Regorafenib, a Multikinase Inhibitor Therapy for Pulmonary Arterial Hypertension

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Rationale: Pulmonary arterial hypertension (PAH) is characterized by elevated mean arterial pressure followed by right ventricular failure and death. Previous studies have shown that targeting receptor tyrosine kinases (RTKs) is beneficial in treatment of pulmonary hypertension. Regorafenib (BAY 73-4506) is a kinase inhibitor that targets PDGFR, RET, C-KIT, FGFR, RAF-1, VEGFR 1-3 and p38 MAP Kinases. Regorafenib has been clinically approved for the treatment of both metastatic colorectal cancer and gastrointestinal stromal tumours in Imatinib and Sunitinib non-responders. As PDGFRβ and p38 MAPK inhibition were known to reverse PAH phenotype and Regorafenib has demonstrated PDGFRβ and P38 MAPK inhibitory effects in numerous studies, we hypothesized the potential of Regorafenib as a therapeutic strategy for PAH.

Methods: *In vitro* functional parameters were studied by proliferation and migration assays in pulmonary arterial smooth muscle cells (hPASMCs) of non-PAH controls and patients with idiopathic PAH (IPAH). Proliferation and migration, induced by Platelet derived growth factor (PDGF-BB) were determined by 5-bromo-2'-deoxyuridine (BrdU) incorporation assay and Transwell Chamber assays, respectively. Effect on RTK activity in hPASMCs were analyzed by Western Blot analysis. *In vivo* studies include chronic hypoxic mice (HOX) and monocrotaline (MCT) induced rat PH models. Functional parameters were analyzed by hemodynamic and echocardiographic measurements. Vascular remodeling was studied by degree of muscularization.

Results: Regorafenib demonstrated strong anti-proliferative effects on PDGF-BB induced proliferation in both non-PAH and IPAH hPASMCs. Anti-migratory effects were observed in non-PAH hPASMCs in a dose dependent manner. Regorafenib has shown strong inhibition of RTKs like p38 MAPK and PDGFRβ in hPASMCs. Although reduced pulmonary vascular remodeling was observed only in HOX model, functional parameters demonstrated improved cardiac function with reduced pulmonary vascular resistance upon Regorafenib treatment in both *in vivo* models.

Conclusion: Our data suggests that treatment with Regorafenib can be a novel therapeutic approach for the treatment of PAH.