P138 PRECLINICAL AND CLINICAL CHARACTERIZATION OF CENERIMOD, A POTENT, SELECTIVE, AND ORALLY ACTIVE SPHINGOSINE-1-PHOSPHATE RECEPTOR 1 MODULATOR IN SLE

[1]Daniel S Strasser, [1]Estelle Gerossier, [1]Virginie Sippel, [1]Ursula Grieder, [2]Andrea Kieninger-Graefitsch, [1]Gabin Pierlot, [1]Hervé Farine, [1]Paulina Kulig, [1]Marcel Keller, [1]Sylvie Froidevaux, [2]Marten Trendelenburg, [1]Mark Murphy, [1]Marianne Martinic. *[1]Idorsia Pharmaceuticals Ltd, Allschwil; [2]Division of Internal Medicine and Clinical Immunology, University Hospital Basel, Basel, Switzerland*

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Background Reported here is the characterization of cenerimod, a novel, potent, selective, and orally active sphingosine-1-phosphate receptor 1 ($S1P_1$) modulator in the context of SLE.

Methods Lymphocytes from patients with SLE and healthy subjects were assessed for cenerimod-induced $S1P_1$ receptor internalization. Efficacy of cenerimod was evaluated in the MRL/lpr lupus mouse model. In a 12-week phase 2 clinical trial in SLE subjects treated with multiple doses of cenerimod (NCT02472795), lymphocyte subsets and inflammatory biomarkers were characterized.

Results Cenerimod was potent and efficacious at inducing $S1P_1$ receptor internalization in T and B lymphocytes with an EC_{50} of ~15 nM in both healthy subjects and patients with SLE. In lupus-like MRL/lpr mice treated with cenerimod, circulating T and B lymphocytes were reduced, which resulted in reduced immune infiltrates into tissue, reduced autoantibody production and inflammation, preserved organ function, and increased survival. In SLE subjects treated with cenerimod for 12 weeks, a dose-dependent reduction of circulating T cells (95%), B cells (90%), and antibody-secreting cells (85%) was evident. Furthermore, a reduction in anti-dsDNA antibodies and IFN-α, two key inflammatory molecules, was observed.

Conclusion Cenerimod was potent and efficacious in reducing $S1P_1$ receptor surface expression on lymphocytes, resulting in reduced circulating T and B lymphocyte populations, including antibody-secreting cells, and a decrease in inflammatory biomarkers in SLE subjects. Furthermore, cenerimod significantly ameliorated systemic and organ-specific autoimmunity in a mouse model of SLE. These results warranted the further investigation of the clinical efficacy and safety of cenerimod in the ongoing phase 2b clinical trial (NCT03742037).

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P140 VERDINEXOR, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE), AMELIORATES CELLULAR AND MOLECULAR PATHOGENIC IMMUNE MECHANISMS OF SYSTEMIC LUPUS ERYTHEMATOSUS

[1]Javier Rangel-Moreno, [1]Nida Meednu, [1]Neha Nandedkar-Kulkarni, [2]Douglas G Widman, [1]Jennifer Anolik. *[1]Dept. of Medicine, University of Rochester, Rochester; [2]Karyopharm Therapeutics, Newton, USA*

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Background SLE is an autoimmune disease characterized by activation of the innate and adaptive arms of the immune system. Recently the nuclear export protein exportin-1 (XPO1) has surfaced as an attractive target for the treatment of SLE. Verdinexor is a potent, orally available and well-tolerated XPO1 inhibitor. Verdinexor inhibits the nuclear export of ~220 cargoes, and this pleiotropic effect leads to dampening of the NF-κB and IL-6 responses and is linked to its global anti-inflammatory effects. Thus, we examined the ability of verdinexor to alleviate the pathogenic mechanisms underlying SLE.

Methods The minimal efficacious dose of verdinexor was determined in mice with established disease. Mice were dosed with verdinexor for four weeks, followed by treatment cessation for four weeks. Then, escalating doses of verdinexor were tested for their ability to control recurrent disease. We enumerated pathogenic plasma cells (PC), plasmablasts (PB), and T cells in the spleen and bone marrow (BM) and measured systemic inflammatory cytokines and chemokines. Elucidation of the mechanism of PC and PB depletion in human BM from healthy and SLE patients is underway.

Results Verdinexor treatment at 7.5 mg/kg weekly significantly decreased germinal center B cells, PC and PB in the BM and the spleen four weeks after resumption of treatment without affecting normal cells. Furthermore, levels of pro-inflammatory cytokines, chemokines, and B cell survival factors were all significantly decreased. Results from assays in human BM have confirmed these findings.

Conclusions Verdinexor has demonstrated efficacy in a murine model of SLE by reducing generation, survival and function of auto-reactive immune cells without affecting normal cells. It is likely that inhibition of the NF-κB pathway and impaired IL-6 production underlie verdinexor's efficacy. Taken together with our findings in human BM cells, these data suggest the potential of verdinexor to have a significant impact on disease progression in lupus patients.

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P141 OCCURRENCE OF NEUROPSYCHIATRIC MANIFESTATIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM THE SWISS LUPUS COHORT AND META-ANALYSIS OF THE PERTINENT LITERATURE

[1,2]Aline Meier, [2]Lucas M Bachmann, [1]Urs Steiner. *[1]Dept. of Immunology, University Hospital of Zürich, Zürich; [2]Medignition healthcare innovations, Zürich, Switzerland*

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Background Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, often presenting with neuropsychiatric manifestations. Reports on the frequency and patterns of these manifestations vary substantially and remain incompletely understood. We examined neuropsychiatric manifestations in the prospective nationwide cohort of Swiss SLE (SSCS) patients and conducted a systematic literature review to contextualise our findings.

Methods We reviewed all patients included in the SSCS from 2007–2019 and classified severe neuropsychiatric manifestations. Searches were performed in relevant electronic databases from 1.1999–1.2020 and by checking reference lists of the pertinent literature. Authors of important papers were contacted to obtain further (unpublished) studies. We included