

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

1. Classification of systemic sclerosis (SSc), as defined using the 2013 American College of Rheumatology/European Union League Against Rheumatism classification of SSc [73].
2. Diagnosis of dcSSc, as defined by LeRoy and Medsger [74].
3. Disease duration \leq 60 months (defined as time from the first non-Raynaud phenomenon manifestation).
4. mRSS units \geq 15 and \leq 45, and both of the following:
 - a. At least mild skin thickening (\geq 1+ mRSS) of the forearm, and
 - b. At least moderate skin thickening (\geq 2+ mRSS) at the planned forearm skin biopsy site.
5. Documentation of at least 12 weeks of ongoing immunosuppressive therapy for SSc at the time of enrollment, and at least 4 weeks at a stable dose, of one of the following:
 - a. Methotrexate \leq 25 mg/week, or
 - b. Mycophenolate mofetil \leq 3 grams/day or mycophenolate sodium \leq 2.16 grams/day, or
 - c. Azathioprine \leq 3mg/kg/day.
6. Age 18-70 years inclusive.
7. Ability to provide informed consent.

Patients who meet any of the following criteria will not be eligible for this study:

1. Rheumatic disease other than dcSSc; it is acceptable to include patients with osteoarthritis, fibromyalgia, sicca symptoms, and scleroderma-associated myopathy.
2. Limited cutaneous SSs or sine scleroderma.
3. Pulmonary disease with FVC \leq 60% of predicted, or DLCO (corrected for hemoglobin) \leq 60% of predicted.
4. Pulmonary hypertension (PH) or moderate to severe left ventricular dysfunction, defined as one of the following:
 - a. Transthoracic echocardiography demonstrating at least one of the following (unless subsequent right heart catheterization does not demonstrate PH; or unless prior right heart catheterization within one year did not demonstrate PH and echocardiography results are not significantly changed):
 - i. Tricuspid regurgitation jet $>$ 2.8 m/sec or estimated right ventricular systolic pressure $>$ 42 mm Hg, or
 - ii. At least one of the following:
 1. Abnormality of right atrial size, shape, or wall thickness consistent with PH, or
 2. Abnormality of right ventricular size, shape, or wall thickness consistent with PH, or
 3. Abnormal septal wall shape consistent with PH
 - iii. Left Ventricular Ejection Fraction (LVEF) $<$ 50%.
 - b. Right heart catheterization showing mean pulmonary artery pressure \geq 25 mm Hg at rest.
 - c. Current use of approved medications for PH. It is acceptable to use phosphodiesterase type 5 (PDE-5) inhibitors for Raynaud's, digital ulcers, and intermittently for erectile dysfunction.
5. Active scleroderma renal crisis within the 4 months prior to enrollment.
6. History of moderate-to-severe lower gastrointestinal dysmotility such as current use of parenteral nutrition and/or recent history of intestinal pseudo-obstruction within 3 months prior to enrollment.
7. The following medications:
 - a. Oral corticosteroids $>$ 10 mg/day of prednisone or equivalent within 2 weeks prior to enrollment.
 - b. Treatment with intravenous immunoglobulin (IVIG) within 12 weeks prior to enrollment.
 - c. Treatment with cyclophosphamide within 6 months prior to enrollment.
 - d. Use of investigational biologic or non-biologic medication within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater.
 - e. Use of anti-TNF medication or other biologic medications within the past 90 days, or 5 half-lives prior to enrollment, whichever is greater.
 - f. Prior treatment with anti-CD20 if either of the following are true:
 - i. B cells \leq lower limit of normal (LLN), or
 - ii. Treatment with anti-CD20 has been within 12 months prior to enrollment.
 - g. Any prior treatment with cell-depleting therapies other than anti-CD20, including investigational agents, including but not limited to, CAMPATH $\text{\textcircled{R}}$, anti-CD4, anti-CD5, anti-CD3, anti-CD19.
 - h. Any prior treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation.
8. Receipt of a live-attenuated vaccine within 3 months of study enrollment.
9. Concomitant malignancies or a history of malignancy, with the exception of adequately treated basal and squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.
10. Major surgery (including joint surgery) within 8 weeks prior to enrollment.
11. History of solid organ or hematopoietic stem cell transplantation.
12. History of primary immunodeficiency.
13. Comorbidities requiring corticosteroid therapy, including those which have required three or more courses of systemic corticosteroids within the 12 months prior to enrollment.
14. Current substance abuse or history of substance abuse within 12 months prior to enrollment.
15. History of severe depression or severe psychiatric condition.
16. Lack of peripheral venous access.
17. Known hypersensitivity to brentuximab vedotin, a component thereof, or the excipient contained in the drug formulation.

18. Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study), including but not limited to:
 - a. Uncompensated congestive heart failure (New York Heart Association Class III or VI).
 - b. Clinically significant active coronary artery disease (e.g., unstable angina or acute myocardial infarction within 6 months prior to enrollment).
 - c. Recently active cerebrovascular disease (e.g., stroke or transient ischemic attack within 6 months prior to enrollment).
 - d. Uncontrolled systemic hypertension.
 - e. Confirmed diagnosis of diabetes mellitus.
 - f. Pancreatitis within 30 days prior to enrollment.
 - g. History of peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, or drug related neuropathy or neuritis.
19. Evidence of infection:
 - a. Any infected ulcer at enrollment.
 - b. Active bacterial, viral, fungal, or opportunistic infections requiring systemic anti-infective therapy.
 - c. Evidence of current or prior infection with tuberculosis
 - i. Positive QuantiFERON® – TB Gold or TB Gold Plus test results. Purified protein derivative (PPD) tuberculin test may be substituted for QuantiFERON® – TB Gold or TB Gold Plus test.
 - ii. Indeterminant QuantiFERON® – TB Gold test or TB Gold Plus results, unless followed by a subsequent negative PPD or negative QuantiFERON® and clearance by local Infectious Disease department.
 - d. Evidence of current or prior infection with human immunodeficiency virus (HIV), hepatitis B (as assessed by hepatitis B surface antigen, HBsAg and antibody to hepatitis B core antigen, anti-HBc) or hepatitis C.
 - e. History of progressive multifocal leukoencephalopathy (PML).
- f. Hospitalization for treatment of infections, or parenteral (intravenous or intramuscular) antibacterials, antivirals, anti-fungals, or anti-parasitic agents within the past 60 days prior to enrollment.
- g. Chronic infection that is currently being treated with systemic suppressive antibiotic or antiviral therapy, including but not limited to tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, and atypical mycobacteria.
- h. History of significant infection or recurrent infection that, in the investigator's opinion, places the participant at risk by participating in this study.
20. The following laboratory abnormalities:
 - a. Neutropenia (absolute neutrophil count $<1500/\text{mm}^3$).
 - b. Thrombocytopenia (platelets $<100,000/\text{mm}^3$).
 - c. Moderately severe anemia (hemoglobin $< 10 \text{ g/dL}$).
 - d. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase) results that are ≥ 1.5 times the upper limit of normal.
 - e. Serum total bilirubin > 1.5 times the upper limit of normal, or > 3 times the upper limit of normal in the presence of Gilbert's syndrome.
 - f. Serum amylase and serum lipase > 1.5 times the upper limit of normal.
21. Renal dysfunction, defined as either one of the following:
 - a. Serum creatinine > 1.5 times the upper limit of normal.
 - b. Estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73m}^2$.
22. Pregnancy.
23. Breastfeeding.
24. Unwillingness to use two forms of medically acceptable contraception methods by participants and their partners (if of reproductive potential) during the study and for at least 6 months after last dose of study drug.
25. Inability to comply with study and follow-up procedures.