MCRD WASOG SARCOID CLINIC

Pharmacological Management of Interstitial Lung Diseases

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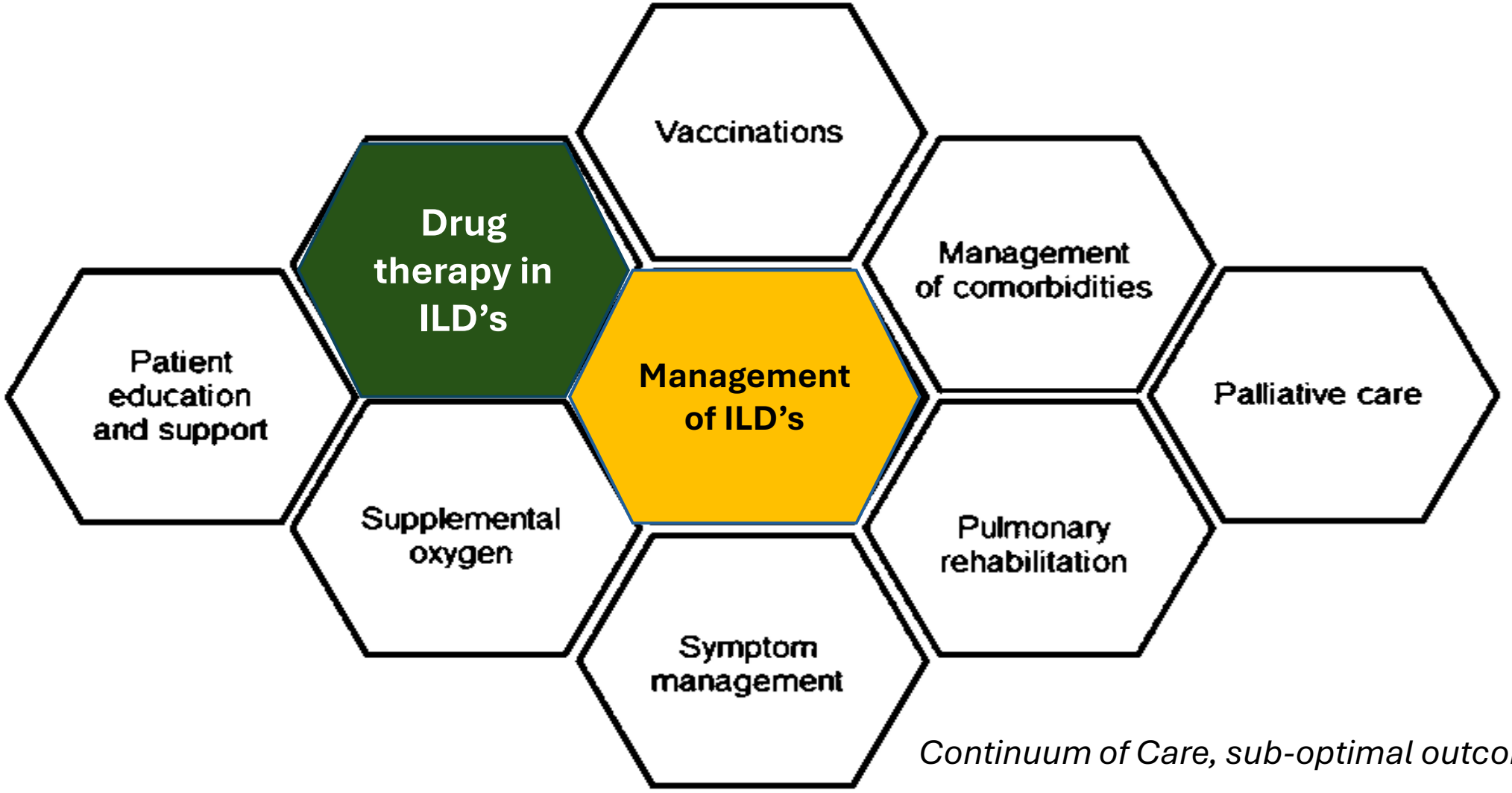
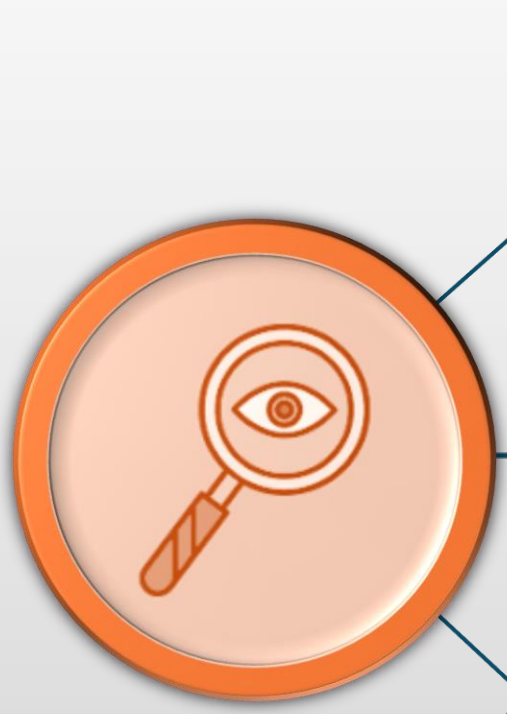
Management of ILD's : *Multidimensional*



Continuum of Care, sub-optimal outcomes

Response to Treatment in ILD : *Complex & Variable ?*



Clinical :

