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Title: Effects of broad spectrum tyrosin kinase inhibitor on pulmonary circulation homeostasis

Dr. Andrei 9800 Seferian andreiseferian@yahoo.com MD [1,2], Dr. Ly 9801 Tu lyieng@gmail.com [2], Dr. Alice 9802 Huertas alicehuertas@gmail.com MD [1,2], Mrs. Carole 9803 Phan phancarole@gmail.com [2], Mrs. Morane 9804 Le Hiress moranelh@gmail.com [2], Dr. Nicolas 9805 Ricard nic.ricard@gmail.com [2], Dr. Frederic 9806 Perros fredericperros@gmail.com [2], Dr. Peter 9807 Dofmüller peter.dorfmuller@u-psud.fr MD [2], Prof. Dr Gerald 9808 Simonneau gerald.simonneau@bct.aphp.fr MD [1,2], Prof. Dr Marc 9809 Humbert humbert.mjc@gmail.com MD [1,2], Dr. David 9810 Montani davidmontani@gmail.com MD [1,2] and Dr. Christophe 9811 Guignabert guignabert@gmail.com [2]. [1] Service De Pneumologie, Hôpital Bicêtre, Le Kremlin Bicêtre, France, 94270 and [2] Inserm U999, DHU TORINO, LabEx Lermit, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France, 92350 .

Body: The platelet derived growth factor (PDGF) pathway is altered in pulmonary hypertension (PH) and imatinib a tyrosine kinase inhibitor (TKI) of PDGF has shown encouraging results in animal models of PH. In the meantime, there is an increasing number of PH cases induced by dasatinib, a broad spectrum TKI. We studied the effects of dasatinib administration in rats: i) chronically and ii) as a pre-treatment before monocrotaline (MCT) injection; and secondary, the impact of dasatinib on cultured human pulmonary endothelial cells was examined by MTT and AnnexinV-PI assay. Forty rats, divided into three groups received daily intraperitoneal (IP) injections of: vehicle, dasatinib 1x and 10x the clinical dose/day, for maximum 8 weeks. Three rats developed mild PH with a normal cardiac output, but with pulmonary arterial remodeling. One-week pretreatment by dasatinib (same doses) before MCT administration was dose-dependently associated with a more severe hemodynamic profile, greater right ventricular hypertrophy and increased muscularization of distal pulmonary arteries, while imatinib (clinical dose) had a protective effect. In vitro, dasatinib had an important cytotoxic effect on cultured human pulmonary endothelial cells - MTT(50) between 100-200nM, effect due to a dose-dependent increase in apoptosis. In conclusion, chronic dasatinib treatment in rats causes mild PH and as pretreatment aggravates the MCT-induced PH model. Pulmonary endothelial dysfunction may play a fundamental role in dasatinib-induced PH.