2021.04.10

제 50차 대한결핵 및 호흡기학회 WORKSHOP

# Interstitial Lung Disease (ILD)

## Respiratory Review of 2021

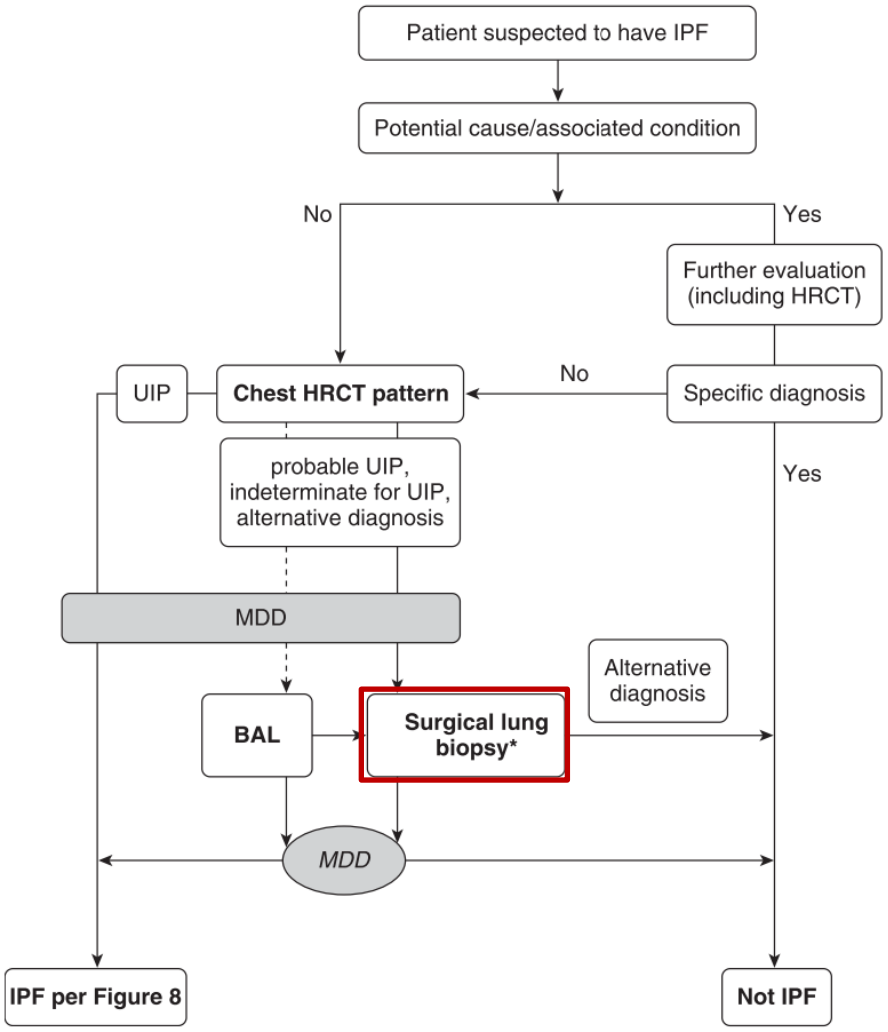
유 홍 석

성균관대학교 의과대학
삼성서울병원 호흡기내과

# CONTENTS

# CONTENTS

# Transbronchial Cryobiopsy (TBLC) in ILD




**Question 6: For Patients with Newly Detected ILD of Unknown Cause Who Are Clinically Suspected of Having IPF, Is Transbronchial Lung Cryobiopsy a Reasonable Alternative to SLB to Ascertain the Histopathology Diagnosis of UIP Pattern?**

*ATS/ERS/JRS/ALAT recommendations.*

- For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate for UIP, or an alternative diagnosis, the panel made no recommendation regarding lung cryobiopsy.

Raghu G *et al*. *Am J Respir Med*. 2018; 198(5)

# TBLC for diagnosis of ILD

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

## Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial

Jürgen Hetzel[1,26], Athol U. Wells[2], Ulrich Costabel[3], Thomas V. Colby[4], Simon L.F. Walsh[5], Johny Verschakelen[6], Alberto Cavazza[7], Sara Tomassetti[8], Claudia Ravaglia[8], Michael Böckeler[1], Werner Spengler[1], Michael Kreuter[9,10], Ralf Eberhardt[10,11], Kaid Darwiche[12], Alfons Torrego[13], Virginia Pajares[13], Rainer Muche[14], Regina Musterle[1], Marius Horger[15], Falko Fend[16], Arne Warth[17,18], Claus Peter Heußel[10,19], Sara Piciucchi[20], Alessandra Dubini[21], Dirk Theegarten[22], Tomas Franquet[23], Enrique Lerma[24], Venerino Poletti[8,25] and Maik Häntschel[1,26]

# Study Design

- Multicenter prospective observational study (5 centers)
- 128 patients with idiopathic interstitial pneumonia
- Endpoint
  - ✓ Impact of TBLC on level of confidence

| Step | Information provided | | | | Participants | Output |
|---|---|---|---|---|---|---|
| 1 | CR | | | | Clinicians, radiologists | Consensus on diagnosis (yes/no)<br>If yes, consensus on likelihood in % |
| 2 | CR | BAL | | | Clinicians, radiologists, pathologists | Consensus on diagnosis (yes/no)<br>If yes, consensus on likelihood in % |
| 3 | CR | BAL | TBLC | | Clinicians, radiologists, pathologists | Consensus on diagnosis (yes/no)<br>If yes, consensus on likelihood in % |
| 4 | CR | BAL | TBLC | SLB | Clinicians, radiologists, pathologists | Consensus on diagnosis (yes/no)<br>If yes, consensus on likelihood in % |

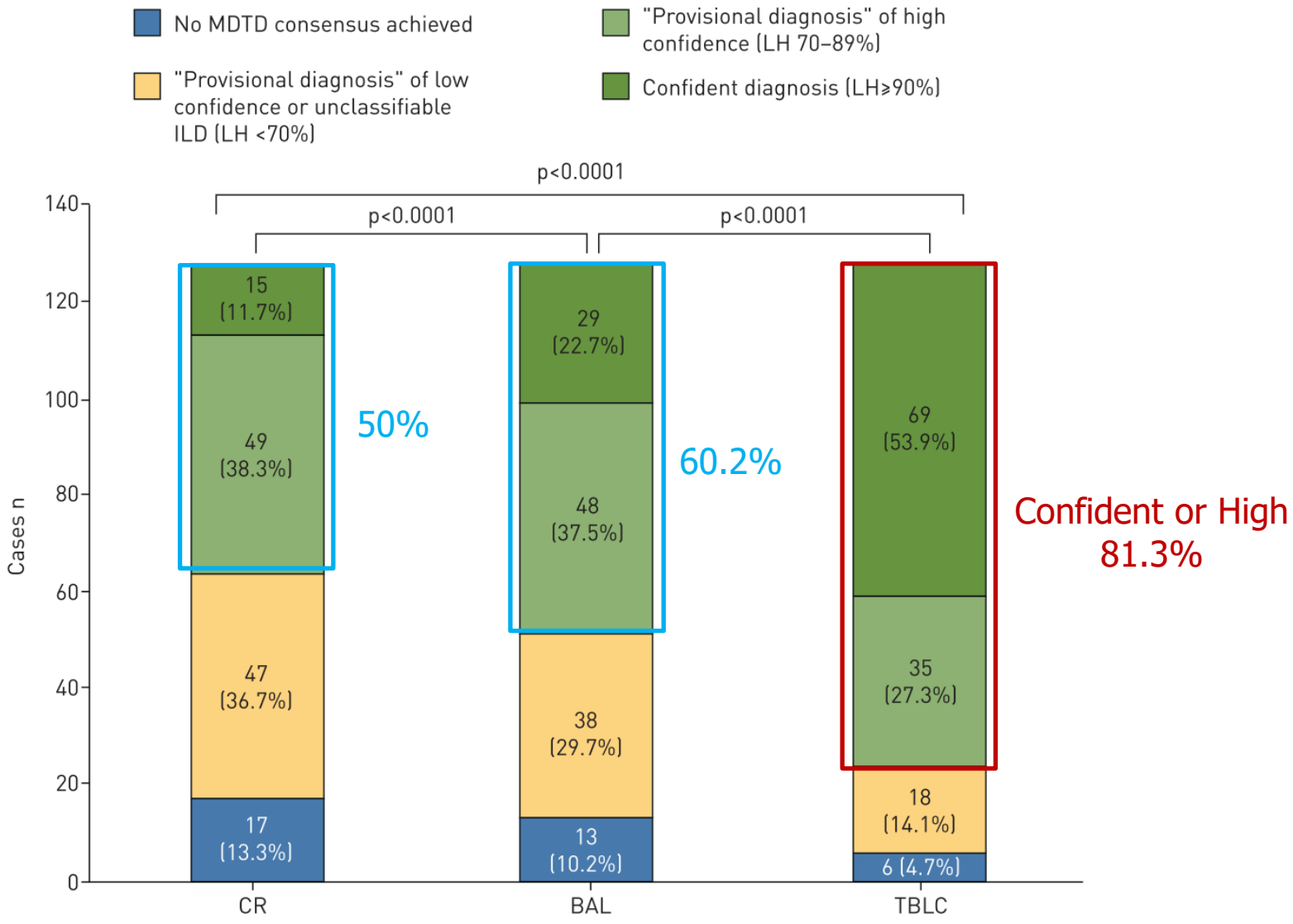
TABLE 2 Likelihood of diagnosis of interstitial lung disease allocated to a confidence level of diagnosis according to RYERSON *et al.* [26].

| | Confidence level of diagnosis |
|---|---|
| **≥90%** | Confident diagnosis |
| **70–89%** | "Provisional diagnosis" with high confidence |
| **<70%** | "Provisional diagnosis" with low confidence (likelihood 51–69%) and unclassifiable (likelihood ≤50%) |
| **No consensus** | |

Hetzel J *et al*. *Eur Respir J*. 2020; 56(6)

## TBLC for diagnosis of ILD

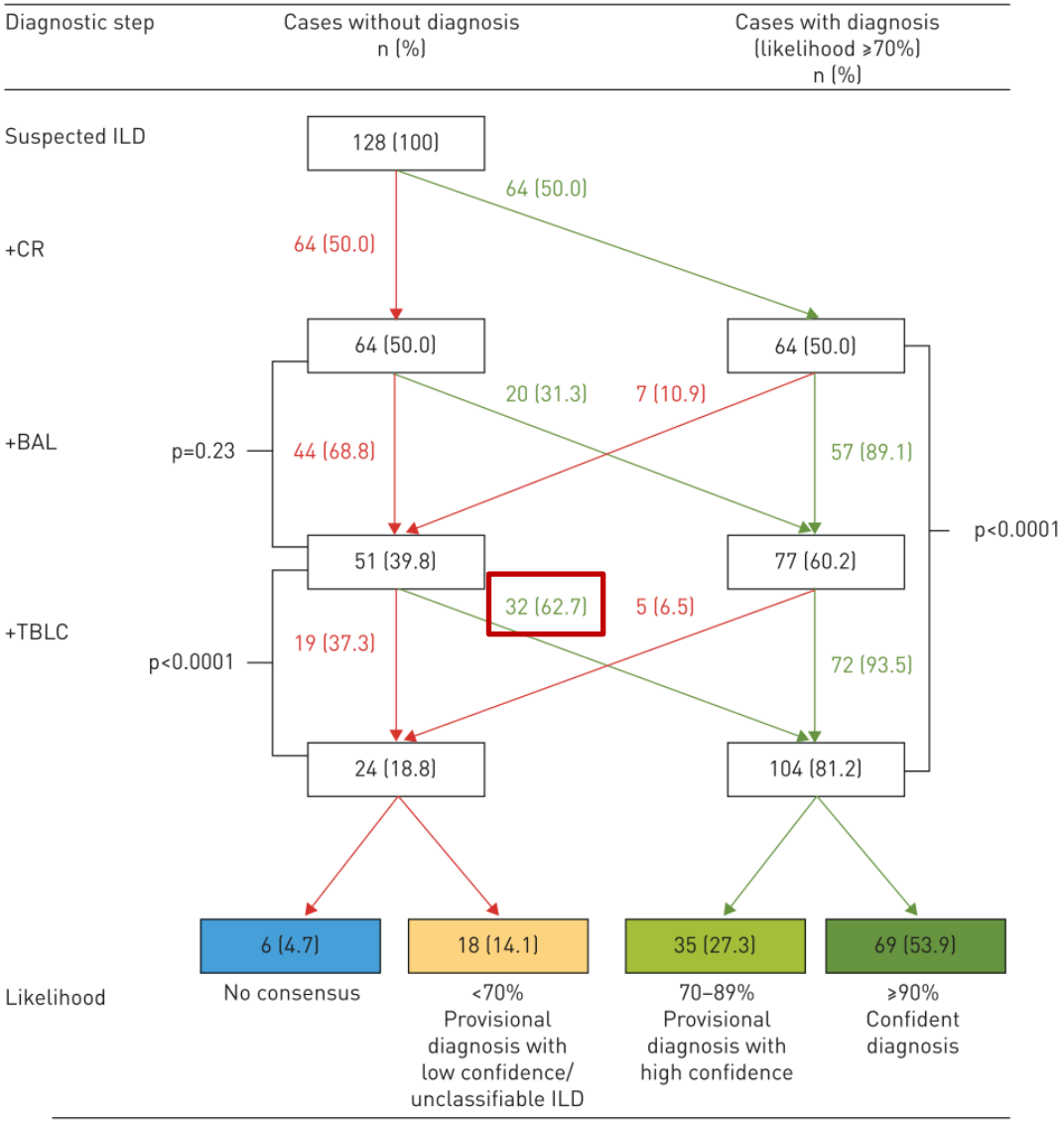
# Results




Hetzel J *et al*. *Eur Respir J*. 2020; 56(6)