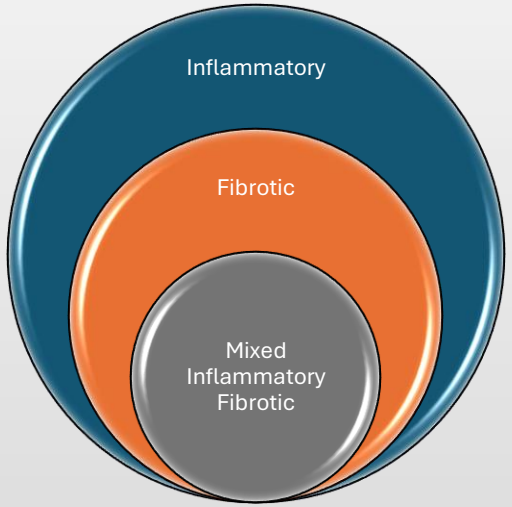
- Exposures
- AI features
- Drugs

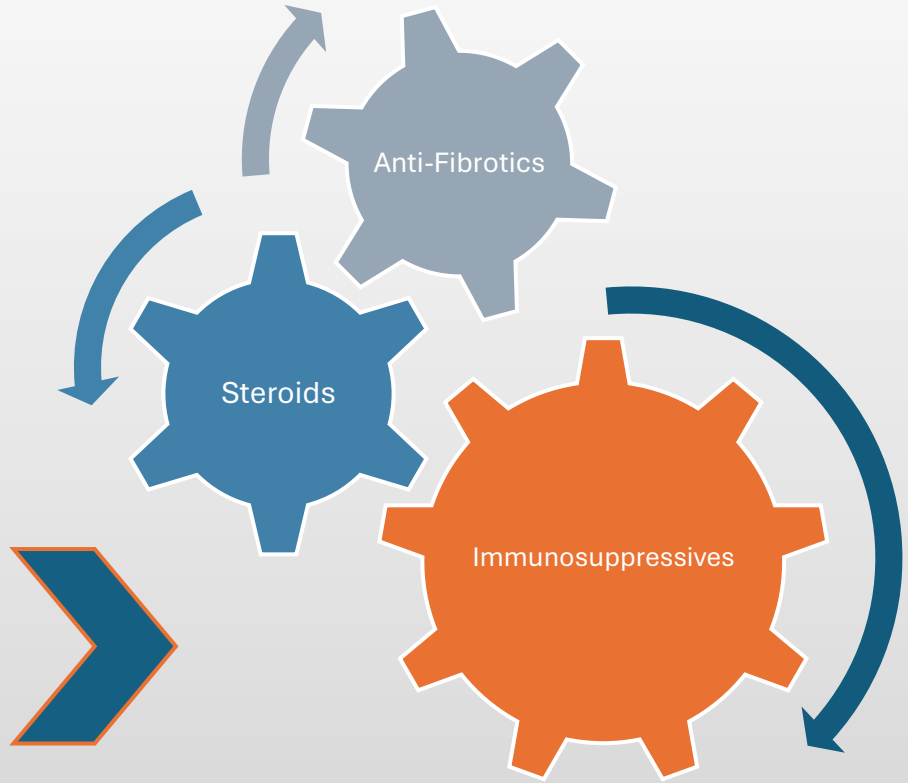
Physiological

- Type
- Severity

Imaging

- UIP
- Probable UIP
- Unclassifiable
- Alternate diagnosis





- Guidelines ?
- Algorithms ?

Med J Aust. 2022 Apr 18;216(7):331-333.

Immunosuppressives in ILD's : *Mainstay in Non IPF ILD's*

Corticosteroids

Cyc / RTx / Toci

MMF/AZT/ MTX

Which & When ?

Corticosteroids : *Upfront Anti-inflammatory Drug*

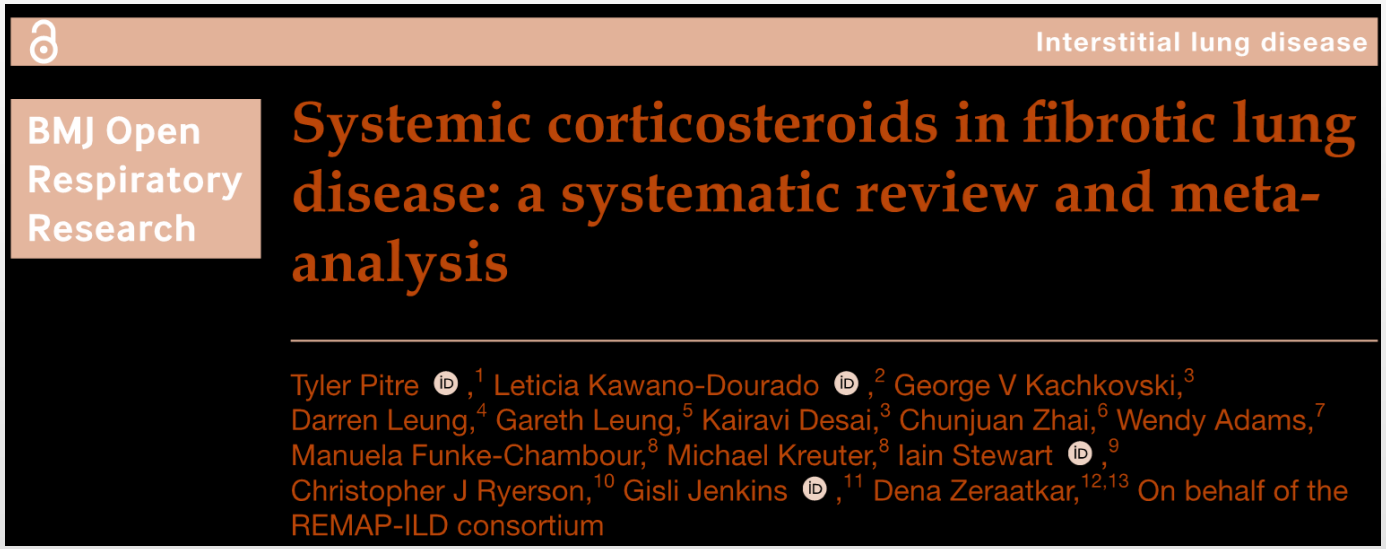
Drug	Condition studied	Efficacy observed[a]	Level of evidence[b]
Prednisone	Eosinophilic pneumonia	Improvement in FVC	B
	Sarcoidosis	Improvement in FVC, DLCO	C
	HP (non-fibrotic)	Improvement in FVC, DLCO	C
	SSc	Decline of FVC	C

Ther Adv Respir Dis 2022, Vol. 16: 1–16

- No High-quality Data
- Good Response : Non-Fibrotic HP, OP & NSIP – CTD, Sarcoidosis, Eosinophilic Pneumonia
- Partial Response : Fibrotic HP and CTD-ILD's (Except SSc-ILD), iNSIP

