Methods: SLS I randomized 158 SSc-ILD patients to 12 months of cyclophosphamide (CYC) vs. placebo. SLS II randomized 142 SSc-ILD patients to 12 months of CYC, followed by 12 months of placebo vs. 24 months of mycophenolate (MMF). QILD-WL scores were calculated at baseline and 12 months (SLS I) and 24 months (SLS II). Participants were followed for up to 12 (SLS I) and 8 years (SLS II). Using landmark survival analysis, Kaplan Meier curves were generated to compare survival between participants who had worse QILD-WL scores ($\geq 2\%$ increase) and those who had stable/improved QILD-WL scores ($< 2\%$ increase). Cox proportional hazards models were created to determine whether the change in QILD-WL scores predicted survival after controlling other variables found to affect survival in these cohorts.

Results: Among all the SLS I and II participants, 82 and 90 had follow up HRCT scans, respectively, and were included in these analyses. SLS I participants with an increase in QILD-WL scores of $\geq 2\%$ at 12 months had significantly worse long-term survival ($P = 0.01$; Figure). Similarly, SLS II participants with an increase in QILD-WL scores of $\geq 2\%$ at 24 months had significantly worse long-term survival ($P = 0.019$; Figure). After adjusting for baseline FVC, age, and modified Rodnan skin score (mRSS), an increase in QILD-WL scores of $\geq 2\%$ remained associated with worse long-term survival in SLS I (*trend*: $P = 0.089$) and SLS II ($P = 0.014$).

Conclusion: Progression of the radiographic extent of ILD of $\geq 2\%$ was associated with worse long-term survival in two independent SSc cohorts with extensive long-term follow up. The findings provide compelling evidence that short-term changes in the radiographic extent of ILD may serve as a surrogate endpoint for mortality in patients with SSc.

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OP0268

TREATMENT STATUS AFFECTS HOW PULMONARY BIOMARKERS PREDICT PROGRESSION OF SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE

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Background: The course of interstitial lung disease (ILD) varies considerably in patients with systemic sclerosis (SSc), and no biomarkers have been found to

consistently predict ILD progression in this population. Treatment may affect how a candidate biomarker correlates with improvement/worsening of SSc-ILD. We hypothesized that specific proteins recovered from bronchoalveolar lavage (BAL) would differentially predict progression of SSc-ILD based on whether a patient was receiving ILD therapy.

Objectives: (1) To assess the relationship between 68 unique BAL proteins measured in participants of Scleroderma Lung Study (SLS) I¹ and changes in radiographic extent of SSc-ILD; (2) To determine if treatment affects whether a specific protein predicts improvement or worsening of SSc-ILD.

Methods: Bronchoscopy was performed on 144 of the 158 participants in SLS I (Cyclophosphamide [CYC] vs. placebo) with 103 BAL samples available for analysis. BAL was lyophilized, concentrated 10X and used in a multiplex protein analysis of 68 distinct cytokines, chemokines and growth factors. Quantitative imaging analysis (QIA) was used to calculate the extent of radiographic fibrosis (QLF) in the whole lung using HRCT of the chest at baseline and 12 months. Multivariable linear regression models were created to determine the key BAL proteins associated with change in QLF scores using a backward selection process adjusting for treatment arm and ILD severity. The bootstrap procedure was employed for internal validation.

Results: A number of BAL proteins were significantly associated with change in QLF scores at 12 months; however, the directionality of these associations was often based on the presence/absence of treatment. For example, increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1, monocyte chemoattractant protein (MCP)-3, chemokine ligand (CCL)-5, transforming growth factor (TGF)- β , hepatocyte growth factor (HGF), stem cell factor (SCF), IL-4, TGF- α , were associated with worse QLF scores in patients who received placebo; whereas, increased levels of these same proteins were associated with improved QLF scores in patients who received CYC (Figure). Increased levels of Fractalkine were associated with worse in QLF scores, and increased levels of IL-7 were associated with improved QLF scores, regardless of treatment arm. In the multivariable model adjusting for treatment arm and baseline severity of ILD, IL-1, MCP-3, surfactant protein C, IL-7, and CCL-5 were independently associated with change in QLF scores.

Figure 1. Example of a specific BAL protein (GM-CSF) that predicts worse QLF scores in patients receiving placebo (Group B, Red dotted line) and improved QLF scores in patients receiving CYC (Group A, Blue solid line). Shaded areas represent 95% confidence intervals.

Conclusion: Proteins that mediate both inflammation and fibrosis differentially affected progression of SSc-ILD based on treatment status. Higher levels of certain proteins predicted worsening of ILD in patients receiving placebo, but improvement in patients receiving CYC. Measuring these proteins could help to identify patients who: (1) are at risk for ILD progression, and (2) may preferentially benefit from treatment with immunosuppression.

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OP0269

A COMBINED CLINICAL AND BIOMARKER ALGORITHM TO PREDICT FVC DECLINE IN SYSTEMIC SCLEROSIS ASSOCIATED INTERSTITIAL LUNG DISEASE: RESULTS FROM AN INTERNATIONAL MULTICENTRE OBSERVATIONAL COHORT

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