## TBLC for diagnosis of ILD

# Results




Hetzel J *et al*. *Eur Respir J*. 2020; 56(6)

TBLC for diagnosis of ILD

# Results

TABLE 5 Transbronchial lung cryobiopsy-associated complications

| | |
|---|---|
| **Patients** | 128 (100) |
| **Bleeding** | |
| No | 37 (28.9) |
| Yes | 90 (70.3) |
| Mild (suction alone) | 70 (54.7) |
| Moderate (additional intervention) | 19 (14.8) |
| Severe (prolonged monitoring or fatal) | 1 (0.8) |
| **Clinically relevant bleeding** | |
| No (no bleeding or mild) | 107 (84.3) |
| Yes (moderate or severe) | 20 (15.7) |
| **Intervention for bleeding control** | |
| No | 6 (4.7) |
| Yes | 58 (45.3) |
| Suction alone | 19 (14.8) |
| Cold saline | 0 (0) |
| Vasoconstrictive drugs | 0 (0) |
| Compression | 28 (21.9) |
| Combination of interventions | 11 (8.6) |
| **Pneumothorax** | |
| No | 99 (77.3) |
| Yes | 21 (16.4) |
| Insertion of/need for thoracic drainage | 11 (8.6) |

Hetzel J *et al*. *Eur Respir J*. 2020; 56(6)

# Conclusions

**Conclusions**

- TBLC increases diagnostic confidence in ILD patients with an uncertain noninvasive diagnosis
- Complications of TBLC were manageable

# TBLC for MDD of IPF

Articles

## Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study

*Sara Tomassetti, Claudia Ravaglia, Athol U Wells, Alberto Cavazza, Thomas V Colby*, Giulio Rossi, Brett Ley, Jay H Ryu, Silvia Puglisi, Antonella Arcadu, Martina Marchi, Fabio Sultani, Sabrina Martinello, Luca Donati, Carlo Gurioli, Christian Gurioli, Paola Tantalocco, Jurgen Hetzel, Alessandra Dubini, Sara Piciucchi, Catherine Klersy, Federico Lavorini, Venerino Poletti*

# Study Design

- Single-center, retrospective, investigator-initiated comparative study
- 426 ILD patients who underwent TBLC or SLBx (266 TBLC and 160 SLBx)
- Endpoint
  - ✓ Prognostic significance of MDT in patients who underwent TBLC

    (Transplant-free survival for IPF vs. non-IPF ILD)
  - ✓ Prognostic significance of UIP vs. non-UIP who underwent TBLC
  - ✓ Prognostic significance of MDT (TBLC vs. SLBx)
  - ✓ Prognostic significance of UIP vs. non-UIP (TBLC vs. SLBx)

Tomassetti S *et al*. *Lancet Respir Med*. 2020; 8(8)

TBLC for MDD of ILD

# Results

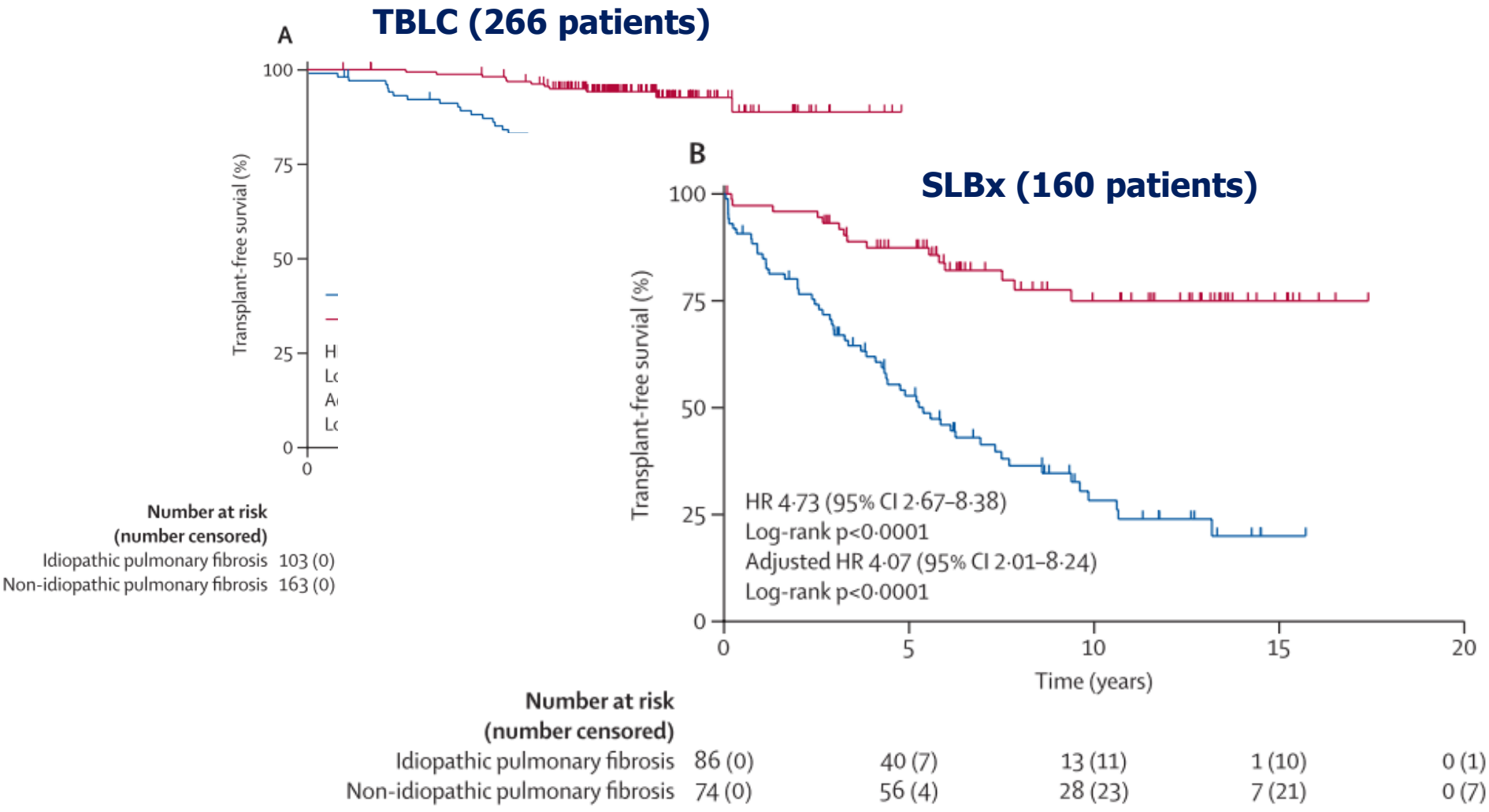
| | Transbronchial lung cryobiopsy (n=266) | Surgical lung biopsy (n=160) | p value |
|---|---|---|---|
| Sex | | | |
| Men | 154 (58%) | 90 (56%) | 0·74 |
| Women | 112 (42%) | 70 (44%) | .. |
| Age, years | 58·5 (11·2) | 55·9 (11·8) | 0·021 |
| Current or former smokers | 143 (54%) | 91 (57%) | 0·53 |
| Patients with comorbidities | 226 (85%) | 113 (71%) | <0·0001 |
| Number of comorbidities | 2 (1–3) | 1 (0–2) | <0·0001 |
| Charlson comorbidities index | 2·3 (1·7) | 1·9 (1·8) | 0·027 |
| Malignancies | 32 (12%) | 19 (12%) | 0·88 |
| Chronic heart failure | 5 (2%) | 5 (3%) | 0·35 |
| Pulmonary hypertension | 17 (6%) | 12 (8%) | 0·54 |
| High-resolution CT findings | | | |
| Probable UIP | 58 (22%) | 35 (22%) | 0·83 |
| Indeterminate UIP | 83 (31%) | 65 (41%) | 0·069 |
| Alternative diagnosis | 125 (47%) | 60 (38%) | 0·12 |
| Percentage of predicted FVC | 84·5 (19·9) | 79·6 (22·2) | 0·020 |
| Percentage of predicted $FEV_1$ | 87·3 (19) | 82·1 (23·2) | 0·012 |
| Percentage of predicted DLco | 60·2 (16·6) | 58·1 (19·7) | 0·26 |

Data are number (%), mean (SD), or median (IQR). UIP=usual interstitial pneumonia. FVC=forced vital capacity. $FEV_1$=forced expiratory volume in the first second. DLco=diffusing capacity of the lungs for carbon monoxide.

***Table 1:*** **Patient characteristics of all cases**

Tomassetti S *et al*. *Lancet Respir Med*. 2020; 8(8)

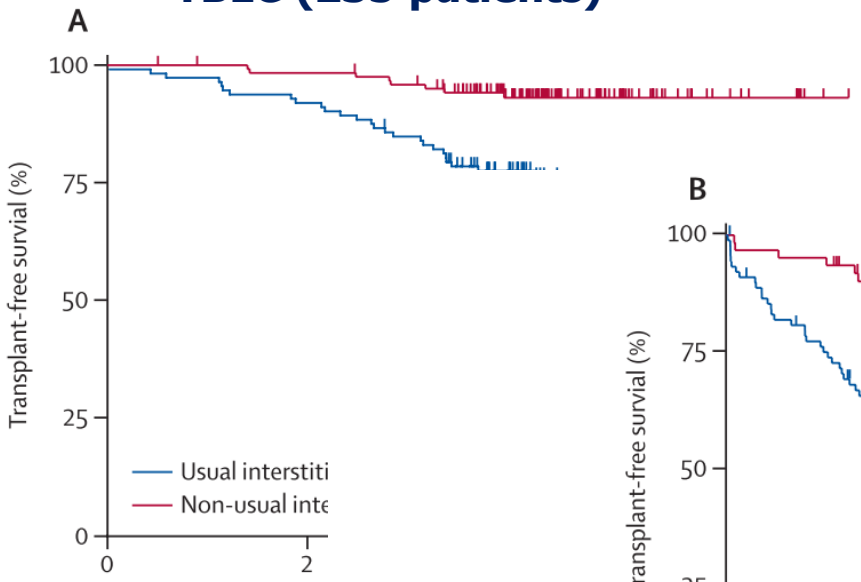
# Results




Tomassetti S *et al*. *Lancet Respir Med*. 2020; 8(8)

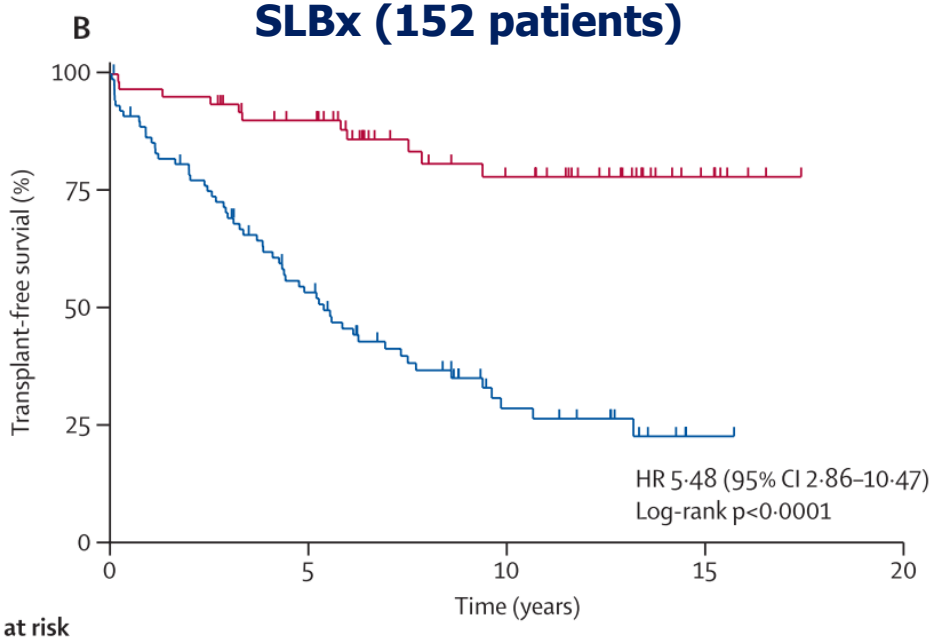
# Results

## TBLC (235 patients)




| Number at risk (number censored) | | |
|---|---|---|
| Usual interstitial pneumonia | 112 (0) | 103 ( |
| Non-usual interstitial pneumonia | 123 (0) | 119 ( |

## SLBx (152 patients)




| Number at risk (number censored) | | | | | |
|---|---|---|---|---|---|
| Usual interstitial pneumonia | 89 (0) | 43 (6) | 13 (14) | 1 (10) | 0 (1) |
| Non-usual interstitial pneumonia | 63 (0) | 50 (7) | 27 (18) | 7 (10) | 0 (7) |

Tomassetti S *et al*. *Lancet Respir Med*. 2020; 8(8)

# Conclusions

**Conclusions**

- TBLC provides diagnostic contribution in MDT of ILD based on the prognostic distinction

# CONTENTS

# Inhaled Treprostinil in PH due to ILD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

# Pulmonary Hypertension in ILD

- **Prevalence of PH in ILD**
  - ✓ Most data from IPF: 15%~50% (ranging from 3%~86%)
  - ✓ Prevalence increases over severity of ILD (advanced 50%, end-stage > 60%)

- **Prognostic significance of PH**
  - ✓ Reduced exercise capacity, decreased quality of life (QoL)
  - ✓ Increased risk of acute exacerbation (HR 2.217)
  - ✓ Poor survival compared to non-PH ILD or IPAH