Dose & Duration of Oral Steroids :

- HP : 20-40 mg/day and taper to 10 mg/day
- Sarcoidosis : 20-40 mg/day tapered to 10 mg/day in 3 months and maintain for ~1-2 years
- iNSIP : 0.5 mg /kg/day taper 10 mg/day in 6 months and continue as per response
- CTD ILD's (Except SSc) : Minimum in RA-ILD (10mg/day) & maximum in IM-ILD (80mg/day)



Corticosteroids may improve lung function in patients with non-IPF f-ILD, but impact on mortality is uncertain

Pitre T, et al. BMJ Open Respir Res 2023

Immunosuppressives in F-ILD's : *1st & 2nd Line*

Steroids are 'Not Recommended for Prolonged Use' due its side effects

Mycophenolate mofetil	SSc	Improvement in FVC	A
	HP	Stabilization of FVC	B
		Improvement in DLCO	
	CTD-ILD	Improvement in FVC, DLCO	C
	Sarcoidosis	Decline of FVC, DLCO	C
Azathioprine	HP	Decline of FVC	B
		Improvement in DLCO	
	Sarcoidosis	Improvement in FVC, DLCO	B
	CTD-ILD	Stabilization of FVC, DLCO	C
	SSc	Stabilization of FVC	A
Methotrexate	Sarcoidosis	Improvement in FVC, DLCO	B
	RA-ILD	Protective against ILD development	B

Ther Adv Respir Dis 2022, Vol. 16: 1–16

Mycophenolate Mofetil : MMF

1st line to reduce Steroids & Stabilize FVC & DLco

Sarcoidosis : Negative Study

Inhibits inosine monophosphate dehydrogenase

Exerts cytostatic effect on lymphocytes

Currently most widely used 1st line steroid- sparing agent in fibrosing ILD

It is generally effective, well tolerated and less toxic than CYC

SSc-ILD, IPAF, CTD-ILD, IM-ILD and FHP : Positive

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Azathioprine

2nd line agent to reduce Steroids in CTD / FHP ILD's

- Inhibits purine synthesis and DNA replication in lymphocytes
- Widely used as 2nd line therapy in fibrosing ILD's
- Most data in SSc-ILD and other CTD ILD's
- Sarcoidosis AZT is 2nd line, effective as MTX in steroid sparing & Stabilizing FVC & DLco
- FHP AZT reduced OCS dose and FVC and DLco as also seen in MMF

Ther Adv Respir Dis 2022, Vol. 16: 1–16

Methotrexate

2nd line agent to reduce Steroids in RA & Sarcoid ILD's

- Folate analogue that interferes with purine and pyrimidine synthesis
- Anti-inflammatory and immunosuppressant effects
- Pulmonary Toxicity is very rare
- RA-ILD : prevents progression to ILD, improve lung functions & survival
- Sarcoid –ILD : ↓Steroids requirement and↑ FVC and ↑DLco

Ther Adv Respir Dis 2022, Vol. 16: 1–16

Cyclophosphamide & Rituximab: *3rd Line Therapy*

Drug	Condition studied	Efficacy observed[a]	Level of evidence[b]
Cyclophosphamide	SSc	Improvement in FVC	A
	NSIP	Stabilization of FVC, DLCO	C
Rituximab	SSc	Improvement in FVC	A
	Sarcoidosis	Stabilization of FVC	B
	CTD-ILD	Improvement in FVC	B
		Stabilization of DLCO	
	RA-ILD	Stabilization of FVC	C

