(n=80), endocrine irAEs (n=67), rheumatic (n=49) and pulmonary irAEs (n=17). So far, evaluation of tumour response was available for 551 patients, including 190 responders (complete response n=36 and partial response n=154), 192 patients with stable disease and 169 with progressive disease. 122/189 responders (65%) and 107/192 with stable disease (56%) experienced at least one irAE while reported only in 40/169 non responders (24%). Patients experiencing at least one irAE had an increased overall survival (median of 1169 days versus 224 days, $p<0.0001$, figure 1), without statistical difference according to organ system. Of note, there was also no statistical difference regarding tumour response or irAEs occurrence among the 9.4% of patients with preexisting inflammatory or autoimmune disease (60/636).

Abstract OP0088 – Figure 1. Overall survival according to irAE occurrence

Conclusions: Although irAE occurrence is not required for treatment benefit, it strongly associates with overall survival. Optimal multidisciplinary management of irAEs, including rheumatologists when needed, is worthwhile to maintain beneficial responses.

Disclosure of Interest: None declared

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New driving molecules in systemic sclerosis

OP0089 ABATACEPT IS EFFECTIVE IN EXPERIMENTAL DIGESTIVE AND LUNG TISSUE FIBROSIS

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Background: Cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) is an immunoregulatory membrane receptor resulting in the down-regulation of T-cell responses. A previous report showed that abatacept (CTLA4-Ig) prevented and induced regression of inflammation-driven dermal fibrosis in two different mouse models of systemic sclerosis (SSc).¹

Objectives: We aimed to assess the effects of abatacept in two complementary mouse models reflecting digestive involvement, lung fibrosis and pulmonary hypertension (PH), mimicking severe SSc organ damage.

Methods: Abatacept was given in the chronic graft-versus-host disease (cGvHD) mouse model, characterised by digestive involvement, and in the Fra-2 mouse model which is characterised by non-specific interstitial pneumonia and pulmonary vascular remodelling leading to PH. Mice were treated by intraperitoneal injections of abatacept (1 mg/mL in the cGvHD model for 6 weeks; 1 mg/mL or 10 mg/mL in the Fra-2 mouse model for 4 weeks) or human IgG1 (100 mg) used as a negative control.

Results: In the cGvHD model, treatment of allogeneically mice with abatacept led to a significant reduction of alanine aminotransferase (24%, $p=0.014$) and aspartate aminotransferase levels (61%, $p<0.001$). Pathological analysis of colon revealed decreased inflammatory infiltrates and destruction of crypts in allogeneically mice receiving abatacept.

When assessed by chest micro-CT imaging, Fra-2 mice treated with abatacept displayed a 12% decrease in lung density (10 mg/mL, $p=0.037$) as well as an increase in functional residual capacity as compared to IgG1-treated mice (16% for 1 mg/mL, $p=0.001$ and 14% for 10 mg/mL, $p=0.005$).

Consistent with these results, abatacept 10 mg/L decreased histological fibrosis score (Ashcroft score) as well as hydroxyproline content by 79% ($p=0.009$) and 31% ($p=0.044$) respectively, as compared to IgG1-treated mice.

Treatment with abatacept 10 mg/mL markedly reduced protein levels in the lesional lungs of Fra-2 mice of the fibrogenic markers MCP1 by 79% ($p=0.043$) and osteopontin by 87% ($p=0.039$). Levels of TGF- β were also reduced with abatacept (61% for 1 mg/mL, $p=0.037$ and 69% for 10 mg/mL, $p=0.013$). Further, abatacept decreased M1 and M2 macrophages infiltration as well as T-cell proliferation in the lesional lungs of Fra-2 mice.

Upon treatment with abatacept a reduction of right ventricular systolic pressure (28.1 ± 1.5 mmHg vs 36.0 ± 5.1 mmHg, $p=0.037$ for 10 mg/mL) and right ventricular hypertrophy (0.29 ± 0.01 vs 0.33 ± 0.010 , $p=0.037$ and 29 ± 0.01 vs 0.33 ± 0.01 for 10 mg/mL, $p=0.037$) was observed compared to IgG1-treated mice. Consistent with these findings, abatacept 10 mg/mL was associated with significant decrease in percent medial wall thickness and numbers of muscularized distal pulmonary arteries.

Conclusions: We demonstrate that treatment with abatacept improves digestive involvement, prevents lung fibrosis and attenuates PH in SSc pre-clinical mice models. These findings suggest that abatacept might be an appealing therapeutic approach for severe internal organ involvement in SSc beyond its already demonstrated effects on skin fibrosis.

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OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS

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Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis.

Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger of ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with idiopathic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and compared with biopsies from 13 healthy controls (HC). From 17 patients we had simultaneous biopsies from the upper and lower lung.

Results: Malondialdehyde as a marker of ROS formation was increased in ILD ($p=0.007$). The median proportion of mtDNA containing the pathogenic common deletion was 22.5% in ILD patients, compared to 0% in HC. This translated into a 3.8-fold diminishment of mtDNA-encoded cytochrome c-oxidase (COX2), but not nucleus-encoded (COX4) respiratory chain subunits in ILD compared to controls ($p<0.0001$) and a 33% diminishment of mtDNA-encoded cytochrome c-oxidase activity ($p=0.001$ vs controls). In all patients, the more fibrotic lower lungs had significantly more malondialdehyde ($p=0.0004$), mtDNA deletions ($p=0.0006$), and cytochrome c-oxidase dysfunction ($p=0.0003$) than the less-fibrotic upper lung counterparts. Conversely, lower lungs had significantly less ($p=0.0003$) mtDNA-encoded COX2 subunits in comparison to non-mtDNA-encoded COX4 subunits (figure 1). There was no association of any mitochondrial parameter with smoking status or age, and no difference between biopsies from patients with systemic sclerosis and non-specific interstitial pneumonitis.