Nathan SD *et al*. *Eur Respir J*. 2019; 53

# Clinical Trials of IPF

| Trial | Drug | Patients | Endpoint | Outcome |
|---|---|---|---|---|
| BUILD-1 (2008) | Bosentan | IPF | 6 MWD at 12 mo | (-) |
| STEP-IPF (2010) | Sildenafil | IPF | 6 MWD over 12 weeks<br>Dyspnea score at 6 mo | (-)<br>Improvement in dyspnea |
| BUILD-3 (2011) | Bosentan | IPF | Time to disease progression or death over 8-32 weeks | (-) |
| ARTEMIS-IPF (2013) | Ambrisentan | IPF<br>(10% with PH) | Time to disease progression or death over 4 yrs | (-)<br>Early termination (Prog) |
| MUSIC (2013) | Macitentan | IPF | FVC decline over 12 mo | (-) |
| BPHIT (2014) | Bosentan | Fibrotic IIP, PH | Pulmonary vascular resistance indiex (PVRi) over 16 weeks | (-) |
| ARTEMIS-IPF F/U (2015) | Ambrisentan | IPF, PH group 3 | Mean difference in PAP after 12 months | (-) |
| INSTAGE (2018) | Nintedanib<br>± Sildenafil | IPF, RHD | Change in SGRQ at 12 weeks | (-) |
| RISE-IIP (2019) | Rociguat | ILD, PH group 3 | 6 MWD at 26 weeks | (-)<br>Early termination (SAE) |

Rafii R *et al*. *J Thorac Dis*. 2013;15(1)
Nathan SD *et al*. *Eur Respir J*. 2019;53

Inhaled Treprostinil in PH due to ILD

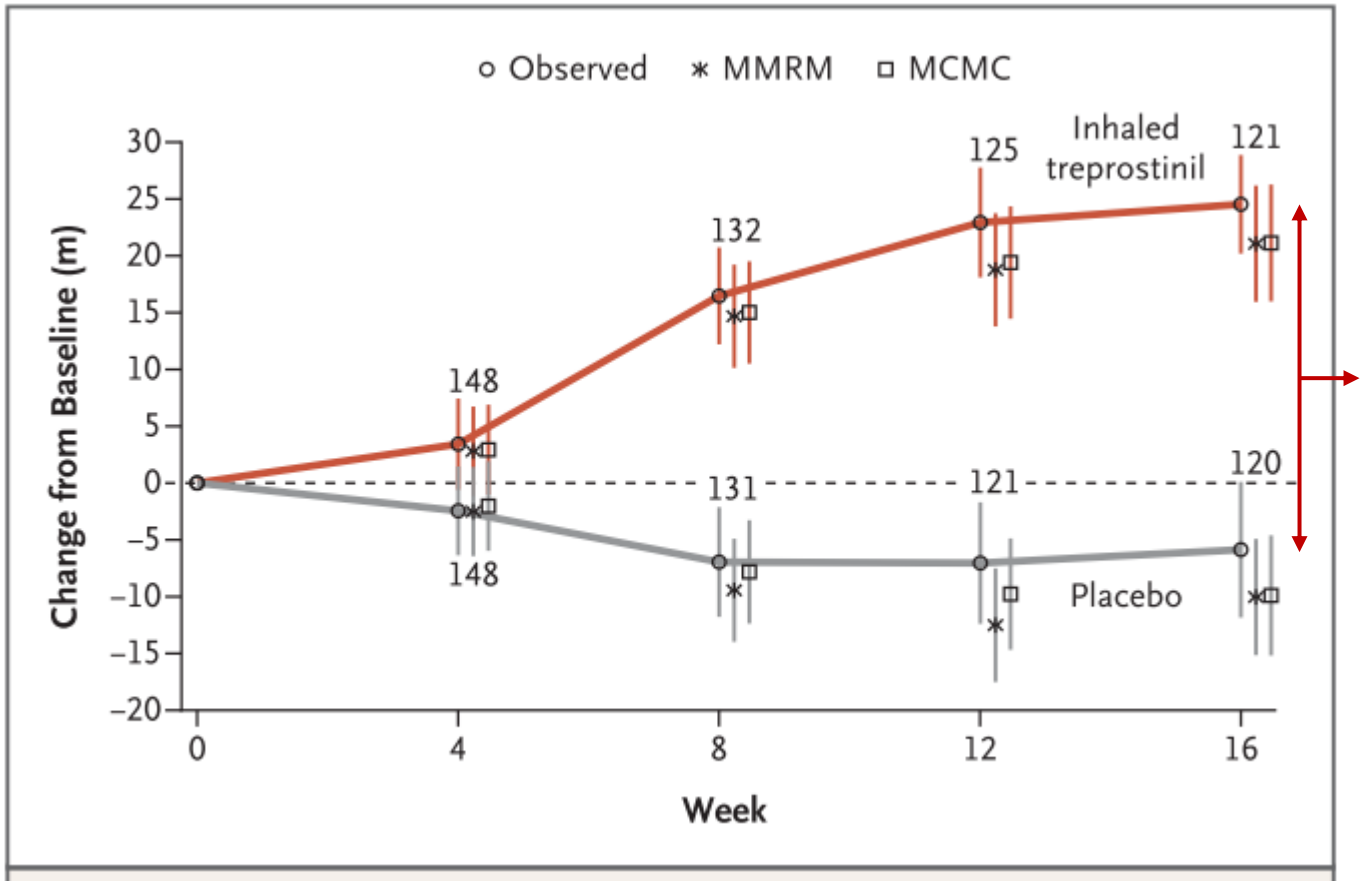
# Study Design

- Double-blind, randomized, placebo-controlled trial (INCREASE trial)
- 326 patients with ILD and PH (group 3)
- Inclusion
  - ✓ ILD (Chest HRCT within 6 months)
  - ✓ Group 3 PH (PVR > 3 Wood units, PCWP ≤ 15 mmHg, mean PAP ≥ 25mmHg)
- Protocol
  - ✓ (1:1 ratio) Inhaled Treprostinil neb. vs. placebo for 16 weeks
- Endpoint
  - ✓ Change in peak 6-MWD at 16 week
  - ✓ Change in NTproBNP, Time to clinical worsening

Waxman A *et al*. *N Engl J Med*. 2021; 384(4)

## Inhaled Treprostinil in PH due to ILD

# Results




Treprostinil
21.08 m ± 5.12

Mean difference
31.12 m (16.85 – 45.39)

Placebo
-10.04 m ± 5.12

Waxman A *et al*. *N Engl J Med*. 2021; 384(4)

## Inhaled Treprostinil in PH due to ILD

# Results

**Table 2. Summary of Primary and Secondary End Points.***

| End Point | Inhaled Treprostinil (N=163) | Placebo (N=163) | Treatment Effect (95% CI) | P Value |
|---|---|---|---|---|
| **Primary end point** | | | | |
| Change in peak 6-minute walk distance from baseline to wk 16 — m† | 21.08±5.12 | −10.04±5.12 | 31.12±7.25 (16.85 to 45.39)‡ | <0.001 |
| **Secondary end points§** | | | | |
| Change in plasma concentration of NT-proBNP from baseline to wk 16¶ | | | | |
| Mean (±SD) change — pg/ml | −396.35±1904.90 | 1453.95±7296.20 | | |
| Median — pg/ml | −22.65 | 20.65 | | |
| Range — pg/ml | −11,433.0 to 5373.1 | −5483.3 to 87,148.3 | | |
| Ratio to baseline | 0.85±0.06 | 1.46±0.11 | 0.58±0.06 (0.47 to 0.72)‖ | <0.001 |
| Occurrence of clinical worsening — no. (%) | | | 0.61 (0.4 to 0.92)** | 0.04 |
| Any event | 37 (22.7) | 54 (33.1) | | |
| Hospitalization for cardiopulmonary indication | 18 (11.0) | 24 (14.7) | | |
| Decrease in 6-minute walk distance of >15% from baseline | 13 (8.0) | 26 (16.0) | | |
| Death from any cause | 4 (2.5) | 4 (2.5) | | |
| Lung transplantation | 2 (1.2) | 0 | | |
| Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m† | 18.77±4.99 | −12.52±5.01 | 31.29±7.07 (17.37 to 45.21)‡ | <0.001 |
| Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m | 9.3±5.5 | −12.7±5.5 | 21.99±7.7 (6.85 to 37.14)‡ | 0.005†† |

Waxman A *et al*. *N Engl J Med*. 2021; 384(4)

## Inhaled Treprostinil in PH due to ILD

# Results

**Table 3. Summary of Adverse Events.**

| Variable | Inhaled Treprostinil (N=163) | Placebo (N=163) | P Value* |
|---|---|---|---|
| Total no. of adverse events | 890 | 793 | |
| Patients with ≥1 adverse event — no. (%) | 152 (93.3) | 149 (91.4) | 0.68 |
| Total no. of serious adverse events† | 53 | 89 | |
| Patients with ≥1 serious adverse event — no. (%) | 38 (23.3) | 42 (25.8) | 0.70 |
| Total no. of adverse events leading to withdrawal of treprostinil or placebo | 47 | 38 | |
| Most frequently occurring adverse events — no. of patients (%)‡ | | | |
| Cough | 71 (43.6) | 54 (33.1) | 0.07 |
| Headache | 45 (27.6) | 32 (19.6) | 0.12 |
| Dyspnea | 41 (25.2) | 51 (31.3) | 0.27 |
| Dizziness | 30 (18.4) | 23 (14.1) | 0.37 |
| Nausea | 25 (15.3) | 26 (16.0) | >0.99 |
| Fatigue | 23 (14.1) | 23 (14.1) | >0.99 |
| Diarrhea | 22 (13.5) | 19 (11.7) | 0.74 |
| Throat irritation | 20 (12.3) | 6 (3.7) | 0.007 |
| Oropharyngeal pain | 18 (11.0) | 4 (2.5) | 0.003 |
| NT-proBNP increased | 9 (5.5) | 25 (15.3) | 0.006 |

Waxman A *et al*. *N Engl J Med*. 2021; 384(4)

# Conclusions

**Conclusions**

- Inhaled Treprostinil improves exercise capacity (6-MWD) in patients with PH group 3 due to ILD
- Common side effects were cough, headache, dyspnea which were tolerable

# Tocilizumab for SSc (focuSSced)

## Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

*Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis*, Christopher P Denton*, for the focuSSced investigators†*

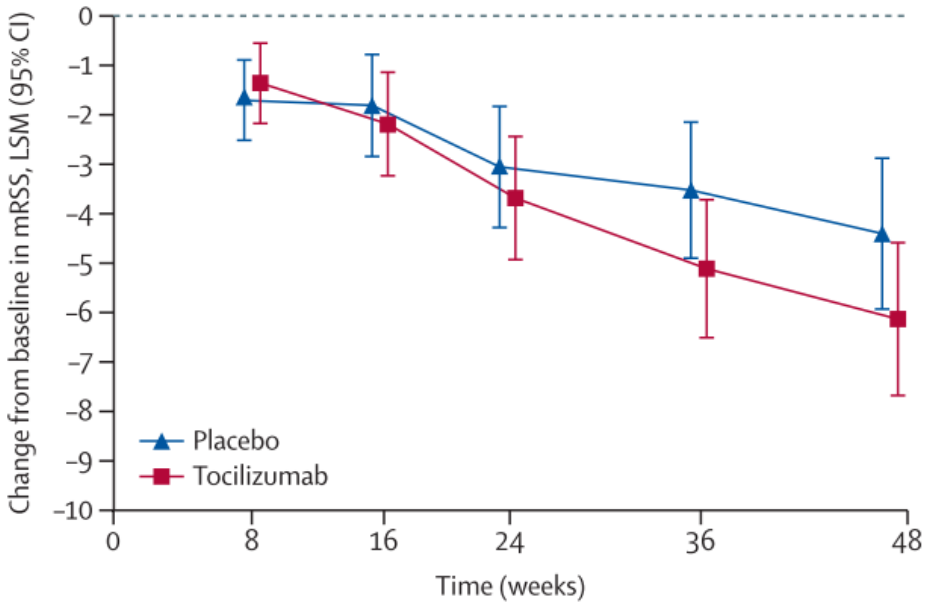
# Study Design

- Double-blind placebo-controlled phase 3 trial (75 sites from 20 countries)
- 210 SSc patients (115 SSc-ILD)
  - ✓ Sx duration (1st non-Raynaud ph) ≤ 60 months
  - ✓ 10 ≤ mRSS ≤ 35
  - ✓ Elevated acute-phase reactant (CRP ≥ 6 mg/L, ESR ≥ 28 mm/h, Plt ≥ $330x10^9$ L)
  - ✓ Active disease (disease duration ≤ 18 months / mRSS increase ≥ 3 or new organ involvement + mRSS ≥ 2, 2 new organ involvement within 6 months)
- Exclusion
  - ✓ FVC ≤ 55% or DLco ≤ 45%
- Protocol
  - ✓ 1:1 (Tocilizumab 162 mg/wk vs. placebo) for 48 weeks
- Endpoint
  - ✓ mRSS change at 48 weeks
  - ✓ Difference in distribution of change in FVC (48 wks), proportion of mRSS improvement (20%, 40%, 60%), time to treatment failure (death, FVC decline > 10%, mRSS > 20% and ≥ 5%, serious adverse event)

Khanna D *et al*. *Lancet Respir Med*. 2020; 8(10)