Immunosuppressives but more toxic and used mostly as Salvage Therapy

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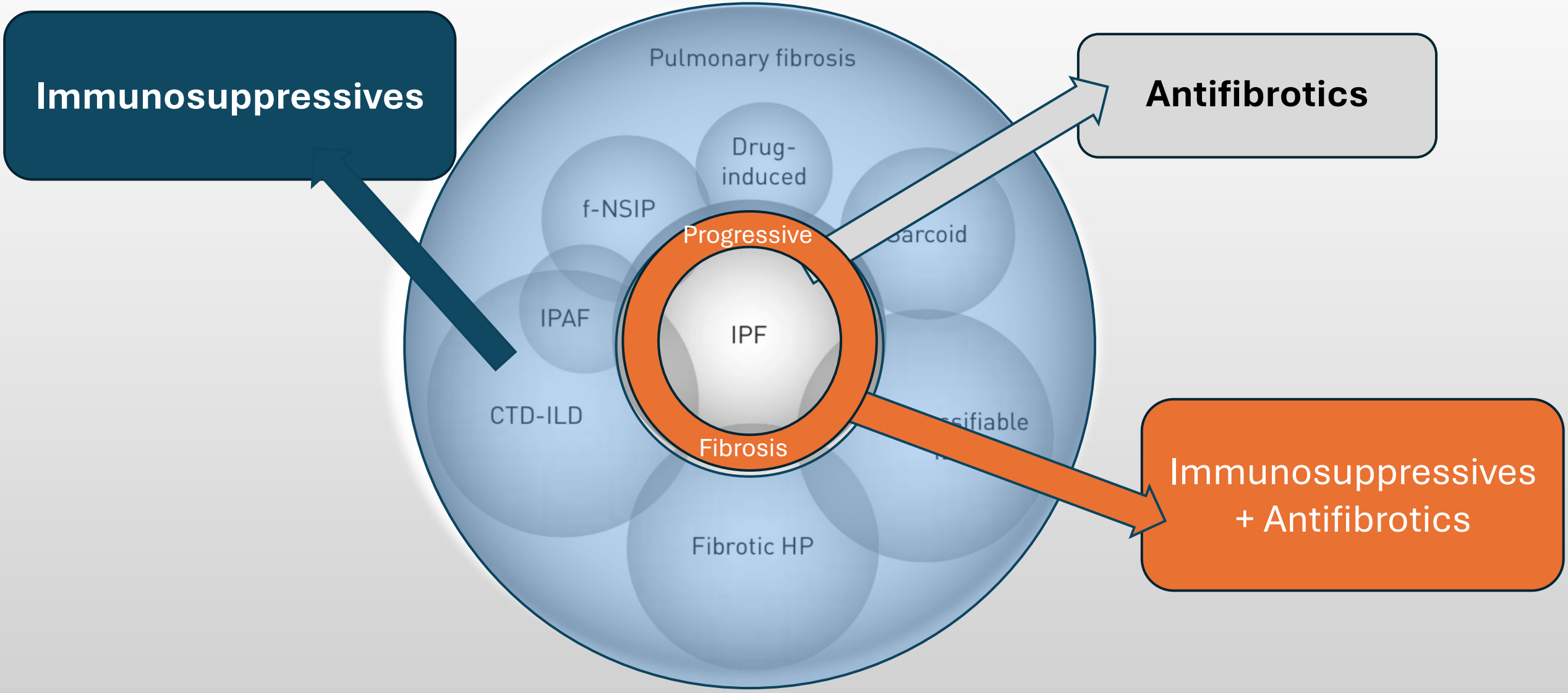
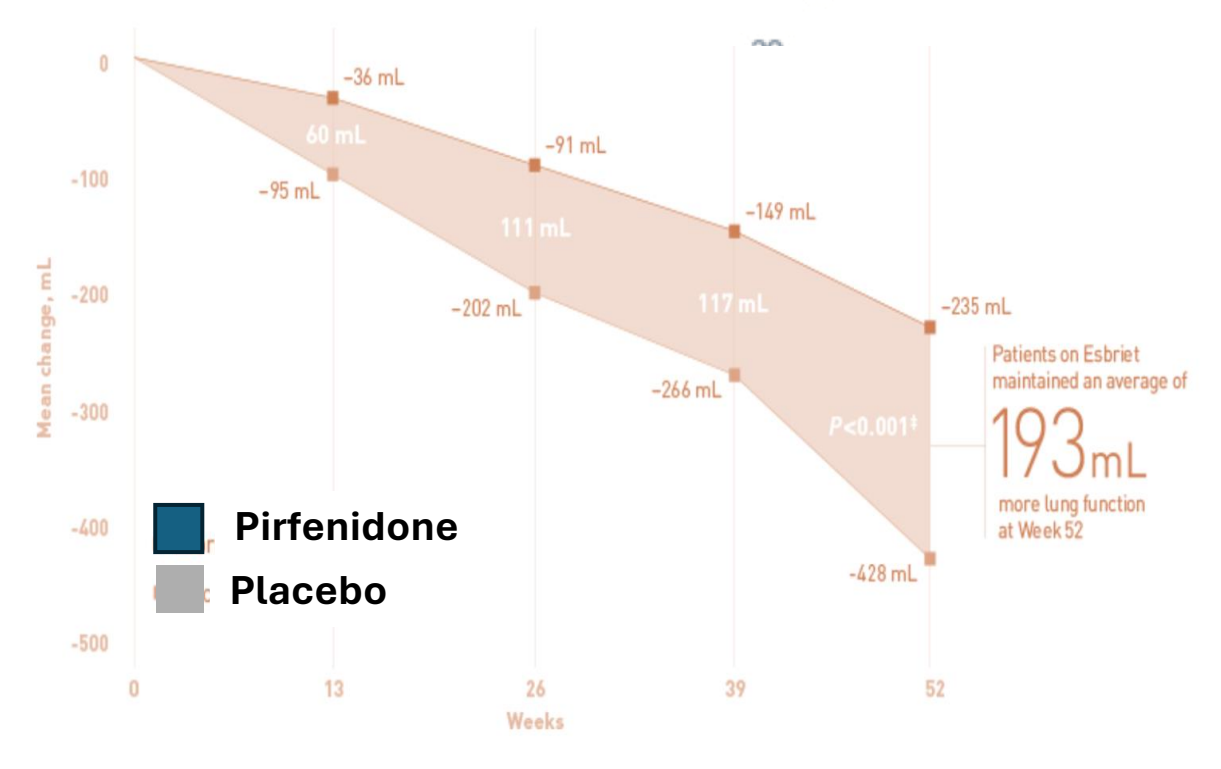
Choice of Immunosuppressives in F-ILD's

FHP	Sarcoidosis	iNSIP	IPAF
1.Steroids	1.Steroids	1.Steroids	1.Steroids
2.MMF	2.MTX	2.MMF	2.MMF
3.AZA	3.AZA	3.AZA	3.AZA
	4.Infliximab	4.CYC	4.RTX / CYC

