# Investigating the association between ALK receptor tyrosine kinase inhibitors and pulmonary arterial hypertension: a disproportionality analysis from the WHO pharmacovigilance database

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**PAH associated with crizotinib seems to be very rare but cases are reported in pharmacovigilance databases with other ALK tyrosine kinases inhibitors, notably lorlatinib. Therefore, the potential emergence of PAH by ALK-TKI needs to be further explored.** https://bit.ly/3k9es94

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*To the Editor*:

Awada *et al.* [1] recently published in the *European Respiratory Journal* an interesting pre-clinical study suggesting that crizotinib may exacerbate and predispose to pulmonary arterial hypertension (PAH). Crizotinib is a first-in-class anaplastic lymphocyte kinase (ALK) inhibitor and is now a standard first-line therapy for advanced ALK-positive non-small cell lung cancer (NSCLC) [2]. Its inconsistent efficacy and its limited ability to control brain metastases pushed the development of second-generation ALK tyrosine kinase inhibitors (TKIs) (ceritinib, alectinib and brigatinib), which are characterised by higher selectivity and distribution to the central nervous system. Furthermore, third-generation ALK-TKIs, such as lorlatinib and entrectinib, have been recently developed to overcome acquired resistance due to secondary ALK mutations, which concern more than half of patients treated by second-generation ALK-TKIs [3]. Cases of PAH onset have also been reported in patients with metastatic NSCLC who received other ALK-TKIs, such as brigatinib and lorlatinib [4, 5]. Subsequently, one can ask if this adverse event is specific to crizotinib or a class effect of ALK-TKIs, and whether on-target or off-target tyrosine kinases are implicated in its pathophysiology. To further add knowledge on this potential adverse drug reaction, we aimed to comprehensively characterise PAH reported with ALK-TKI use, using the World Health Organization (WHO) pharmacovigilance database to describe cases' clinical features and to assess its causality.