Tocilizumab for SSc

# Results



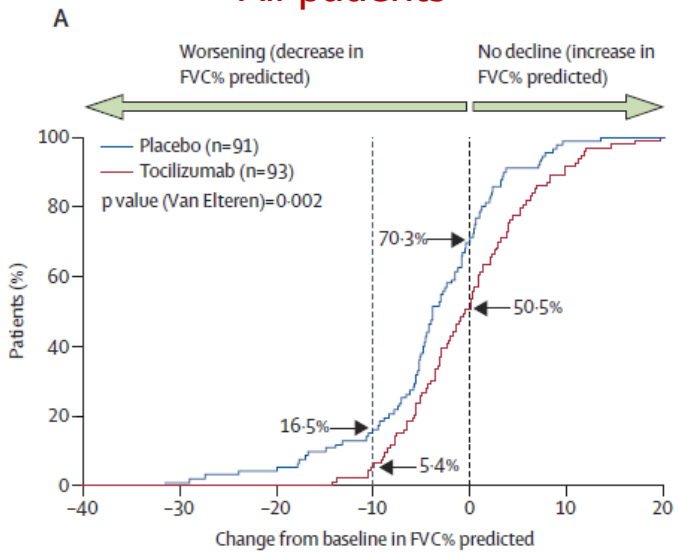

| | Placebo n=106 | Tocilizumab n=104 | |
|---|---|---|---|
| LSM change from baseline at week 48 (primary outcome) | −4·4 | −6·1 | −1·7 (95% CI −3·8 to 0·3); p=0·10 |
| LSM change from baseline at week 24 (exploratory outcome) | −3·1 | −3·7 | −0·6 (95% CI −2·3 to 1·0); nominal p=0·45 |

Khanna D *et al*. *Lancet Respir Med*. 2020; 8(10)

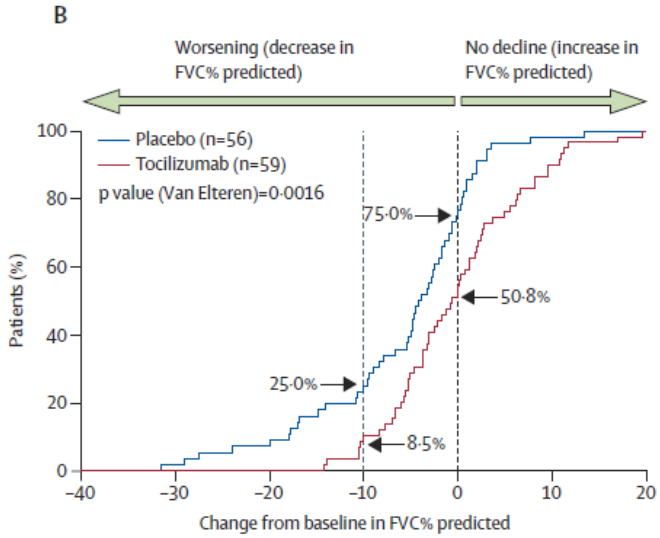
## Tocilizumab for SSc

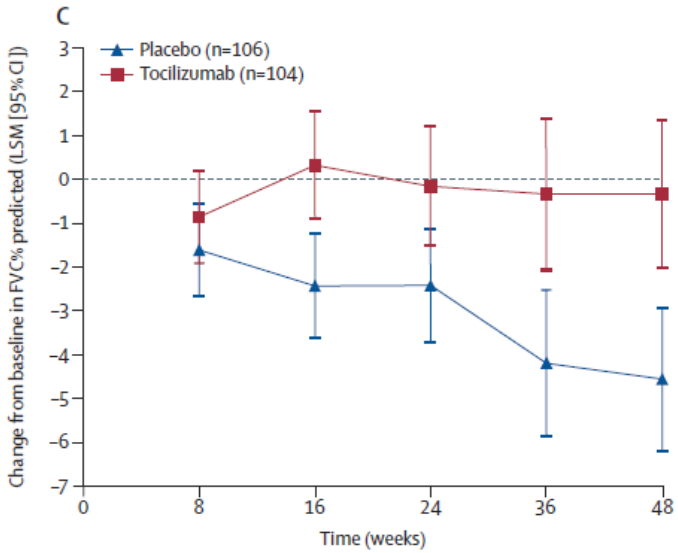
# Results

### All patients



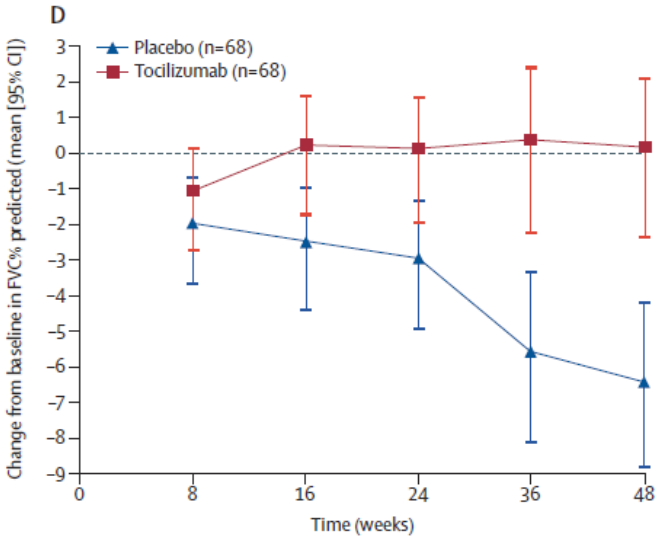

### SSc-ILD




Tocilizumb -0.4%

Placebo -4.6%




Tocilizumb 0.1%

Placebo -6.4%%

# Conclusions

**Conclusions**

- Tocilizumab was not associated with improvement of skin fibrosis
- Tocilizumab was helpful in preservation of lung function in early SSc-ILD with elevated acute phase reactant

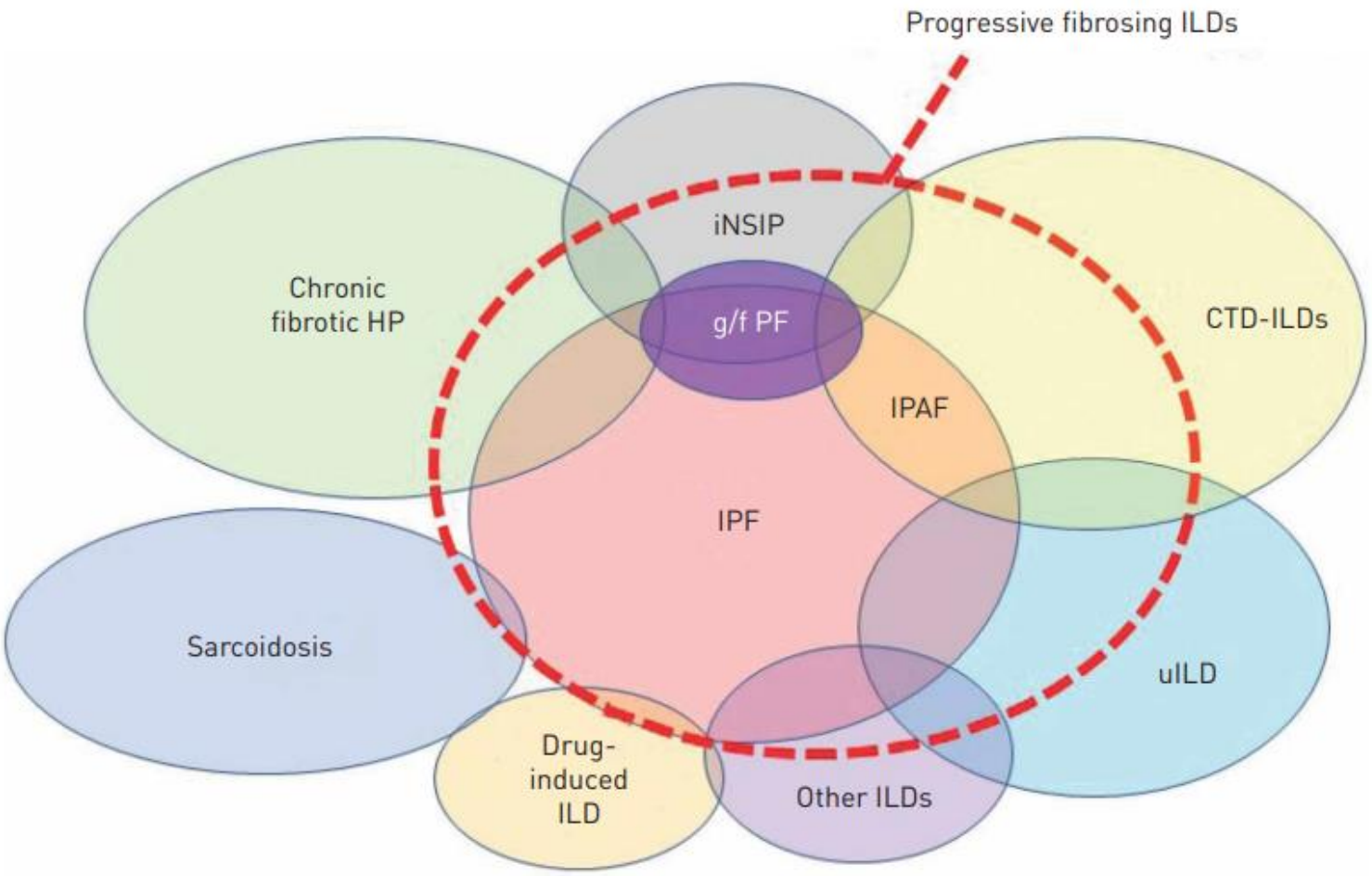
# CONTENTS

# Progressive Fibrosing ILD (PF-ILD)

- Newly suggested classification concept of ILD
- Chronic fibrosing ILD with progressive phenotype (regardless of treatment)
- Examples of PF-ILD
  - ✓ Idiopathic pulmonary fibrosis
  - ✓ Idiopathic fibrotic NSIP, CTD-ILD (eg. RA-ILD, SSc-ILD), fibrotic HP (chronic HP), unclassifiable ILD etc.
- Definition and evaluation of "progressive"
  - ✓ Not yet established
  - ✓ Suggested parameters: FVC decline and/or DLco decline, HRCT extent of progression, symptoms (dyspnea etc.)

Cottin V. Eur *Respir Rev*. 2019; 28
George PM *et al*. *Lancet Respir Med*. 2020; 8

# Progressive Fibrosing ILD (PF-ILD)



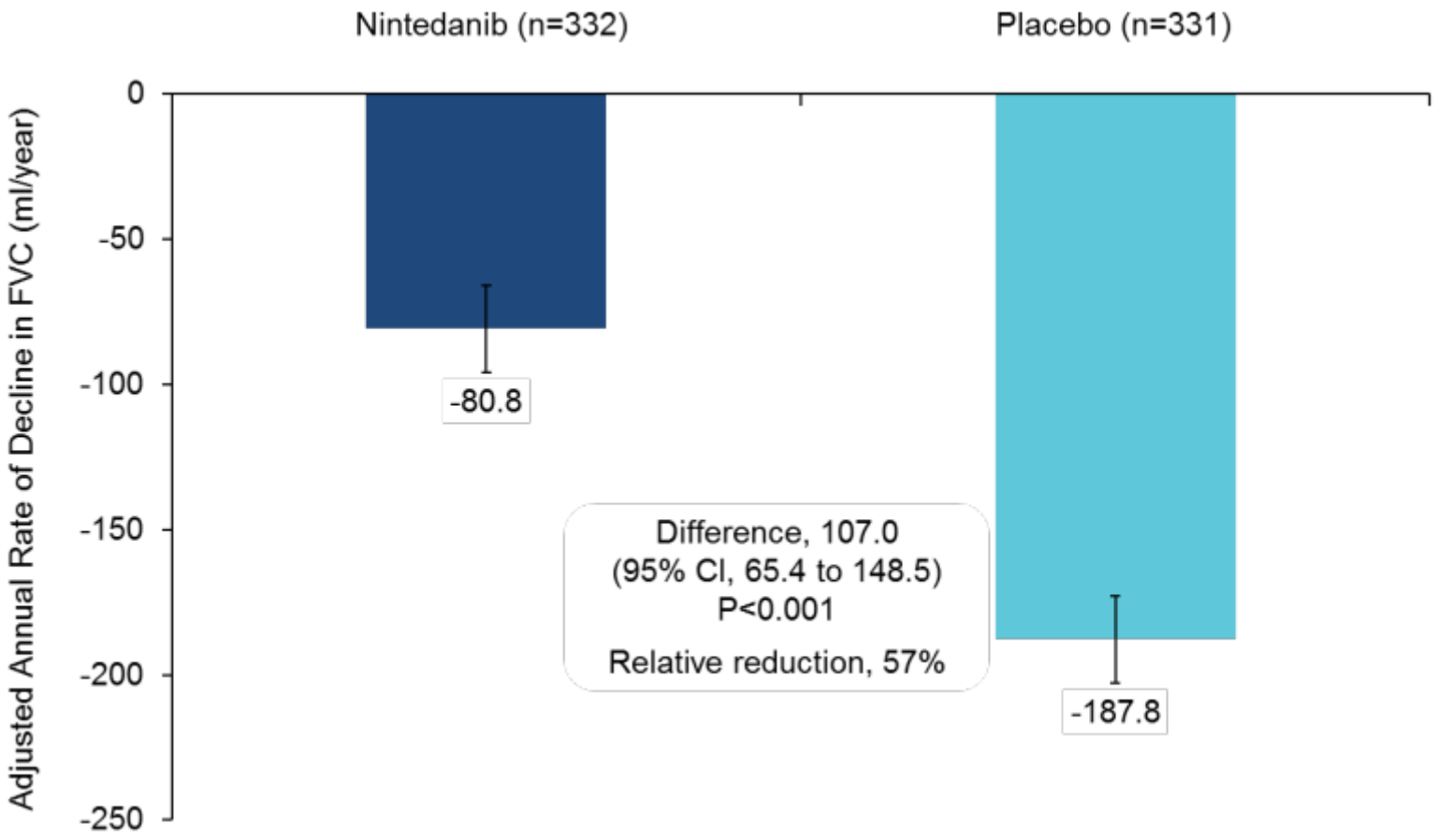

Cottin V. Eur *Respir Rev*. 2019; 28

# Nintedanib for PF-ILD (INBUILD trial)

- Double-blind placebo-controlled phase 3 trial (15 countries)
- 663 Progressive fibrosing ILD [(HP, CTD-ILD, idiopathic NSIP, uIIP etc.)]
- PF-ILD (Progression within 24 months despite standard treatment)
  - ✓ FVC decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT
- Exclusion
  - ✓ AZA, CYC, MMF, Tacrolimus, Rituximab, Cytoxan, Steroid (>20mg)
- Protocol
  - ✓ (1:1 ratio) Nintedanib 150mg bid vs. Placebo for 52 weeks
- Endpoint
  - ✓ Annual rate of FVC decline
  - ✓ Change of K-BILD, time till 1st AE, and time till death