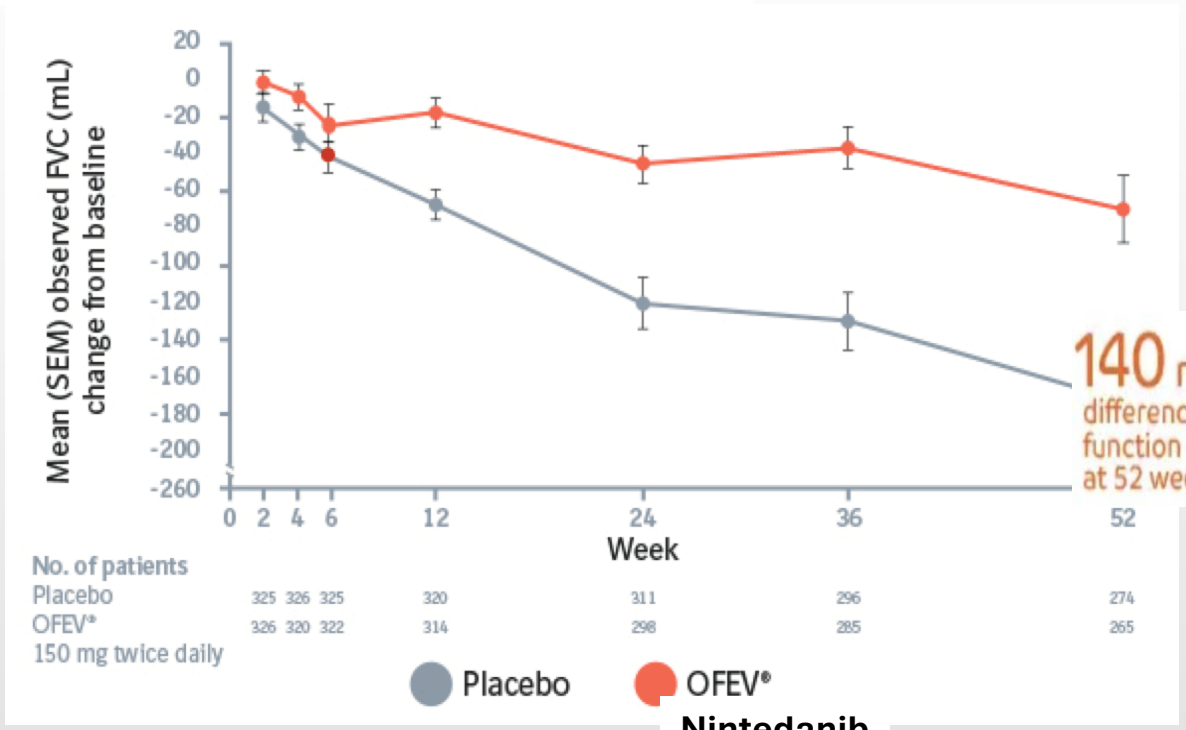
Pharmacological Treatment for Fibrosis



Change from baseline in FVC (mL) over 52 weeks[1]



King TE Jr, et al. *N Engl J Med*, 2011.370(22):2083-92.



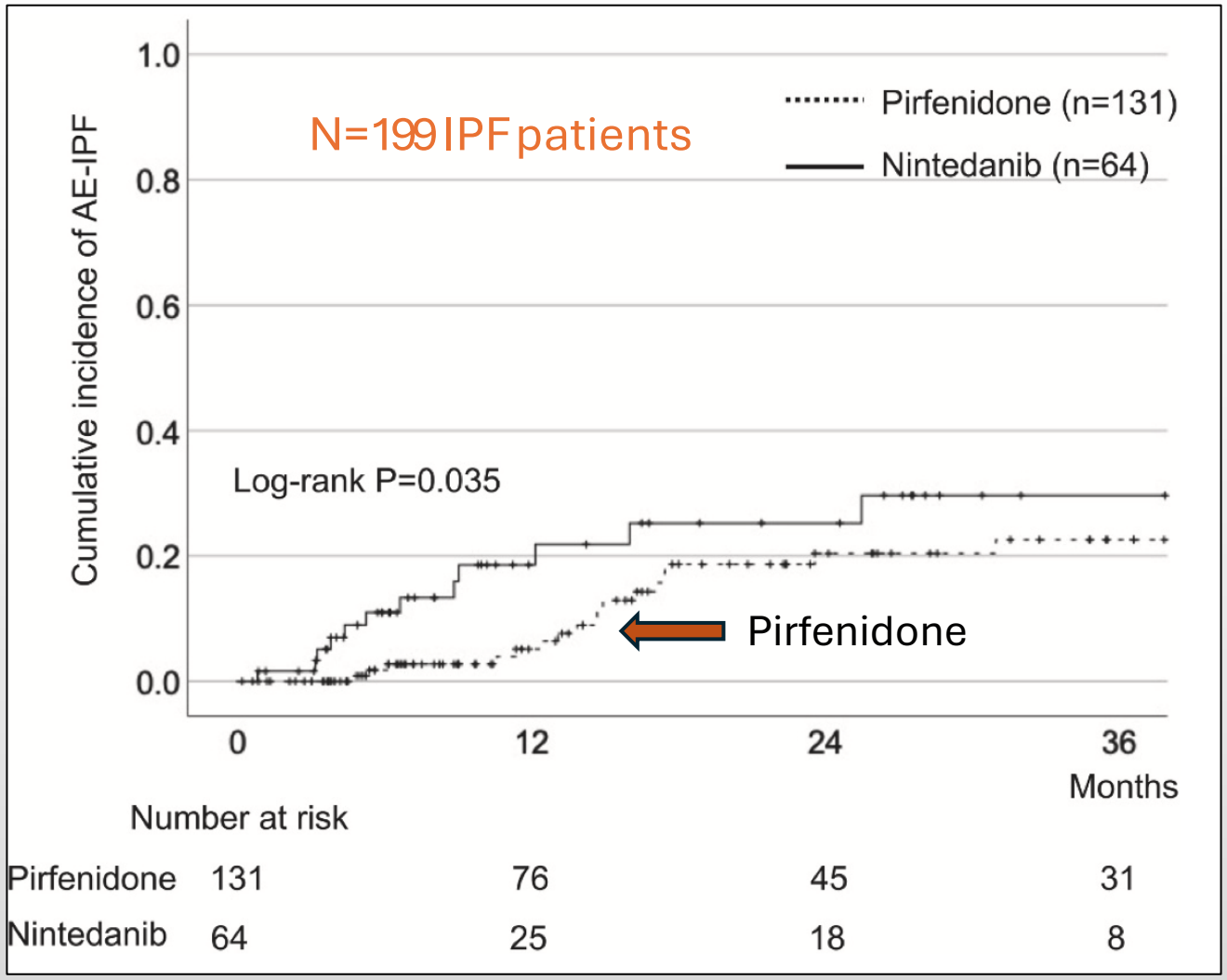
Richeldi L et al; *N Engl J Med*. 2014;370(22):2071-2082.

