# The impact of switching to a second antifibrotic therapy on outcomes in patients with IPF in the EMPIRE registry treated with pirfenidone or nintedanib

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## Introduction

Most patients with idiopathic pulmonary fibrosis (IPF) treated with antifibrotics (AF) have progressive disease despite treatment. A switch of AF gives a chance for longer survival, but evidence from randomized controlled trials is missing. Thus, we aimed to check the efficacy of an AF switch on the overall survival (OS) of patients in the European MultiPartner IPF registry (EMPIRE).

## Methods

Patients in the EMPIRE registry were eligible for this study if they received either nintedanib or pirfenidone, discontinued treatment for any reason and were known to have survived for at least six months after discontinuation. Patients were grouped and analyzed from two perspectives: 1) whether they had received a second antifibrotic treatment after the discontinuation of the first therapy (hereinafter referred to as switch and non-switch group), and 2) a reason for discontinuation of the first AF – "lack of efficacy" (LE) and "intolerance" (INT). Kaplan–Meier methodology was used to estimating the OS 6 months after the first AF discontinuation date. Hazard ratio (HR) values for mortality were adjusted for age, sex, and baseline FVC (l).

## Results

A total of 1164 patients had terminated their first AF in the EMPIRE registry. Of these, 504 with a follow-up of ≥ 6 months after the first AF discontinuation were included in the analysis. 191 (38%) had no second AF ("non-switched"), while 313 (62%) patients switched – 187 (37%) from pirfenidone (PIR) to nintedanib (NIN) and 126 (25%) from NIN to PIR (Table 1). The most common reasons for discontinuing AF were adverse events (52% total, 49% PIR and 58% NIN) and the lack of efficacy (17% overall, 20% PIR and 14% NIN) (Table 2).

The OS rates were longer in patients who received a second AF than those who did not (median 47 vs. 28 months, p = 0.001; adjusted HR 0.81, 95% CI 0.54–1.23, p = 0.33) (Figure 1).

The LE group had lower OS rates in comparison to the INT group in both switched (median 39 vs. 54 months) and non-switched (median 9.9 vs. 41 months) patients (Figures 2 and 3). After adjustment, the switched patients had similar risk for mortality in both LE and INT groups (adjusted HR 1.03, 95% CI 0.56–1.88, p = 0.92). On the other hand, in the non-switched group, the INT patients had a significantly lower risk of death than the LE patients (adjusted HR 0.39, 95% CI 0.18–0.84, p = 0.016). The comparison of switched and non-switched patients and thus the importance of switching in patients discontinued due to the lack of efficacy of the first AF therapy is demonstrated in Figure 4 (the median OS rates 9.9 vs. 39 months; adjusted HR 0.24, 95% CI 0.09–0.61, p = 0.003).

## Conclusions

The results of our study emphasize the importance of switching AF treatment to the second drug if the first drug is discontinued due to side effects or other reasons. Furthermore, our results suggest that patients with progressive disease and ineffective first AF treatment may significantly profit from the switch and have longer overall survival than patients without a second AF.

**Table 1.** Baseline characteristics of patients

| Characteristic | Total, N = 504 | PIR, N = 114 | NIN, N = 77 | PIR -> NIN, N = 187 | NIN -> PIR, N = 126 |
|---|---|---|---|---|---|
| **Men** | 325 (64%) | 76 (67%) | 40 (52%) | 131 (70%) | 78 (62%) |
| **Age at baseline (years)** | 71 (65; 76) | 72 (66; 77) | 72 (64; 78) | 71 (64; 75) | 72 (66; 75) |
| **No. of comorbidities** | 4.00 (3.00; 6.00) | 4.00 (3.00; 5.75) | 4.00 (2.00; 6.00) | 4.00 (3.00; 6.00) | 4.00 (3.00; 6.00) |
| **First AF therapy (months)** | 504 / 8 (3; 17) | 114 / 8 (3; 16) | 77 / 9 (3; 15) | 187 / 8 (3; 18) | 126 / 8 (3; 17) |
| **FVC (%)** | 389 / 77 (65; 88) | 81 / 70 (62; 85) | 65 / 84 (66; 96) | 150 / 75 (65; 85) | 93 / 82 (67; 89) |
| **DLCO (%)** | 367 / 49 (40; 59) | 78 / 46 (39; 57) | 62 / 46 (39; 63) | 138 / 51 (40; 57) | 89 / 50 (43; 60) |
| **6MWT (m)** | 168 / 400 (332; 470) | 40 / 391 (299; 452) | 28 / 362 (298; 479) | 63 / 405 (358; 472) | 37 / 410 (360; 458) |
| **GAP index** | | | | | |
| **I** | 199 (53%) | 28 (35%) | 43 (69%) | 70 (49%) | 58 (64%) |
| **II** | 161 (43%) | 50 (63%) | 18 (29%) | 66 (46%) | 27 (30%) |
| **III** | 15 (4.0%) | 1 (1.3%) | 1 (1.6%) | 7 (4.9%) | 6 (6.6%) |

