Corresponding Author	Simona Stivala
List all other authors	Alina Makeeva, Tiago Almeida Fonseca, Laetitia Clauss, Etnik Sheremeti, Elena Ratti, Martina Konantz, Karin Hartmann
Email-Address	simona.stivala@unibas.ch
Institute/Department	Department of Biomedicine, University Hospital Basel
Address of Institute	Hebelstrasse 20
Title of Presentation	Mice Expressing KitD814V In The Mast Cell Lineage Show a Systemic Mastocytosis Phenotype with Skin Lesions That Can Be Reversed By Treatment With Kit-Targeting Tyrosine Kinase Inhibitors
abstract-hint	
Abstract of Presentation	Research in mastocytosis, a disease with an abnormal expansion of mast cells (MC) in bone marrow (BM) and/or other tissues, has been hampered by the lack of suitable animal models. Therefore, we generated by CRIPSR-Cas9 a novel knock-in mouse line expressing oncogenic Kit D814V and characterized this line as a preclinical model for systemic mastocytosis. Constitutive expression of Kit D814V in the MC lineage (Mcpt5-Cre;KitD814V fl/+) resulted in progressive eczematous skin lesions, located on the neck, between the ears and around the eyes, resulting from a scratching behavior that was absent in control mice. MC accumulated in the skin, BM, spleen liver and stomach, while peripheral blood count was unaltered, consistent with a phenotype of systemic mastocytosis. Expansion of MC resulted in elevated serum levels of murine MC protease-1 (mMCP-1) and markedly reduced body weight. Olink proteomic analysis revealed a significant upregulation of inflammatory cytokines (TNFalpha and IL-6), chemotactic factors (IL-16, Ccl2 and Ccl12), and immune checkpoint molecules (PD-L1 and PD-L2). In a model of IgE-mediated anaphylaxis, Mcpt5-Cre;KitD814V fl/+ mice showed an amplified response with a significantly higher drop in body temperature, delayed recovery and increased mortality. Treatment with 30 mg/kg

	avapritinib daily resulted in a significant reduction in skin MC, a five-fold reduction in mMCP-1 serum levels, as well as resolution of chronic itch, as indicated by the absence of skin lesions. In conclusion, this mouse line could represent an invaluable tool for the investigation of the pathogenesis of systemic mastocytosis, and the identification of novel targetable pathways.