Both Antifibrotics Reduce Decline in FVC

~ 50%

Reducing Risk of IPF-AE : *Both Antifibrotics Work!*

Respiratory Medicine 2021; 187:106551



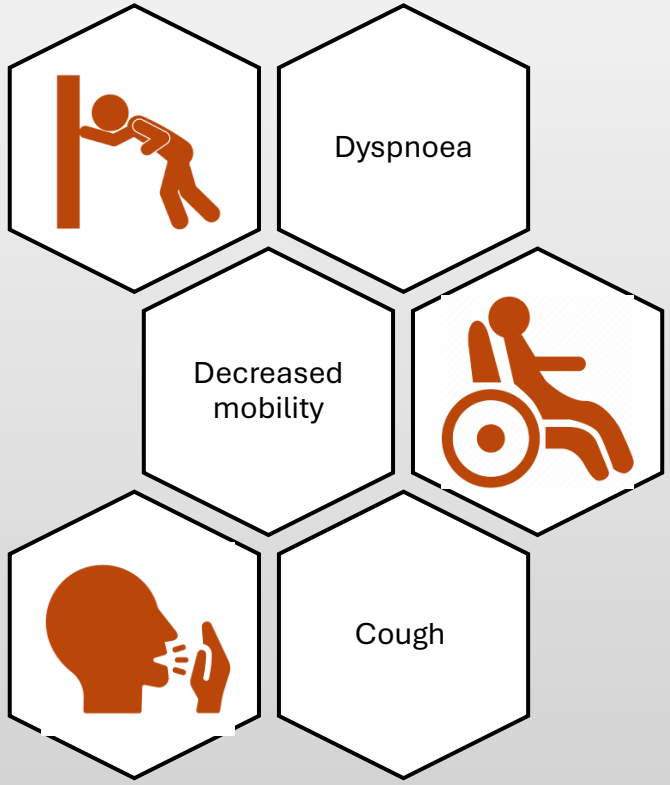
Retrospective study 2010-2018

QoL in IPF ?

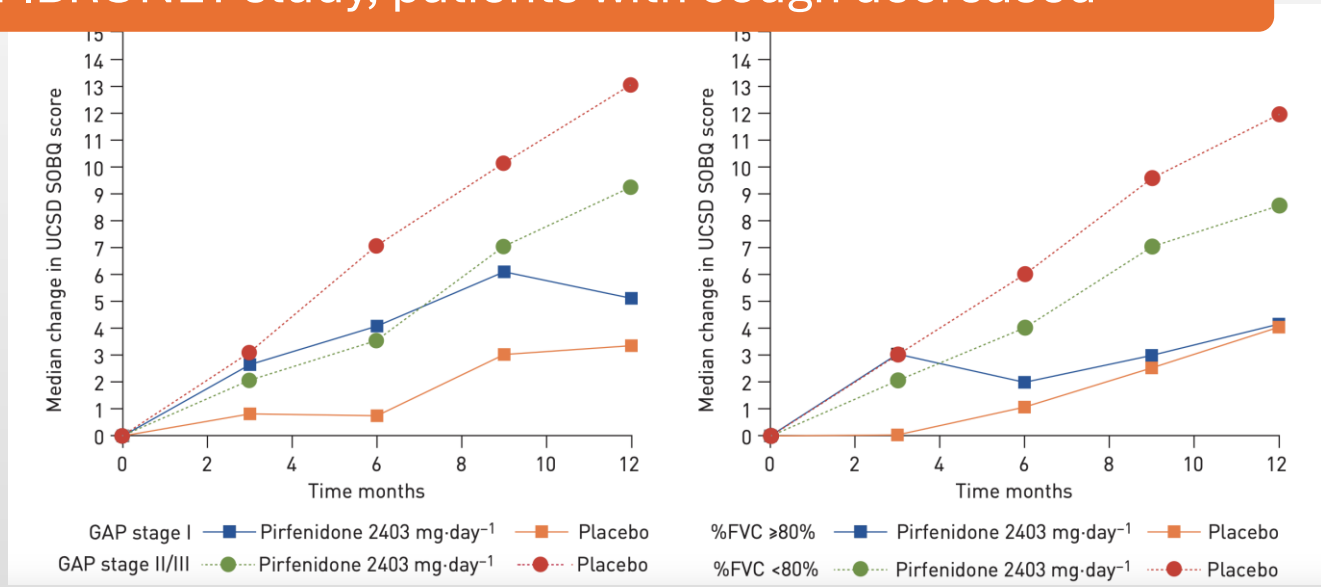
- Pirfenidone Improved cough in 74% @ 12 weeks
- 24-h cough decreased by 34%
- Cough reduction starts within 4 weeks in 70%
- Improved cough related QoL

Eur Respir J. 2017 Oct 19;50(4):1701157.

Patients with IPF on Nintedanib in the FIBRONET study, patients with cough decreased



Respiration (2022) 101 (6): 577–584

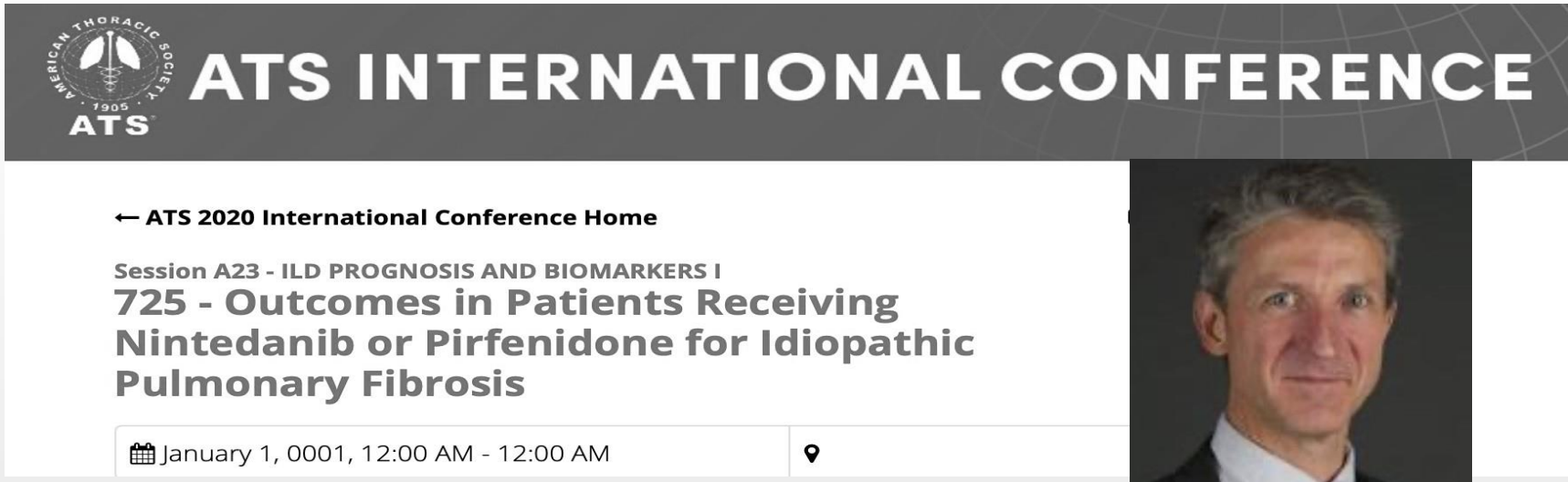


- Pirfenidone Improved SOBQ @ 12 months
- Effective in GAP II & III and FVC < 80%
- RWE also improved dysnea scores

Eur Rrespir J 2019;54:1900399

Headlines ...

