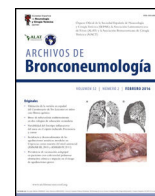




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Discussion Letter

To the Editor:

Combination Antifibrotic Therapy in IPF/PPF: Feasibility is not the Same as Additive Efficacy[☆]

At the bedside, the question is simple. What do we offer the patient with idiopathic pulmonary fibrosis (IPF) or progressive pulmonary fibrosis (PPF) who is doing everything right and still losing ground on monotherapy? Combination antifibrotic therapy feels like the logical next step, and Combi-PF helps anchor that instinct in real-world data [1].

In Combi-PF, 38 patients (84% IPF) received combined nintedanib plus pirfenidone. Adverse drug reactions occurred in 84% (severe in 29%), most commonly weight loss (53%) and diarrhea (37%). Dose reduction occurred in 29%, and 26% discontinued combination therapy [1]. This represents a meaningful feasibility signal, but it also defines the ceiling. Tolerability remains the limiting factor.

That distinction matters because feasibility can be mistaken for additive efficacy. Combi-PF reports a slower pre/post decline in forced vital capacity (FVC), from -26.7 to -11.1 mL per month on combination therapy [1]. However, retrospective practice tends to escalate treatment at a clinical inflection point. Symptoms, oxygen needs, imaging, or clinician concern often trigger escalation. These time-varying factors are difficult to adjust for and can make before-and-after slopes appear more favorable than they truly are. In this context, Combi-PF is best interpreted as persistence and safety evidence. It is also hypothesis-generating for benefit, but it does not establish incremental efficacy [1].

Second, gastrointestinal toxicity that is labeled manageable is not benign in interstitial lung disease. Even moderate diarrhea or anorexia can translate into deconditioning, frailty, and nonadherence. These practical consequences can erase any physiologic gain. The INJOURNEY trial demonstrates a similar pattern, with higher rates of gastrointestinal adverse events in the add-on pirfenidone group compared with nintedanib alone (69.8% vs 52.9% over 12 weeks) [2]. Other safety datasets similarly emphasize that tolerability and persistence are the real-world gatekeepers for combination therapy [3].

Where does combination therapy fit best? A selective niche appears most defensible. This includes patients with objectively progressive IPF or PPF despite optimized monotherapy who lack trial access and for whom transplant is not feasible or is being pursued as a bridge strategy. Combi-PF explicitly raises the transplant bridge concept in this context [1]. Prospective studies should pair lung function endpoints with patient-centered outcomes such as weight trajectory, patient-reported outcomes, and reasons for discontinuation. The question of whether patients can take both drugs is not the same as whether they benefit while remaining on them.

Fig. 1 proposes a pragmatic pathway to guide selection, initiation, and monitoring of combination antifibrotic therapy.

AI assistance disclosure (if required by the journal's submission forms)

I did not use artificial intelligence assistance during the drafting, editing, or completion of this manuscript and its supporting documents.

[☆] **Regarding:** Meersseman et al. Nintedanib combined with pirfenidone in patients with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis: a long-term retrospective multicentre study (Combi-PF).

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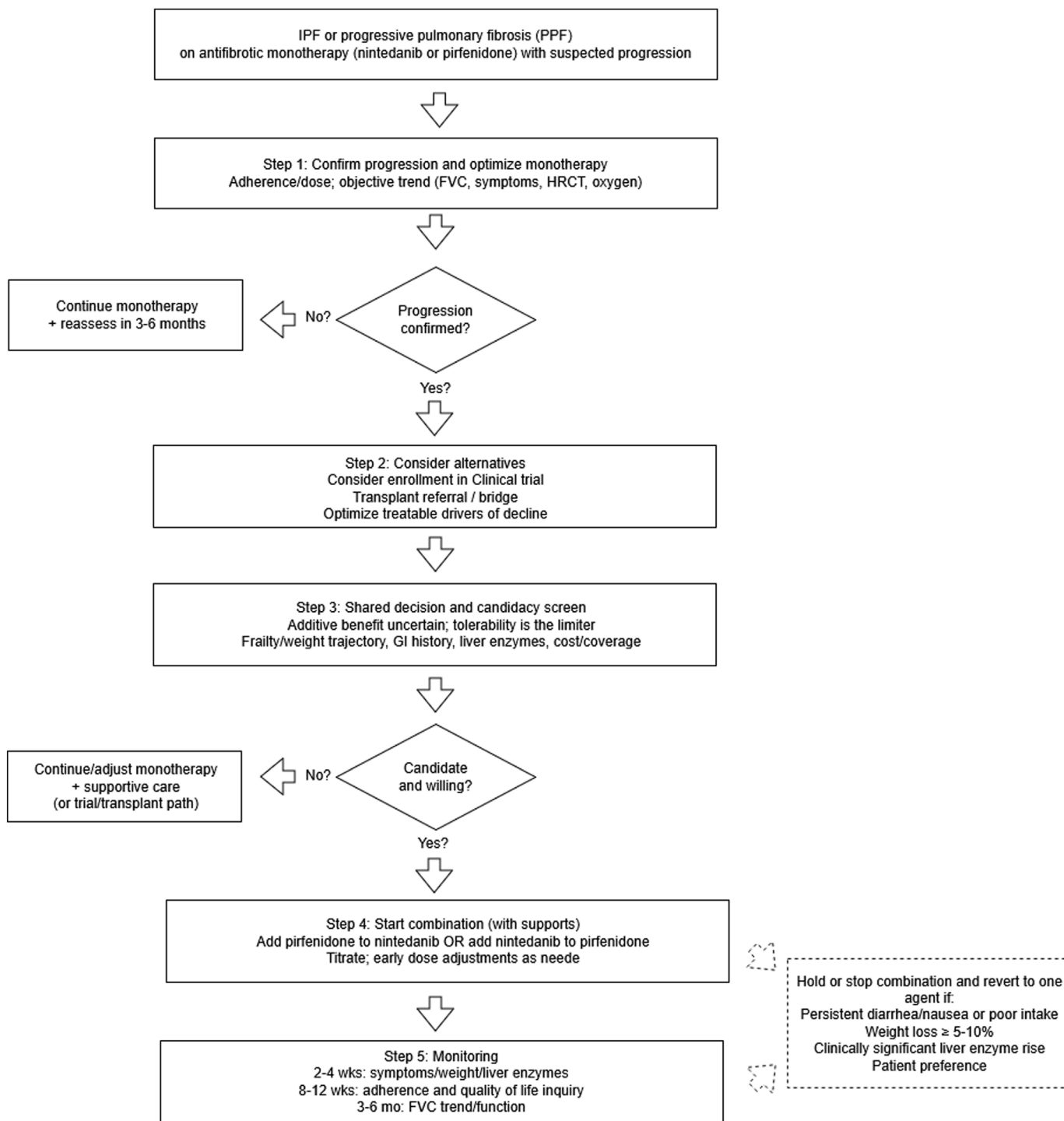


Fig. 1.

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None.

Conflicts of interest

None declared.

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