R-Crizotinib predisposes to and exacerbates pulmonary arterial hypertension in animal models

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To the Editor:

Pulmonary hypertension (PH) is a life-threatening disease of multiple aetiologies. Regardless of the underlying cause, PH is characterised by vasoconstriction and progressive thickening of the pulmonary vessel wall, all of which is initiated by the loss of pulmonary artery endothelial cells (PAECs) [1]. Indeed, a large body of work has shown that damaged or apoptotic PAECs initiate the remodelling process through the release of growth, fibrogenic and pro-inflammatory factors that directly induce contraction and enhance survival and proliferation of adjacent pulmonary artery smooth muscle cells (PASMCs) and fibroblasts [1, 2]. Over the past decade, intense research efforts have been directed at deciphering how PH cells acquire their "cancer-like" properties. As a consequence, the therapeutic potential of numerous anti-neoplastic drugs has been tested in preclinical models, with some of them reaching clinical assays [3]. Considering the biphasic pattern of apoptosis that characterises the disease (*i.e.* PAEC apoptosis that triggers the disease is followed by an apoptosis-resistant state allowing vascular remodelling [4]), it is not surprising that some anticancer agents can both predispose to and treat pulmonary arterial hypertension (PAH). This is exemplified by studies showing that dasatinib, a second-generation tyrosine kinase inhibitor (TKI) approved for Philadelphia chromosome positive chronic myeloid leukaemia, improves established PAH in multiple animal models [5], while its administration before exposure to PH inducers exacerbates pulmonary vascular remodelling and pulmonary artery pressures; histological and haemodynamic changes not observed in rats exposed to dasatinib alone [6].