Anti Fibrotics in IPF
Improve Survival !



The cumulative all-cause mortality @ 3 years:

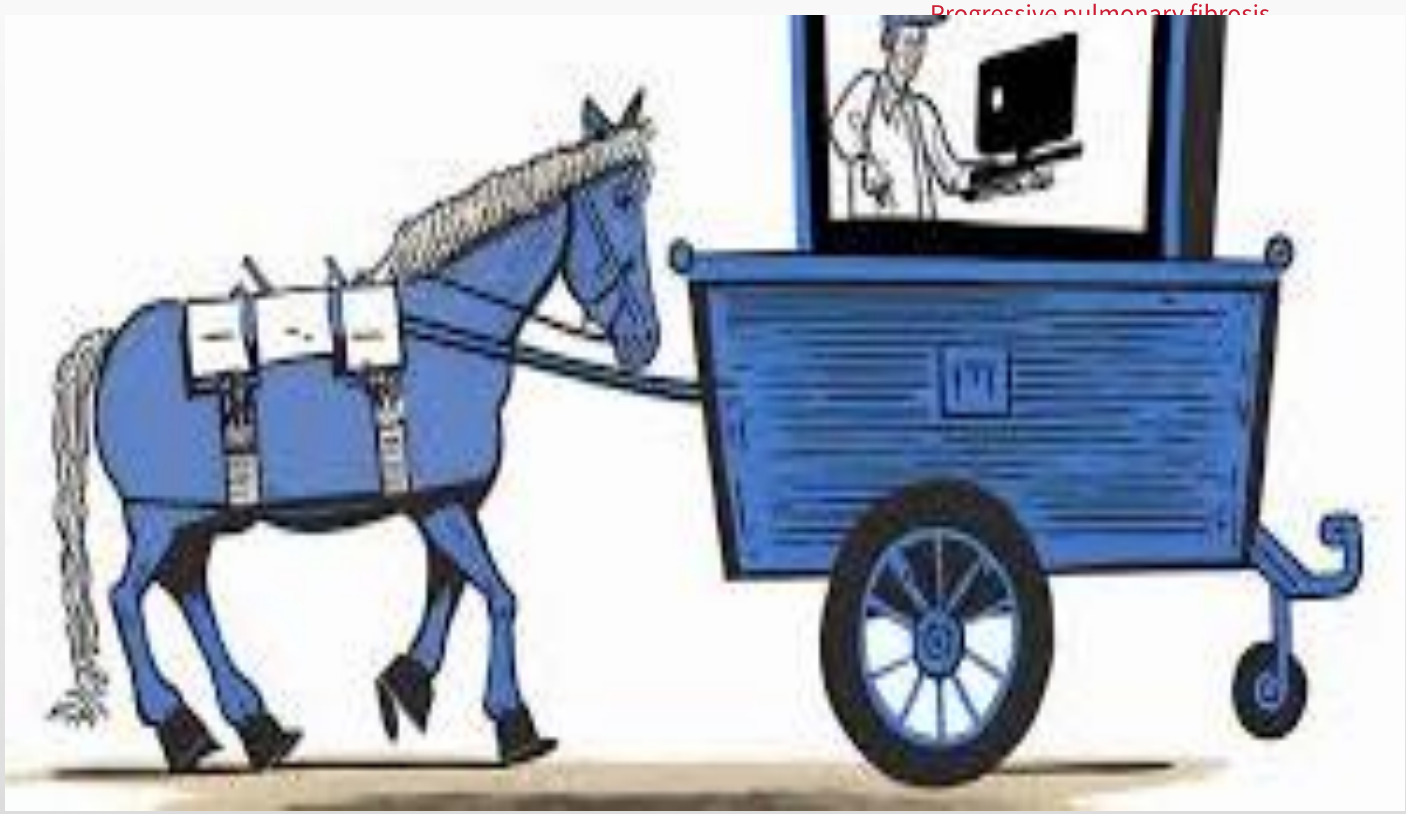
- **50.23% (95% CI=[48.34%-52.09%]) in untreated**
- **25.5% (95% CI=[19.6%-31.7%]) in Pirfenidone**
- **31.1%(95% CI=[21.2%-41.6%] in Nintedanib**

ANTI-FIBROTICS : *Pirfenidone OR Nintedanib : ?*

	Pirfenidone	Nintedanib
Dose Escalation	Required	X
Number of Tablets	3 -12	2
Adverse Effects	UGI Toxicity	Lowe GI Toxicity
Low BMI		**X**
CAD	**+**	
Oral Anti-coagulants	**+**	
Elective Major Surgery	**+**	
QoL	+	+
Prevention of AE / Respiratory Hospitalization	+	+

Progressive Pulmonary Fibrosis in Non IPF ILD's

- Worsening respiratory symptoms;
- Physiological evidence of disease progression
- Radiological evidence of disease progression



18–32% of patients with non-IPF ILDs develop "PPF (despite management)" within 61–80 months from the onset of symptoms

