Supplementary

Table S1 WB and flow cytometry related antibodies information

Antibody	Cat No.	RRID	Dilution ratio	Company
WB				
Primary				
Rabbit				
Jak2	AB108596	AB_10865183	1:5,000	Abcam
p-Jak2	AB32101	AB_775808	1:1,000	Abcam
Stat3	AB10253-2-AP	AB_2302876	1:1,000	Proteintech
p-Stat3	AB76315	AB_1658549	1:5,000	Abcam
Smad3	AB208182	AB_3095071	1:1,000	Abcam
p-Smad3	AB 52903	AB_882596	1:2,000	Abcam
Col-IV	AF0510	AB_2834130	1:1,000	Affinity
CD206	DF4149	AB_2836514	1:500	Affinity
Arg-1	DF6657	AB_2838619	1:500	Affinity
Fibronectin	15613-1-AP	AB_2105691	1:1,000	Proteintech
GAPDH	AF7021	AB_2839421	1:3,000	Affinity
Mouse				
TGF-βR2	66636-1-Ig	AB_2881995	1:2,000	Proteintech
β-actin	EM21002	AB_2819164	1:10,000	huabio
Secondary				
Rabbit				
IgG	E030120-01	AB_3073916	1:5,000	EarthOx (USA)
Mouse				
IgG	E030110-01	AB_2572419	1:5,000	EarthOx (USA)
FCM				
Macrophage				
FITC-conjugated F4/80	E-AB-F0995C	AB_3065037	–	Elabscience
PE-conjugated CD86	E-AB-F0994D	AB_394994	–	Elabscience
APC-conjugated CD163	17-1631-82	AB_2784646	–	eBioscience

WB, western blot; FCM, flow cytometric; FITC, fluorescein isothiocyanate; PE, phycoerythrin; APC, allophycocyanin.

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Table S2 Comparison between pirfenidone and nintedanib

Difference	Pirfenidone (ESBRIET)	Nintedanib (OFEV)
Component	5-methyl-1-phenyl-2-[1H]-pyridone	Small molecule tyrosine kinase inhibitor
Indication	Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis, chronic fibrosing interstitial lung diseases with a progressive phenotype, decline in pulmonary function in patients with SSc-ILD
Dosage forms and strengths	Capsules: 150 and 100 mg	Capsule: 267 mg
Dosage and administration	Recommended dosage: 801 mg (three capsules) three times daily taken with food	Recommended dosages: 150 mg twice daily approximately 12 hours apart taken with food
Absorption	After oral-dose administration of 801 mg, the Cmax was achieved between 30 minutes and 4 hours (median time of 0.5 hours). Food decreases the rate and extent of absorption. Median Tmax increased from 0.5 to 3 hours with food. Maximum plasma concentrations and $AUC_{0\text{-}inf}$ decreased by approximately 49% and 16% with food, respectively. A reduced incidence of adverse reactions was observed in the fed group when compared to the fasted group. So taking with food is accepted	Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7% (90% CI: 3.62% to 6.08%) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism. After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (90% CI: 95.3% to 152.5%) and absorption was delayed (median Tmax fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type
Distribution	Pirfenidone binds to human plasma proteins, primarily to serum albumin, in a concentration independent manner over the range of concentrations observed in clinical trials. The overall mean binding was 58% at concentrations observed in clinical studies (1 to 10 μg/mL). Mean apparent oral volume of distribution is approximately 59 to 71 liters	Nintedanib follows bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution which was larger than total body volume (Vss: 1,050 L) was observed. The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8%. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87
Metabolism	*In vitro* profiling studies in hepatocytes and liver microsomes have shown that ESBRIET is primarily metabolized in the liver by CYP1A2 and multiple other CYPs (CYP2C9, 2C19, 2D6, and 2E1). Oral administration results in the formation of four metabolites. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities. The mean metabolite-to-parent ratio ranged from approximately 0.6 to 0.7. *In vitro* data suggests that metabolites are not expected to be pharmacologically actives	The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage
Excretion	The mean terminal half-life is approximately 3 hours in healthy subjects. Pirfenidone is excreted predominantly as metabolite 5-carboxy-pirfenidone, mainly in the urine (approximately 80% of the dose). The majority of ESBRIET was excreted as the 5-carboxy metabolite (approximately 99.6% of that recovered)	The major route of elimination of drug-related radioactivity after oral administration of [^{14}C] nintedanib was via fecal/biliary excretion (93.4% of dose), and the majority of OFEV was excreted as BIBF 1202. The contribution of renal excretion to the total clearance was low (0.65% of dose). The overall recovery was considered complete (above 90%) within 4 days after dosing

In this table, most information is from label documents of FDA (reference ID: 3643926 for pirfenidone, reference ID: 4572087 for nintedanib), pirfenidone is metabolized mainly in liver and excreted mainly in the urine, the total metabolism time is about 15 hours (5 folds more than half-life). While, nintedanib is metabolized mainly by esterases and excreted via fecal/biliary tract, with a long metabolism time for 4 days. We postulate that because nintedanib exists in the body longer than pirfenidone, its effect on reduction of M2 polarization is stronger. Another possible explanation is that absorption of pirfenidone is influenced by food, although there is influence with nintedanib too, the maximum plasma concentrations and $AUC_{0\text{-}inf}$ decreased obviously with pirfenidone. As a result, it might take a long time to see the obvious effect on M2 polarization of pirfenidone. SSc-ILD, systemic sclerosis-associated interstitial lung disease; FDA, Food and Drug Administration; $AUC_{0\text{-}inf}$, area under blood concentration from time 0 to time infinity.

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