Flaherty KR *et al. N Engl J Med*. 2019; 381(18)

# Nintedanib for PF-ILD (INBUILD trial)




Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

# Nintedanib for PF-ILD (Subgroup)

**Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial**

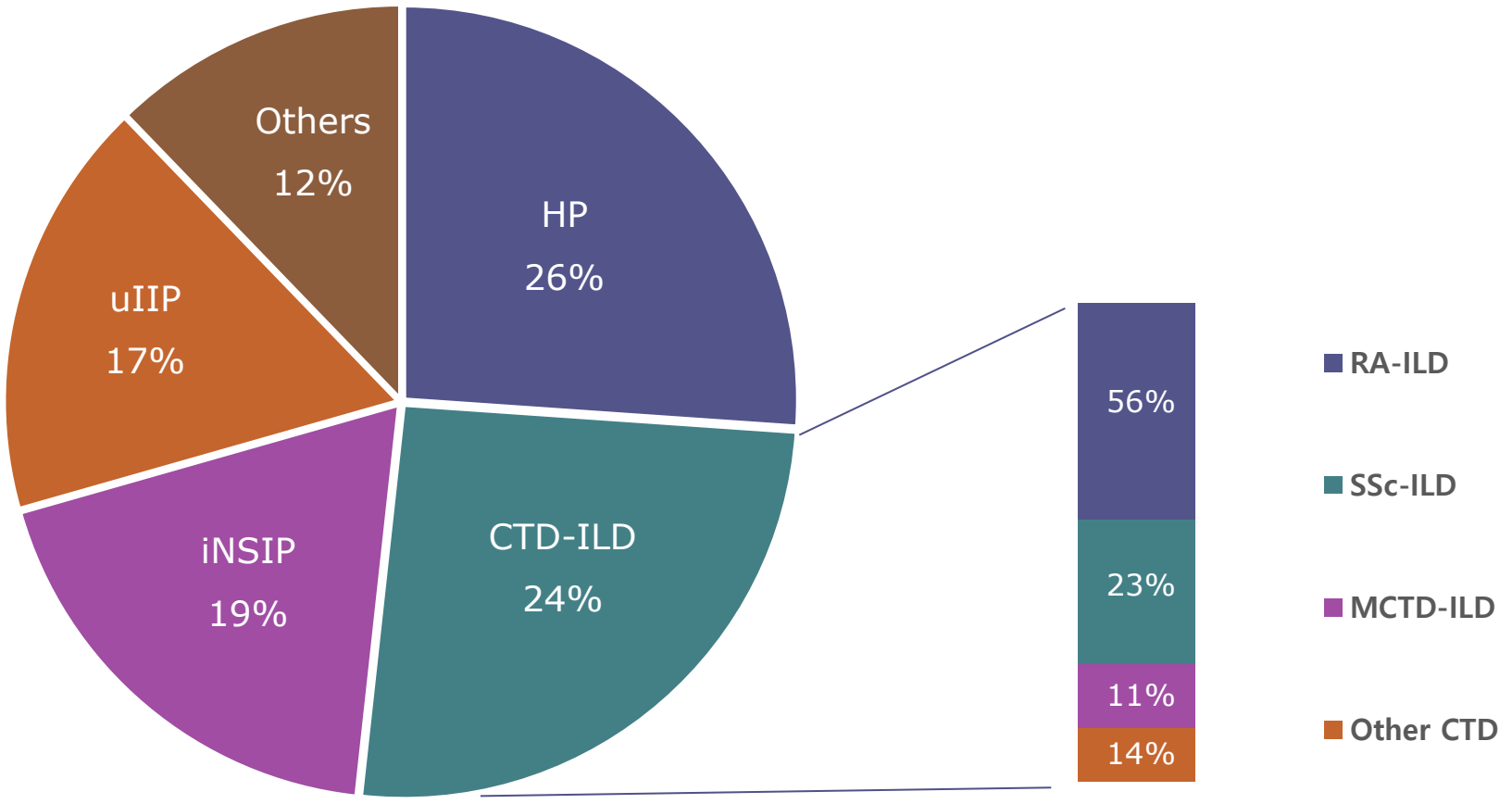
*Athol U Wells, Kevin R Flaherty, Kevin K Brown, Yoshikazu Inoue, Anand Devaraj, Luca Richeldi, Teng Moua, Bruno Crestani, Wim A Wuyts, Susanne Stowasser, Manuel Quaresma, Rainer-Georg Goeldner, Rozsa Schlenker-Herceg, Martin Kolb on behalf of the INBUILD trial investigators**

- Endpoint
  - ✓ Rate of decline in FVC over 52 weeks
  - ✓ Subgroup analysis on 5 prespecified subgroups based on ILD diagnosis

Wells AU *et al*. *Lancet Respir Med*. 2020; 8

Nintedanib for PF-ILD (Subgroup)

# Study Population

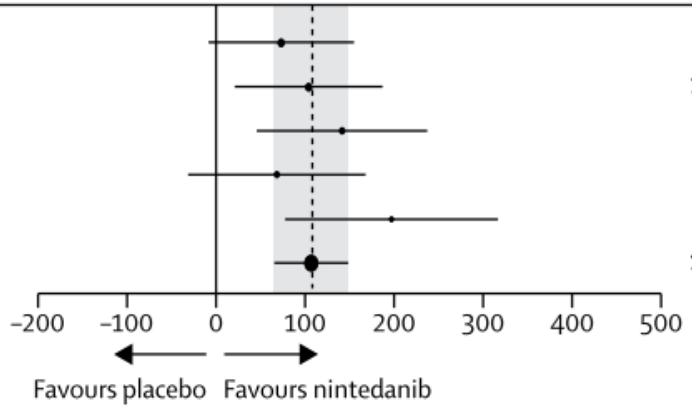



Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

## Nintedanib for PF-ILD (Subgroup)

# Results

| | n analysed | | Difference (95% CI) | Treatment by subgroup by time interaction |
|---|---|---|---|---|
| | Nintedanib | Placebo | | |
| Hypersensitivity pneumonitis | 84 | 89 | 73·1 (−8·6 to 154·8) | p=0·41 |
| Autoimmune interstitial lung diseases | 82 | 88 | 104·0 (21·1 to 186·9) | |
| iNSIP | 64 | 61 | 141·6 (46·0 to 237·2) | |
| Unclassifiable IIP | 64 | 50 | 68·3 (−31·4 to 168·1) | |
| Other interstitial lung diseases | 38 | 43 | 197·1 (77·6 to 316·7) | |
| **All patients** | **332** | **331** | **107·0 (65·4 to 148·5)** | |

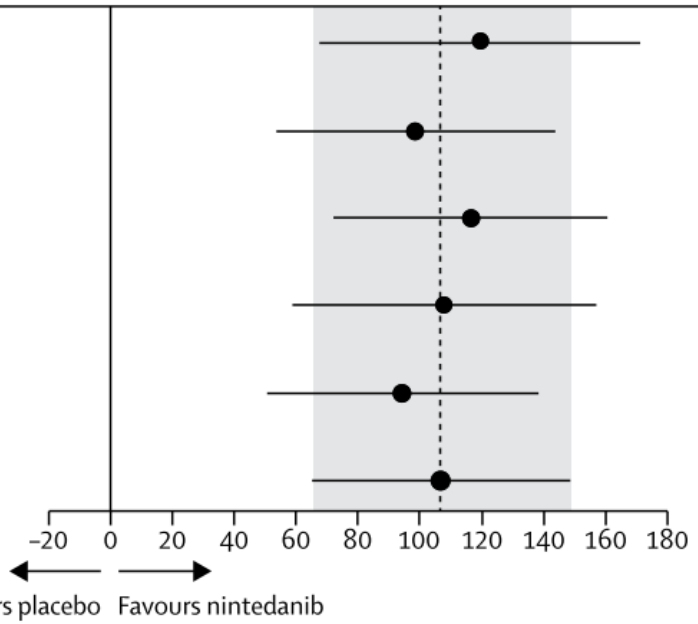



Wells AU *et al*. *Lancet Respir Med*. 2020; 8

## Nintedanib for PF-ILD (Subgroup)

# Results

| | n analysed | | Estimate (95% CI) | p value |
|---|---|---|---|---|
| | Nintedanib | Placebo | | |
| iNSIP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs (excludes HP) | 248 | 242 | 119·4 (67·7 to 171·2) | <0·001 |
| HP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs (excludes iNSIP) | 267 | 270 | 98·7 (53·8 to 143·6) | <0·001 |
| HP, iNSIP, autoimmune ILDs, other fibrosing ILDs (excludes unclassifiable IIP) | 267 | 281 | 116·4 (72·4 to 160·4) | <0·001 |
| HP, iNSIP, unclassifiable IIP, other fibrosing ILDs (excludes autoimmune ILDs) | 250 | 243 | 108·0 (59·1 to 157·0) | <0·001 |
| HP, iNSIP, unclassifiable IIP, autoimmune ILDs (excludes other ILDs) | 293 | 288 | 94·5 (50·7 to 138·2) | <0·001 |
| **All patients** | **332** | **331** | **107·0 (65·4 to 148·5)** | **<0·001** |

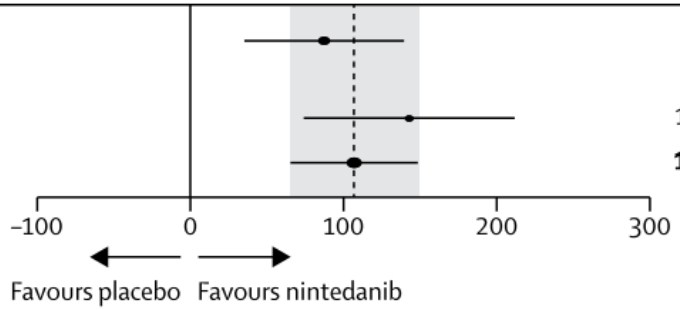



Wells AU *et al*. *Lancet Respir Med*. 2020; 8

## Nintedanib for PF-ILD (Subgroup)

# Results

| | n analysed | | Difference (95% CI) | Treatment by subgroup by time interaction |
|---|---|---|---|---|
| | Nintedanib | Placebo | | |
| Patients with HP, unclassifiable IIP, iNSIP, and IPAF* | 214 | 204 | 87·4 (35·3 to 139·4) | p=0·21 |
| Other patients† | 118 | 127 | 142·9 (74·0 to 211·8) | |
| **All patients** | **332** | **331** | **107·0 (65·4 to 148·5)** | |




Wells AU *et al*. *Lancet Respir Med*. 2020; 8

# Conclusions

**Conclusions**

- Nintedanib may reduce disease progression (measured by FVC decline) in PF-ILD, regardless of underlying ILD diagnosis

# Natural History of PF-ILD

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

CrossMark

## The natural history of progressive fibrosing interstitial lung diseases

Kevin K. Brown[1], Fernando J. Martinez[2], Simon L.F. Walsh[3], Victor J. Thannickal[4], Antje Prasse[5], Rozsa Schlenker-Herceg[6], Rainer-Georg Goeldner[7], Emmanuelle Clerisme-Beaty[8], Kay Tetzlaff[8,9], Vincent Cottin[10] and Athol U. Wells[3,11]

# Study Design

- INPULSIS-1 and -2 trials (1066 IPF)
  - ✓ 50% ≤ FVC ≤ 90% and 30% ≤ DLco ≤ 90% and 6 MWD ≥ 150m and FEV1/FVC ≥ 0.8

- INBUILD trial (663 Non-IPF PF-ILD) (HP, CTD-ILD, idiopathic NSIP, uIIP etc.)
  - ✓ FVC decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT

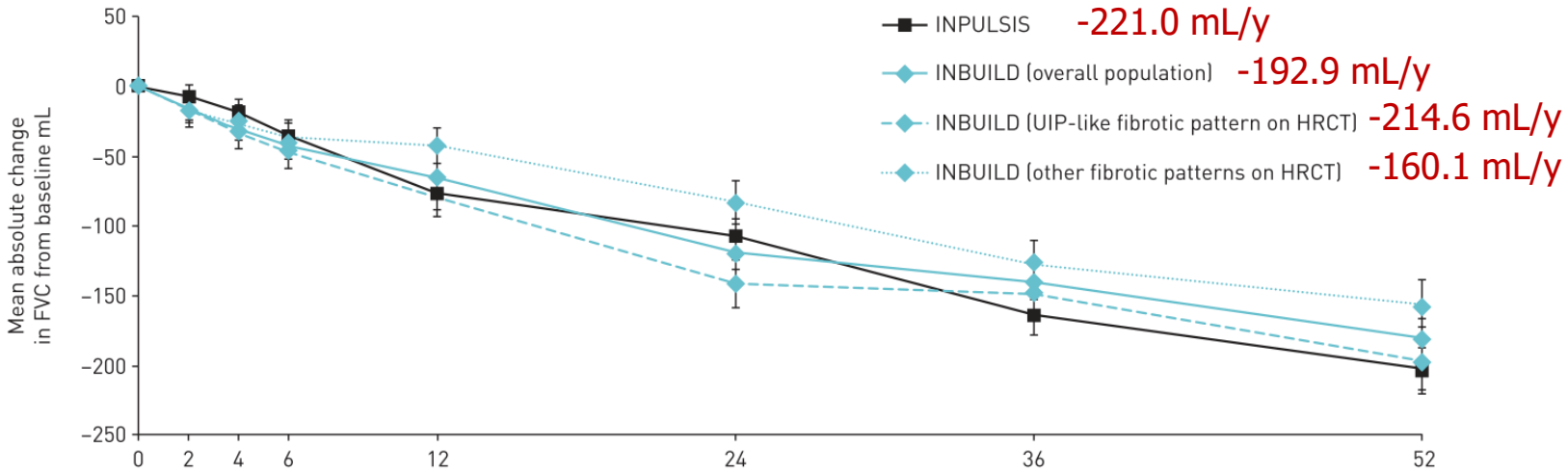
→ Analysis on patients in the placebo group (natural course)