Eur Respir J 2023; 61: 2103187

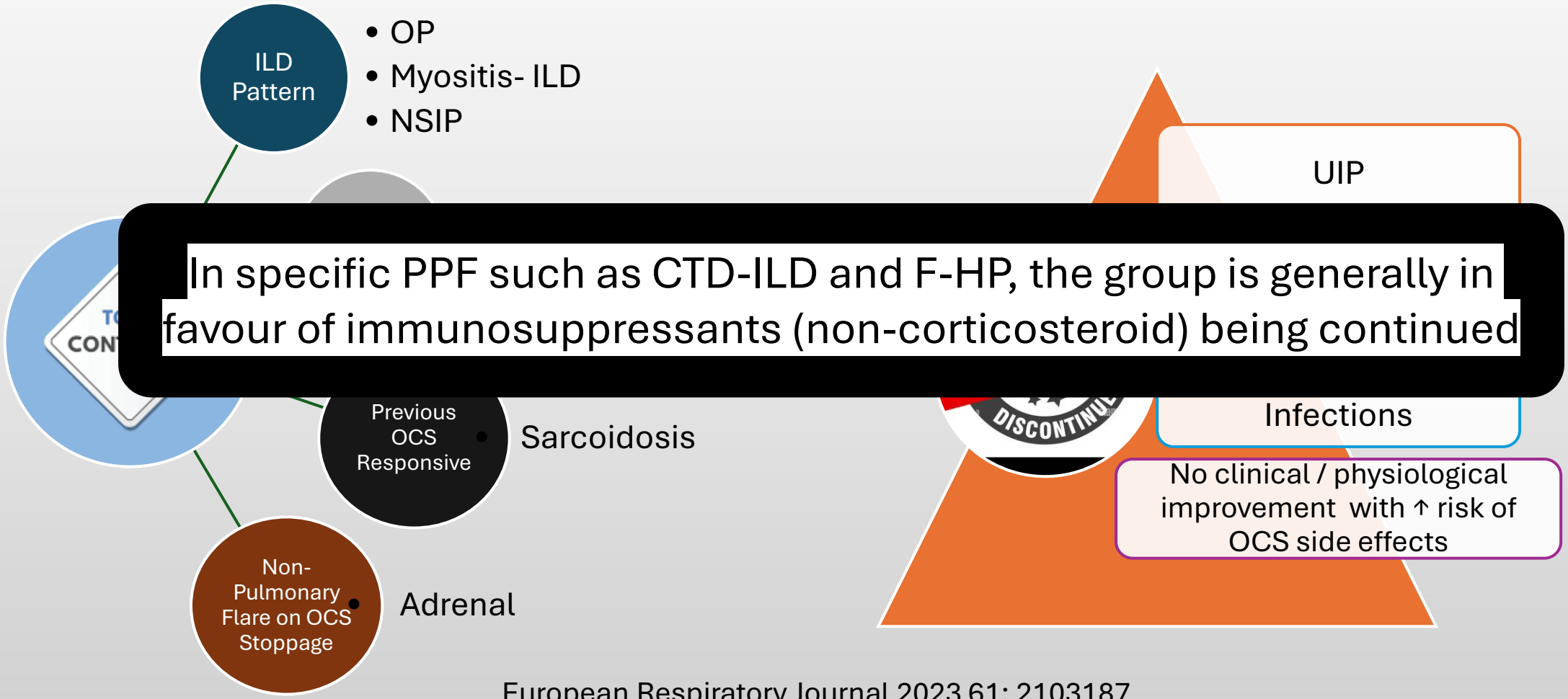
Q? Antifibrotics : Add or Alone in PF- ILD's ?

inBuild

- INBUILD showed decrease progression in PF-ILD's with add on Nintedanib as add on immunosuppression
- Clinical dilemma :
  - Intensify immunosuppressive
  - OR introduce antifibrotic
  - OR use as combination
- Recommended 3-6 months on standard therapy before adding antifibrotic

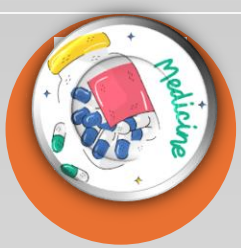
Adverse effects need to monitored more closely, especially Infections, Liver/ Kidney toxicity

How Long to Continue OCS & Immunosuppressives



European Respiratory Journal 2023 61: 2103187

Conclusions:

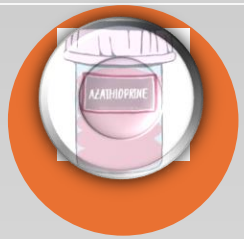


IMMUNOSUPPRESSIVES ± ANTIFIBROTICS

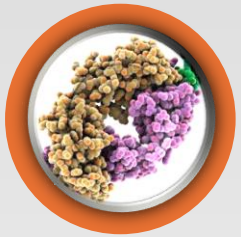
HP, CTD AND SARCOIDOSIS ILD'S, INSIP, IPAF ARE SUITABLE FOR IS

STEROIDS ARE 1ST CHOICE IN MOST (EXCEPT SSC-ILD), BUT NOT INDEFINITELY

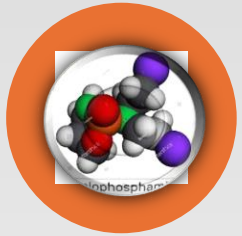
MMF IS 1ST LINE IMMUNOSUPPRESSIVE FOR MOST NON IPF ILD'S (EXCEPT SARCOIDOSIS (MTX))



AZA IS 2ND OPTION IN HP / INSIP

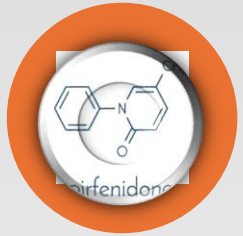


NEWER DRUGS : RTX, TOCI / TOFACITINIB GAINING RECOGNITION IN CTD-ILD'S



CYCLOPHOSPHAMIDE: 3RD LINE / RESCUE IN MOST (NOT IN HP/SARCOIDOSIS)

STOPPING IS IS POSSIBLE IN FEW CASES BUT NEED TO BE INDIVIDUALIZED



ANTIFIBROTICS ARE 1ST LINE IN IPF BUT AFTER IS IN NON IPF ILD'S WHEN ITS PPF

COMBINED IS + ANTIFIBROTICS IN SOME NON IPF ILD'S BUT IS SHOULD BE NON STEROIDS

Thank you