Idiopathic pulmonary fibrosis: is all-cause mortality a practical and realistic end-point for clinical trials?

Dear Editor,

We read with interest the article by Wells *et al*[1] in which the problematic selection of primary end-points for treatment studies in idiopathic pulmonary fibrosis (IPF) patients is addressed. In this document endorsed by respiratory physicians across Europe, the authors explore the implications of using all-cause mortality as a primary end-point in response to a recent statement by a working group on this topic.[2] In a rather controversial statement by this working group, Raghu *et al* suggested that all-cause mortality and all-cause non-elective hospitalisation are the strongest and cleanest clinically meaningful end-points for use in Phase 3 clinical trials in IPF. These authors argue that all-cause mortality is a practical and achievable end-point on the basis that a Phase 3 study (INSPIRE) was completed using all-cause mortality as the primary end-point, and two studies have recently been stopped by the data safety and monitoring boards on the basis of increased all-cause mortality.[3–5]

While we agree that all-cause mortality is certainly the cleanest and most reliable end-point for use in Phase 3 clinical trials, we also agree with the European statement in which the implications of relying on all-cause mortality as a primary end-point in future studies are outlined. We share the concern of our European colleagues that adoption of these views by licensing bodies will necessarily lead to a statistically significant mortality benefit becoming a prerequisite for drug registration, and in turn, will lead to delay in registration of potential new IPF therapies, including pirfenidone and nintedanib.

We echo the sentiments of the European statement that although all-cause mortality is a uniquely reliable and measurable end-point, it is not a practicable primary end-point for Phase 3 clinical trials assessing efficacy of a potential therapeutic agent. There has been no prior study using all-cause mortality in which efficacy has been shown. As pointed out in the European statement, such a study would necessarily be very large, and prohibitively expensive. Additionally, the length of such a study would require patients to remain on placebo for far in excess of the median survival of this progressive condition—perhaps an unreasonable demand when new therapies are available in some countries.

In Australia and New Zealand, there is no licensed therapy for IPF, and we eagerly anticipate the results of Phase 3 clinical trials, which are currently underway. We are hopeful that if one or more of these trials are positive (based on a surrogate end-point) that the availability of these therapies will not be delayed. We

agree that despite their flaws, surrogate end-points, including change in forced vital capacity, should remain the end-point of choice for IPF trials.

Given the challenges of recruiting IPF patients into clinical trials, and the urgency and necessity of finding therapies for this disease, we urge the Interstitial Lung Disease (ILD) physician community to reconcile any differences in opinion, and unite with respect to pragmatic and meaningful outcome measures for IPF clinical trials.

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