- Endpoint
  - ✓ Annual rate of FVC decline
  - ✓ Observed absolute change of FVC
  - ✓ Proportion of patients with FVC ≥ 5% or ≥ 10%, or mortality

Brown KK *et al*. *Eur Respir J*. 2020; 55(5)

## Natural History of PF-ILD

# Results

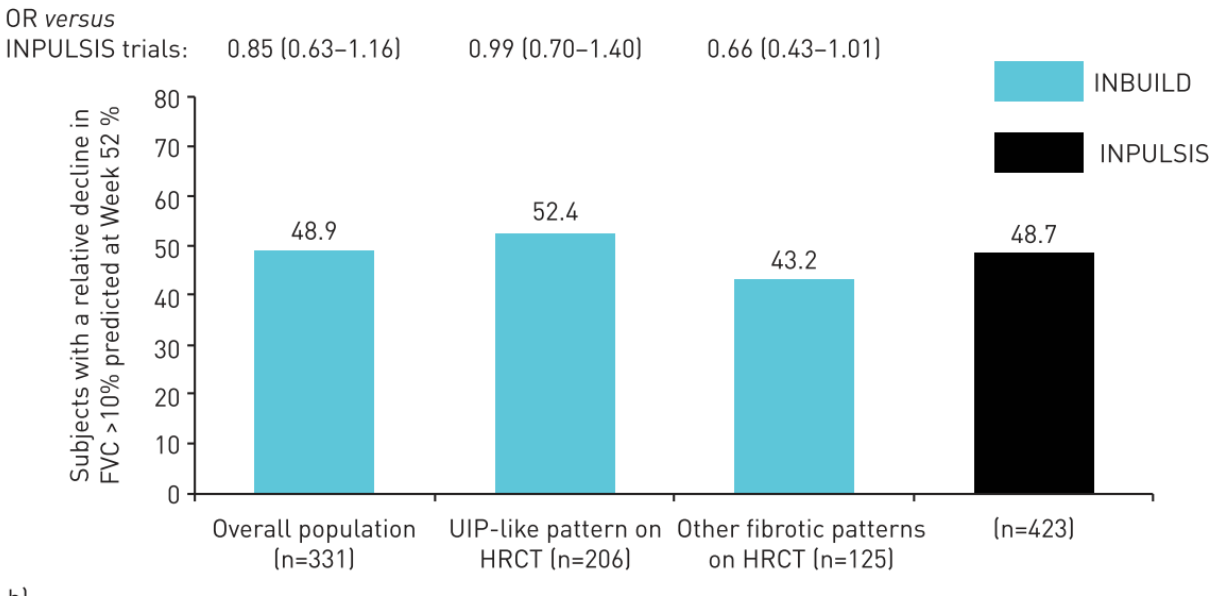



| Number of subjects | | | | | | | |
|---|---|---|---|---|---|---|---|
| INPULSIS | 417 | 408 | 407 | 403 | 395 | 383 | 345 |
| INBUILD (overall population) | 325 | 326 | 325 | 320 | 311 | 296 | 274 |
| INBUILD (UIP-like fibrotic pattern) | 202 | 202 | 201 | 197 | 190 | 176 | 162 |
| INBUILD (other fibrotic patterns) | 123 | 124 | 124 | 123 | 121 | 120 | 112 |

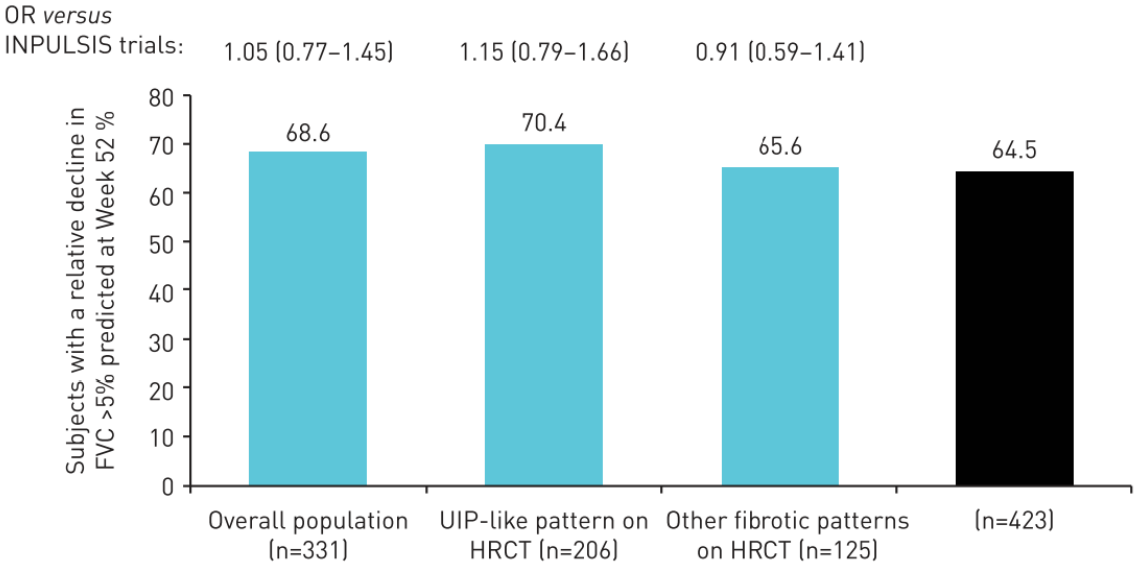
Brown KK *et al*. *Eur Respir J*. 2020; 55(5)

# Study Design

FVC ≥ 10% at 52 weeks




FVC ≥ 5% at 52 weeks



## Natural History of PF-ILD

# Results

TABLE 2 Proportion of subjects who died over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

| | INBUILD trial | | | INPULSIS trials (n=423) |
|---|---|---|---|---|
| | Overall population (n=331) | UIP-like fibrotic pattern on HRCT (n=206) | Other fibrotic patterns on HRCT (n=125) | |
| **Deaths over 52 weeks** | 17 (5.1) | 16 (7.8) | 1 (0.8) | 33 (7.8) |
| Hazard ratio *versus* INPULSIS trials[#] | 0.63 (0.35–1.13) | 0.97 (0.53–1.76) | 0.10 (0.01–0.70) | |
| Nominal p-value[¶] | 0.12 | 0.92 | 0.004 | |

Brown KK *et al*. *Eur Respir J*. 2020; 55(5)

# Conclusions

**Conclusions**

- Non-IPF PF-ILD patients demonstrate similar clinical course compared to IPF
- Non-IPF PF-ILD patients suffer from high risk of disease progression and mortality

# CONTENTS

# Interstitial lung abnormalities (ILA)
## A Position Paper from the Fleischner Society

Position Paper

## Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

*Hiroto Hatabu*, Gary M Hunninghake, Luca Richeldi, Kevin K Brown, Athol U Wells, Martine Remy-Jardin, Johny Verschakelen, Andrew G Nicholson, Mary B Beasley, David C Christiani, Raúl San José Estépar, Joon Beom Seo, Takeshi Johkoh, Nicola Sverzellati, Christopher J Ryerson, R Graham Barr, Jin Mo Goo, John H M Austin, Charles A Powell, Kyung Soo Lee, Yoshikazu Inoue, David A Lynch†*

# Definition of ILA

**What are interstitial lung abnormalities (ILAs)?**

- Incidental identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts
- Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)
- In individuals in whom interstitial lung disease is not suspected

**What are not ILAs?**

*Imaging findings restricted to:*

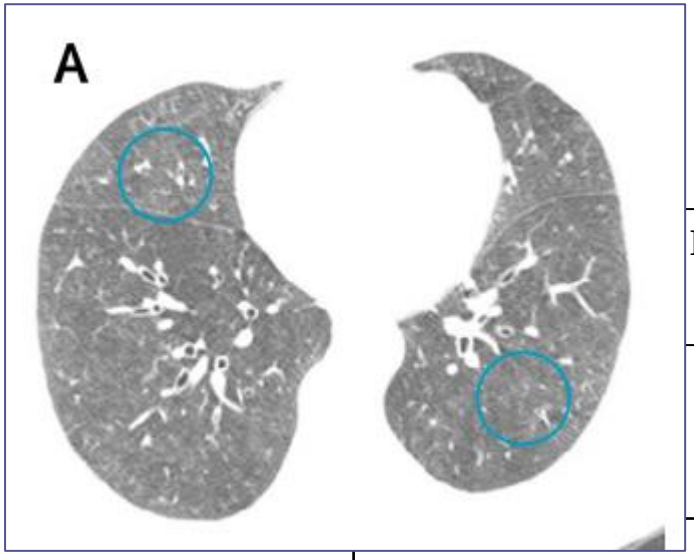
- Dependent lung atelectasis
- Focal paraspinal fibrosis in close contact with thoracic spine osteophytes (figure 2A)
- Smoking-related centrilobular nodularity in the absence of other findings (figure 2B)
- Mild focal or unilateral abnormality (figure 2C)
- Interstitial oedema (eg, in heart failure)
- Findings of aspiration (patchy ground-glass, tree in bud; figure 2C)

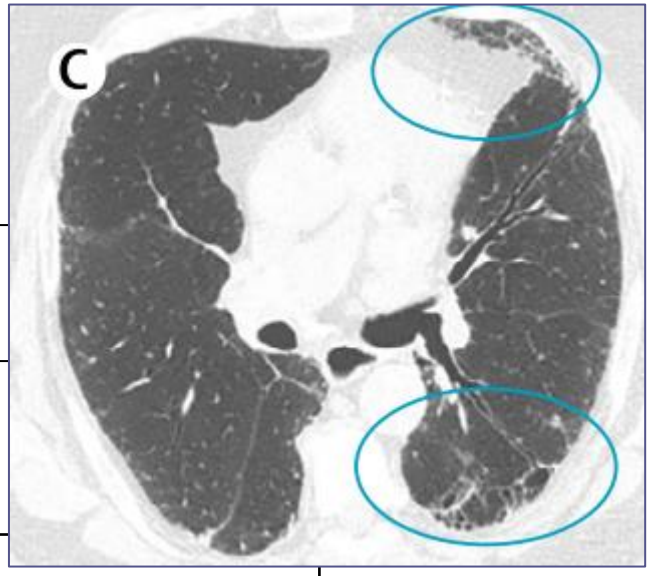
*Preclinical and clinical identification:*

- Preclinical interstitial abnormalities identified during screening of high-risk individuals (eg, those with rheumatoid arthritis, scleroderma, occupational exposure, familial interstitial lung disease)
- Findings in patients with known clinical interstitial lung disease

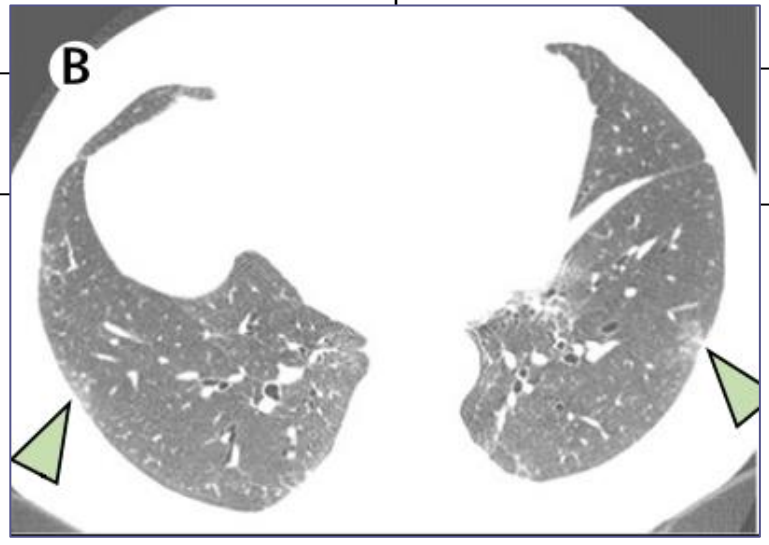
Hatabu H *et al*. *Lancet Respir Med*. 2020; 8(7)

