle 1, Day -2.
5. Patients must have completed treatment with chemotherapy, small molecule inhibitors, immune modulator drugs, rituximab, radiation, and/or treatment with other investigational anticancer agents (excluding investigational monoclonal antibodies) at least 4 weeks prior to Cycle 1, Day -2.
6. Patients must have completed treatment with any monoclonal antibody (other than rituximab), at least 12 weeks prior to Cycle 1, Day -2.
7. Patients must have completed treatment with any radioimmunoconjugate at least 12 weeks prior to Cycle 1, Day -2 and have recovered from all associated toxicity.
8. Either fresh or archived tumor specimen must be available to confirm diagnosis, assess CD40 expression level on tumor cells, and to perform correlative studies.
9. Patients must have the following required baseline laboratory data:
 - Platelet count $\geq 100,000/\text{mm}^3$.
 - Absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5x$ upper limits of normal (ULN).
 - Total serum bilirubin level $\leq 1.5 x$ ULN.
 - Serum creatinine $\leq 1.5 x$ ULN.
10. Females of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to Cycle 1, Day -2, prior to first dose. Females of non-childbearing potential are those who are post-menopausal >1 year or who have had a bilateral tubal ligation or hysterectomy.
 11. Patients must be at least 18 years of age.
 12. ECOG performance status ≤ 2 .
 13. Patients must be available for periodic blood sampling, study-related assessments, and management of toxicity at the treating institution.
 14. Patients or their legally authorized representative understands and voluntarily sign the written informed consent prior to any study-specific procedures. A copy of the signed informed consent form will be retained by the treating institution

Exclusion Criteria

Patients must not meet any of the following exclusion criteria to be eligible for the study:

1. Patients with a documented history within 6 months of Cycle 1, Day -2 of a cerebral vascular event (stroke or TIA), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV.
2. Patients who have received allogeneic stem cell transplant.
3. Patients who have had major surgery within 4 weeks prior to Cycle 1, Day -2.
4. Patients who have demonstrated prior intolerance of gemcitabine, rituximab, or any of the components of SGN-40 or its formulation.
5. Patients who have previously received treatment with an anti-CD40 mAb.
6. Patients with evidence of another invasive primary malignancy within the past three years other than non-melanoma skin cancer, cervical carcinoma in situ, in situ carcinoma of the breast, or fully resected prostate cancer with normal PSA within 8 weeks prior to Cycle 1, Day -2.
7. Patients with any active systemic viral, bacterial, or fungal infection requiring

intravenous anti-infectives within 4 weeks prior to Cycle 1, Day -2.

8. Patients known to be positive for HIV, hepatitis B (by surface antigen expression) or hepatitis C infection.
9. Patients with a history or clinical evidence of leptomeningeal or central nervous system (CNS) lymphoma.
10. Patients on systemic steroids exceeding 20 mg/day prednisone or equivalent at any time during the 7 days immediately prior to Cycle 1, Day -2.
11. Patients who are pregnant or breastfeeding.
12. Patients with any serious underlying medical condition or psychiatric illness that would impair their ability to receive or tolerate the planned treatment and followup.
13. Patients with dementia or altered mental status that would preclude the understanding and/or rendering of informed consent.