*[1] Data presented as N (%) or median (25%; 75%)*

**Table 2.** Reasons for the discontinuation of first antifibrotic therapy

| Reason for discontinuation | Total N = 504 | Non-switched patients | | Switched patients | |
|---|---|---|---|---|---|
| | | Pirfenidone N = 114 | Nintedanib N = 77 | Pirfenidone N = 187 | Nintedanib N = 126 |
| **Lack of efficacy** | 87 (17%) | 19 (17%) | 8 (10%) | 40 (21%) | 20 (16%) |
| **Adverse events** | 264 (52%) | 42 (37%) | 44 (57%) | 104 (56%) | 74 (59%) |
| **Refusal, non-compliance** | 65 (13%) | 24 (21%) | 11 (14%) | 22 (12%) | 8 (6.3%) |
| **Other** | 88 (17%) | 29 (25%) | 14 (18%) | 21 (11%) | 24 (19%) |

*[1] Data presented as n (%)*

**Figure 1.** Overall survival of switched and non-switched patients

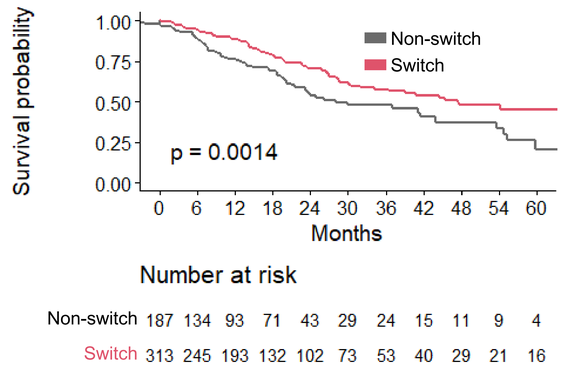



**Figure 2.** Overall survival of switched patients with a different reason for the first therapy discontinuation

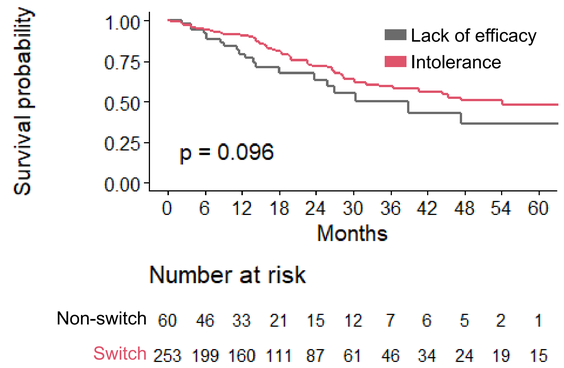



**Figure 3.** Overall survival of non-switched patients with a different reason for the first therapy discontinuation

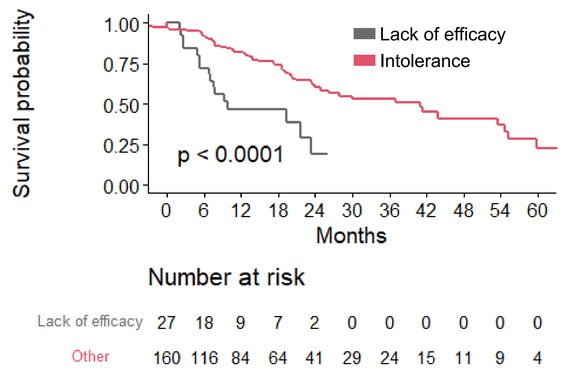
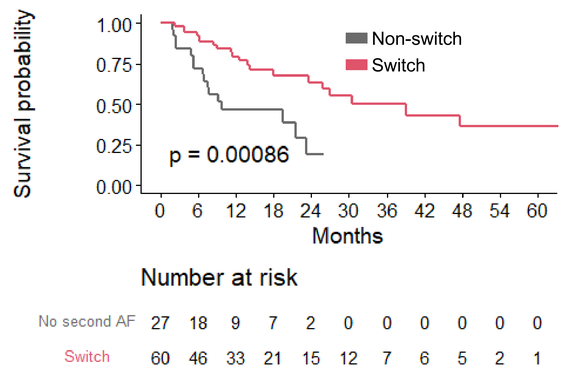



**Figure 4.** Overall survival of patients who discontinued the first therapy due to lack of efficacy

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The study was approved by Ethics Committee of Thomayer Hospital and Institute for Clinical and Experimental Medicine, Prague, Czech Republic, and local ethics committees in individual countries and sites involved in the registry.

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