# Classification of ILA




**Interstitial Lung Abnormality (ILA)**

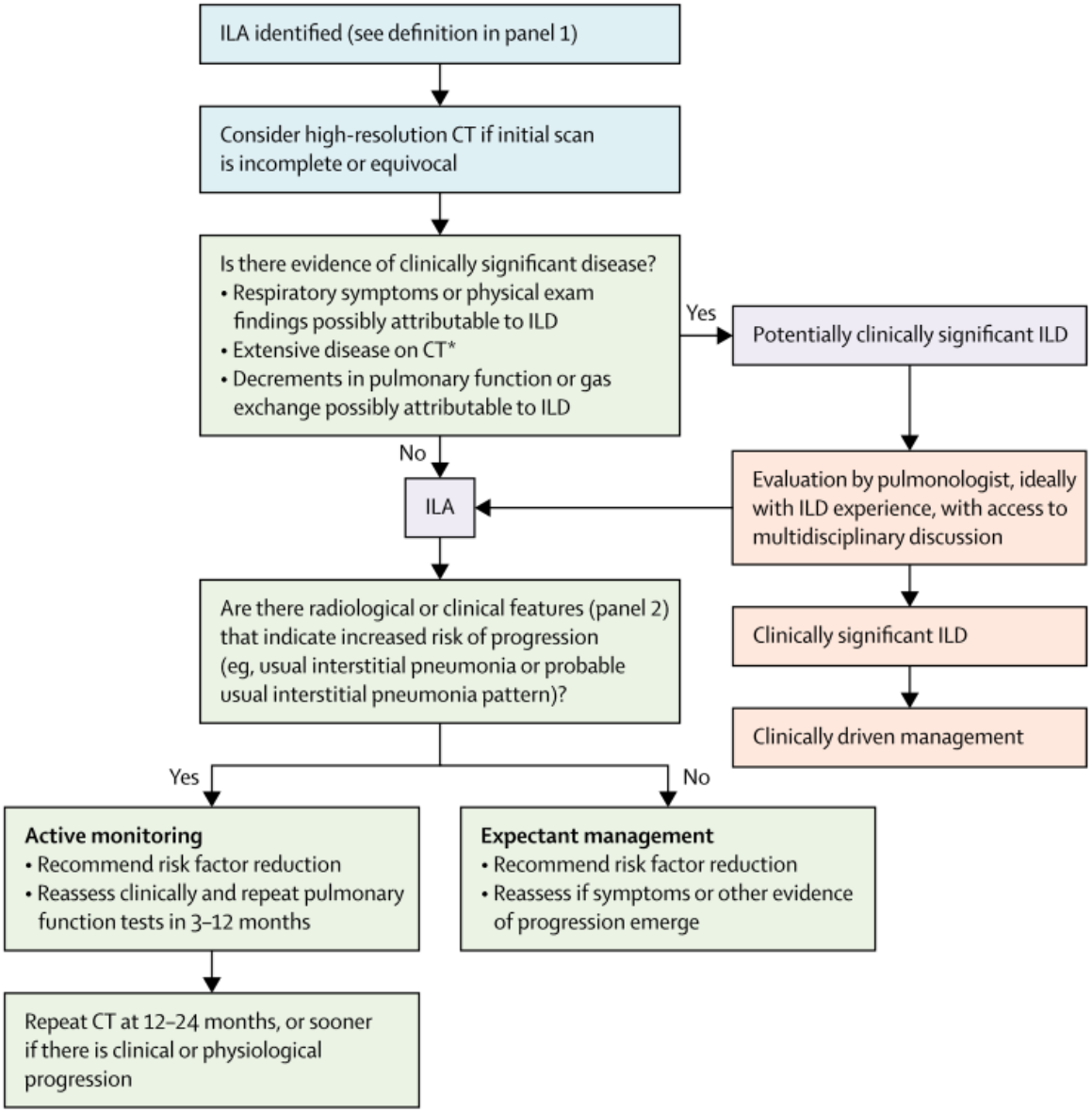



**Nonsubpleural**

**Subpleural fibrotic**

Hatabu H *et al*. *Lancet Respir Med*. 2020; 8(7)

# Proposed schema for management of ILA



# ILA with cancer diagnoses and mortality


ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

## The associations of interstitial lung abnormalities with cancer diagnoses and mortality

Gisli T. Axelsson[1], Rachel K. Putman[2], Thor Aspelund[1,3], Elias F. Gudmundsson[3], Tomayuki Hida[4,5], Tetsuro Araki[4,5], Mizuki Nishino[4,5], Hiroto Hatabu[4,5], Vilmundur Gudnason[1,3], Gary M. Hunninghake[2,5] and Gunnar Gudmundsson[1,6]

ILA with cancer diagnosis and mortality

# Study Design and Aim

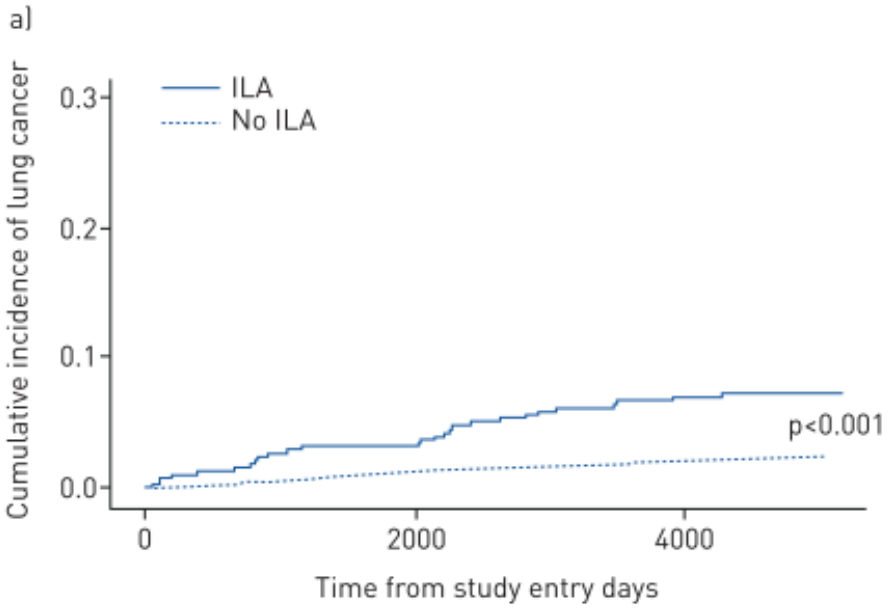
- AGES-Reykjavik cohort
  - ✓ Longitudinal birth cohort of Reykjavik, Iceland (5764 participants)
- The aim of the study
  - ✓ Association of ILA with lung cancer and other cancers
  - ✓ Association ILA with mortality of lung cancer and other cancers

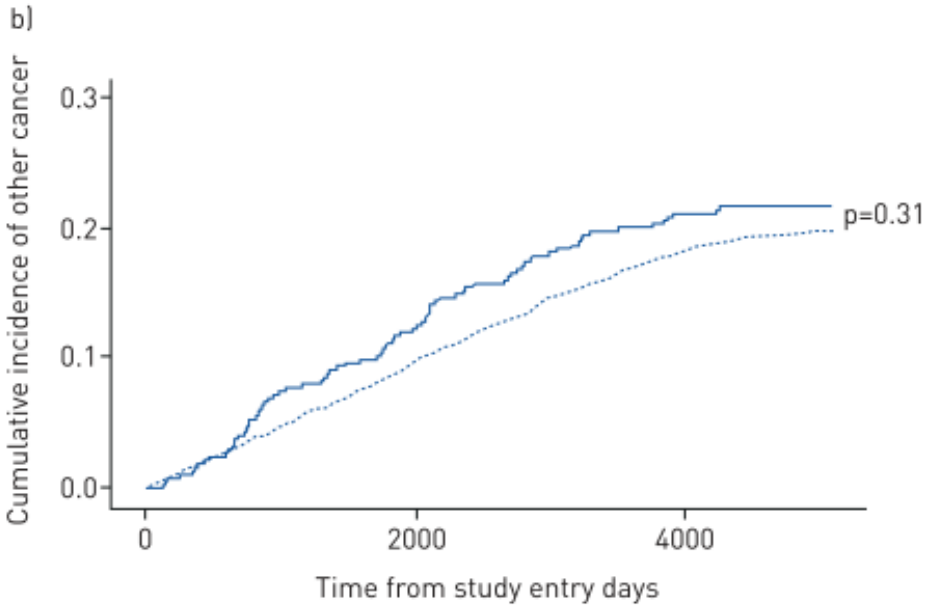
| | 60.4% No ILA | 32.5% Indeterminate for ILA | 7.1% ILA |
|---|---|---|---|
| **Participants n** | 3183 | 1712 | 375 |
| **Age years** | 76.0±5.4 | 77.4±5.7 | 77.8±5.6 |
| **Women** | 1887 (59) | 953 (56) | 170 (45) |
| **BMI kg·m$^{-2}$** | 27.2±4.4 | 26.8±4.4 | 27.0±4.6 |
| **History of smoking** | 1732 (54) | 1013 (59) | 269 (72) |
| **Median pack-years (IQR)** | 0 (0–16) | 2.5 (0–23) | 11 (0–28) |
| **Current smoker** | 368 (12) | 203 (12) | 68 (18) |
| **Days of follow-up to all-cause mortality** | 3675±1228 | 3396±1347 | 2981±1433 |
| **Imaging patterns** | | | |
| Without fibrosis | | | 246 (66) |
| Definite fibrosis | | | 129 (34) |
| **Participants diagnosed with cancer before beginning of study** | | | |
| Overall | 194 (6.1) | 132 (7.7) | 32 (8.5) |
| **Participants diagnosed with cancer after beginning of study** | | | |
| Overall | 668 (21) | 383 (22) | 97 (26) |
| Lung cancer (C34) | 77 (2.4) | 58 (3.4) | 27 (7.2) |
| Gastrointestinal cancer (C15–C26) | 176 (5.5) | 86 (5.0) | 20 (5.3) |
| Skin cancers (C43–C44) | 45 (1.4) | 30 (1.8) | 4 (1.1) |
| Cancers of breasts and female genitalia (C50–C58) | 108 (3.4) | 44 (2.6) | 8 (2.1) |
| Cancers of male genitalia (C60–C63) | 124 (3.9) | 71 (4.1) | 20 (5.3) |
| Urinary tract cancers (C64–C68) | 81 (2.5) | 49 (2.9) | 11 (2.9) |
| Haematologic malignancies (C81–C96) | 57 (1.8) | 34 (2.0) | 9 (2.4) |
| **Mortality due to cancer during study follow-up** | | | |
| Cancer overall | 388 (12) | 232 (14) | 63 (17) |
| Lung cancer (C34) | 65 (2.0) | 61 (3.6) | 25 (6.7) |

Axelsson GT *et al*. *Eur Respir J*. 2020; 56(6)

## ILA with cancer diagnosis and mortality

# Results

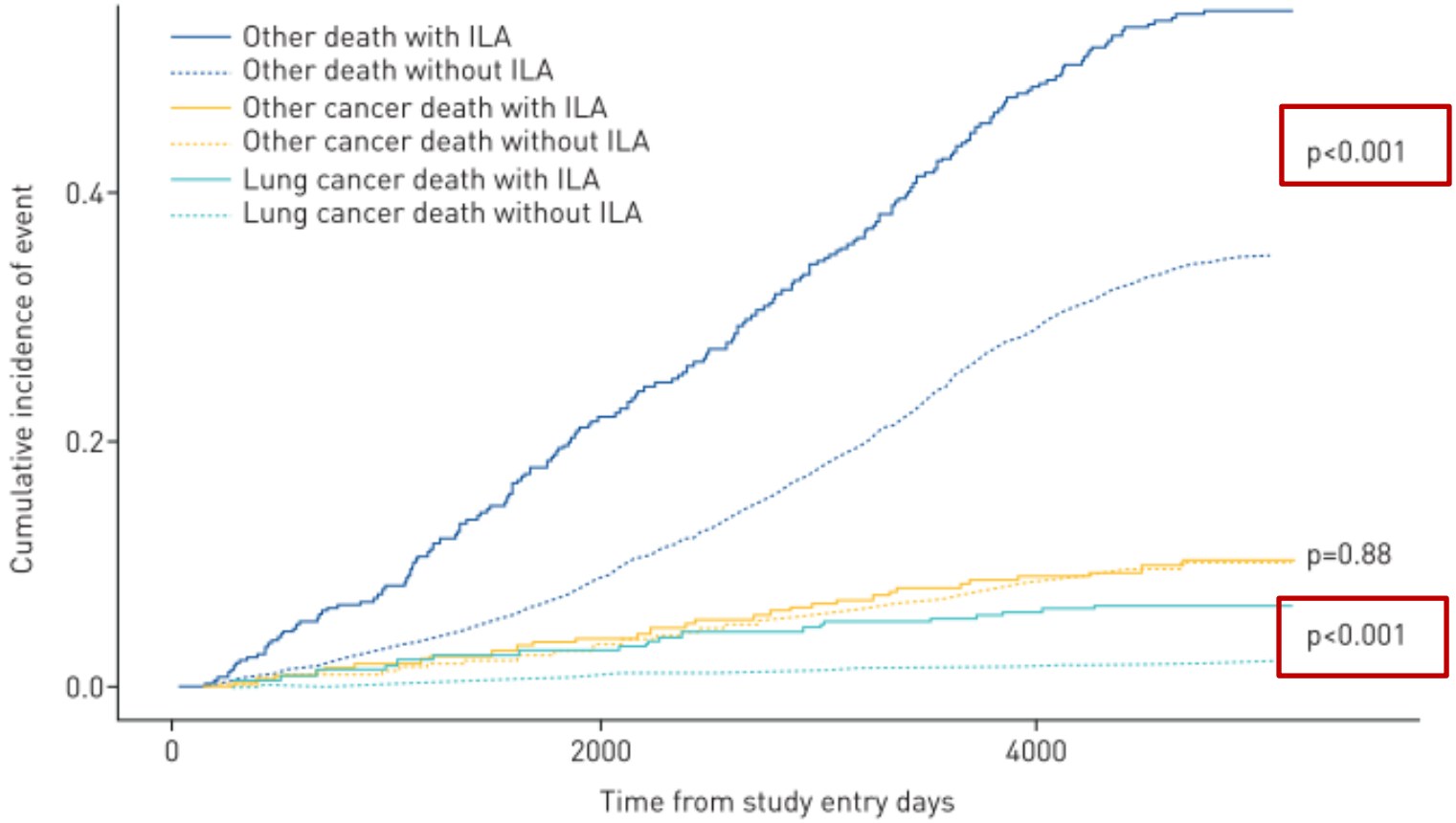



Axelsson GT *et al*. *Eur Respir J*. 2020; 56(6)

## ILA with cancer diagnosis and mortality

# Results




Axelsson GT *et al*. *Eur Respir J*. 2020; 56(6)

## ILA with cancer diagnosis and mortality

# Results

TABLE 2 Associations of interstitial lung abnormalities (ILA) with cancer diagnoses

| Model | HR (95% CI) | p-value |
|---|---|---|
| **Lung cancer diagnoses** | | |
| Unadjusted | 3.76 (2.42–5.84) | $3.59\times10^{-9}$ |
| Adjusted | 2.77 (1.76–4.36) | $1.08\times10^{-5}$ |
| **Cancer diagnoses of all causes** | | |
| Unadjusted | 1.57 (1.27–1.95) | $3.07\times10^{-5}$ |
| Adjusted | 1.35 (1.09–1.68) | 0.006 |
| **Cancer diagnoses of all causes excluding lung cancer** | | |
| Unadjusted | 1.39 (1.11–1.76) | 0.005 |
| Adjusted | 1.24 (0.98–1.57) | 0.07 |

TABLE 4 Associations of interstitial lung abnormalities (ILA) with mortality from cancer

| Model | HR (95% CI) | p-value |
|---|---|---|
| **Mortality from lung cancer** | | |
| Unadjusted | 4.19 (2.64–6.66) | $1.27\times10^{-9}$ |
| Adjusted | 2.89 (1.80–4.66) | $1.26\times10^{-5}$ |
| **Mortality from all cancers** | | |
| Unadjusted | 1.81 (1.39–2.37) | $1.23\times10^{-5}$ |
| Adjusted | 1.47 (1.12–1.94) | 0.005 |
| **Mortality from all cancers excluding lung cancer** | | |
| Unadjusted | 1.32 (0.94–1.85) | 0.10 |
| Adjusted | 1.15 (0.82–1.61) | 0.43 |

Axelsson GT *et al*. *Eur Respir J*. 2020; 56(6)

# Conclusions

**Conclusions**

- ILA is associated with increased risk of lung cancer and mortality
- ILA is not associated with risk and mortality of cancers excluding lung cancer

# CONTENTS

# Diagnosis of HP in Adults
## An Official ATS/JRS/ALAT Clinical Practice Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

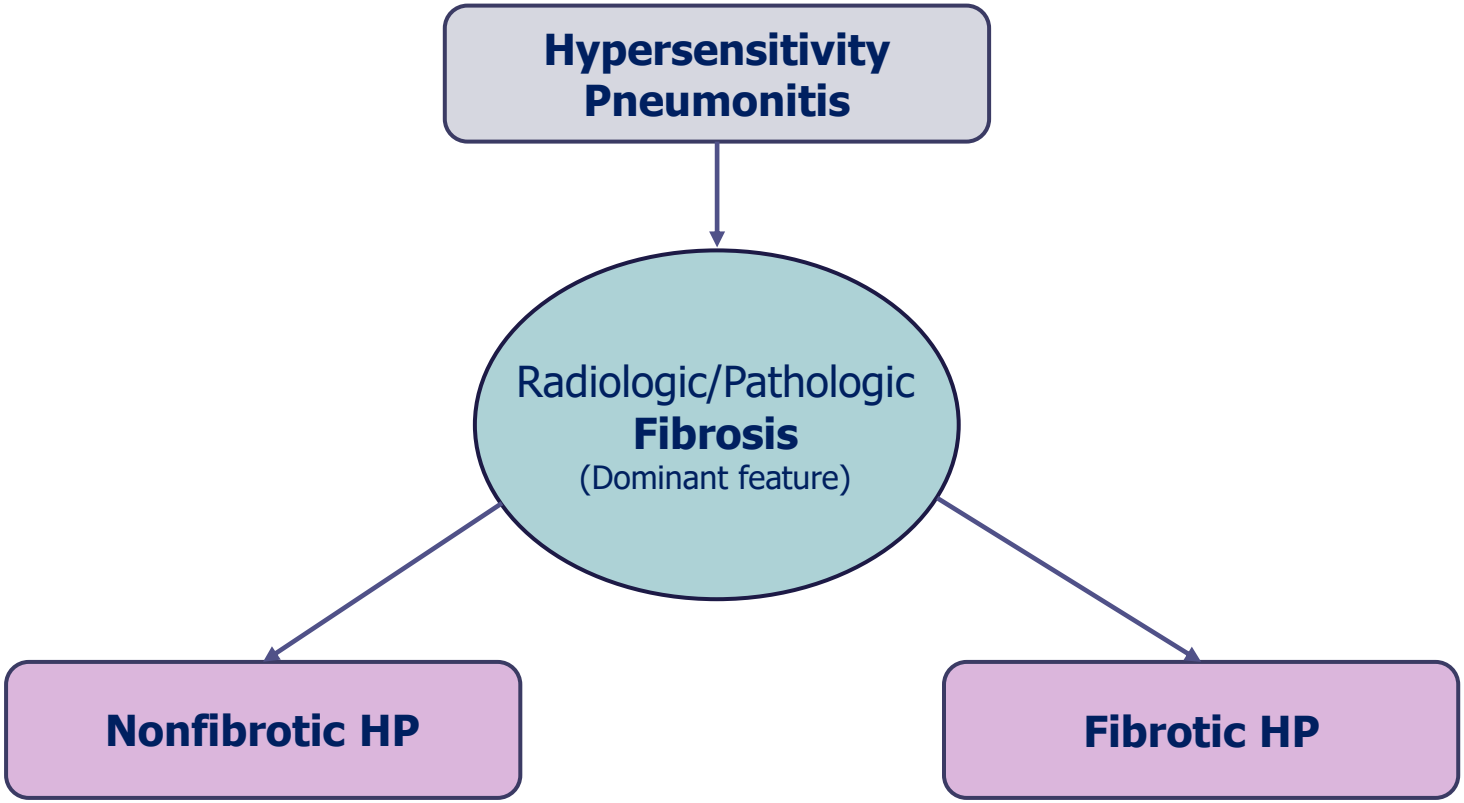
### Diagnosis of Hypersensitivity Pneumonitis in Adults
An Official ATS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson, Jeffrey L. Myers, Michael Kreuter, Martina Vasakova, Elena Bargagli, Jonathan H. Chung, Bridget F. Collins, Elisabeth Bendstrup, Hassan A. Chami, Abigail T. Chua, Tamera J. Corte, Jean-Charles Dalphin†, Sonye K. Danoff, Javier Diaz-Mendoza, Abhijit Duggal, Ryoko Egashira, Thomas Ewing, Mridu Gulati, Yoshikazu Inoue, Alex R. Jenkins, Kerri A. Johannson, Takeshi Johkoh, Maximiliano Tamae-Kakazu, Masanori Kitaichi, Shandra L. Knight, Dirk Koschel, David J. Lederer, Yolanda Mageto, Lisa A. Maier, Carlos Matiz, Ferran Morell, Andrew G. Nicholson, Setu Patolia, Carlos A. Pereira, Elisabetta A. Renzoni, Margaret L. Salisbury, Moises Selman, Simon L. F. Walsh, Wim A. Wuyts, and Kevin C. Wilson; on behalf of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

*This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin† (June 2, 1956–October 17, 2019)*

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX MAY 2020

# New Classification of HP

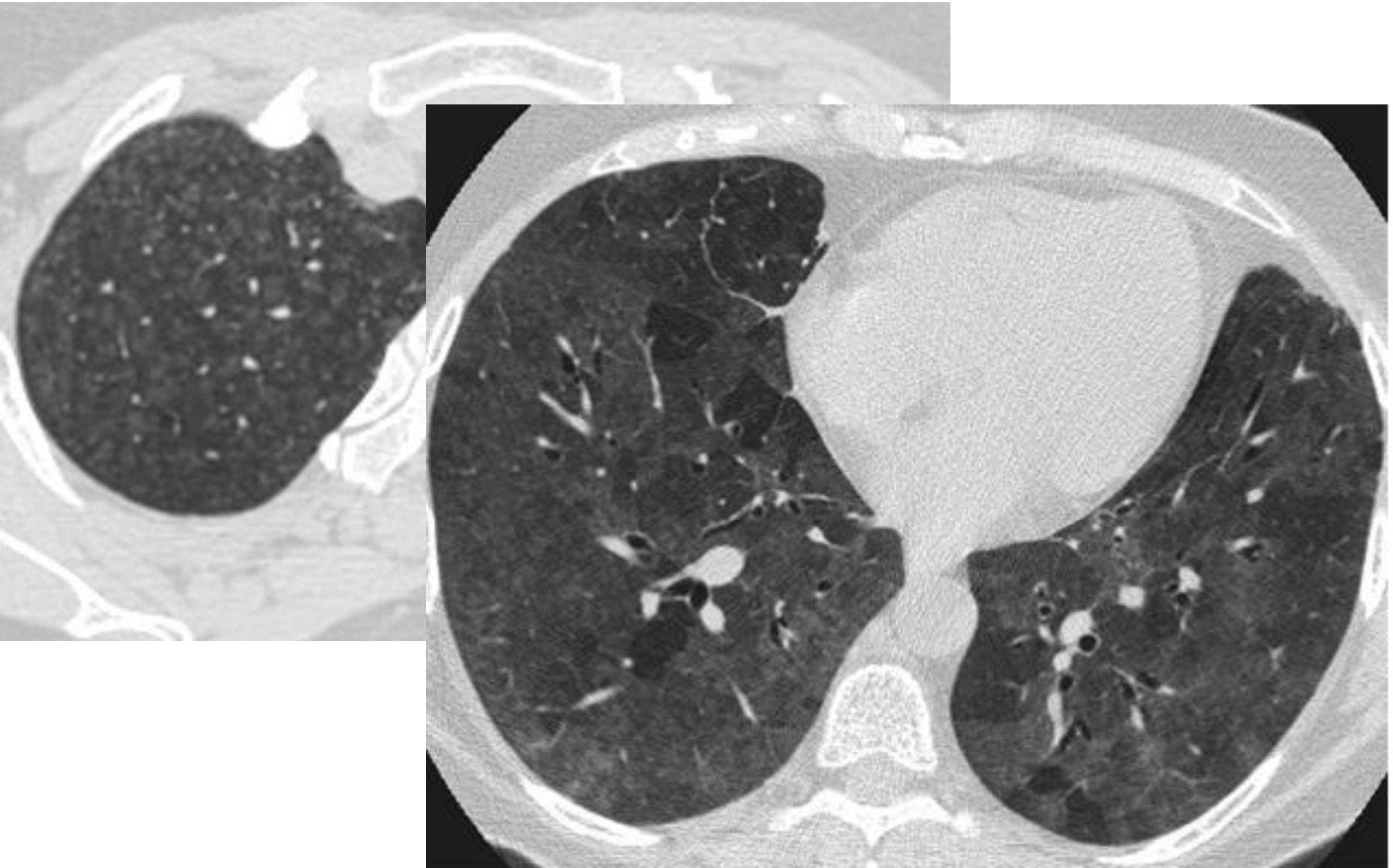



Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

# HRCT Pattern of HP

| Nonfibrotic | | |
|---|---|---|
| **Typical HP** | **Compatible with HP** | **Indeterminate** |
| **- Parenchymal**<br>1) GGO<br>2) Mosaic attenuation<br>**- Small airway**<br>1) Ill-defined, centrilobular nodules<br>2) Air trapping<br>**- Distribution**<br>1) Diffuse | **- Parenchymal**<br>1) Uniform and subtle GGOs<br>2) Airspace consolidation<br>3) Lung cysts<br><br>**- Distribution**<br>1) Diffuse | N/A |
| **Fibrotic** | | |
| **Typical HP** | **Compatible with HP** | **Indeterminate** |
| **- Lung fibrosis**<br>1) Irregular linear opacities/coarse reticulation with lung distortion<br>2) Traction BE/HC (No predominate)<br>**- Distribution (Lung fibrosis)**<br>1) Random both axially or craniocaudally<br>2) Mid lung zone-predominant or relatively spared in the lower lung zone<br>**- Small airway**<br>1) Ill-defined, centrilobular nodules, GGO<br>2) Mosaic attenuation, three-density pattern, and/or air trapping | **- Variant lung fibrosis**<br>1) UIP pattern<br>2) Extensive GGOs c subtle fibrosis<br>**- Distribution (Variant)**<br>1) Axial: Peribronchovascular, subpleural<br>2) Craniocaudal: Upper lung zones<br>**- Small airway**<br>1) Ill-defined, centrilobular nodules and/or GGOs<br>2) Three-density pattern, air trapping | 1) UIP pattern<br>2) Probable UIP<br>3) Indeterminate UIP pattern<br>4) Fibrotic NSIP pattern<br>5) Organizing pneumonia-like pattern<br>6) Truly indeterminate HRCT pattern |

# HRCT Pattern of HP



# Histopathologic Criteria (Nonfibrotic HP)

| HP | Probable HP | Indeterminate for HP |
|---|---|---|
| **Nonfibrotic HP (cellular HP)**<br>Typical histopathological features of nonfibrotic HP; at least one biopsy site showing all three of the following features:<br>1. Cellular interstitial pneumonia<br>• Bronchiolocentric (airway-centered)<br>• Cellular NSIP-like pattern<br>• Lymphocyte-predominant<br>2. Cellular bronchiolitis<br>• Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers<br>• ±Organizing pneumonia pattern with Masson bodies<br>• ±Foamy macrophages in terminal air spaces<br>3. Poorly formed nonnecrotizing granulomas†<br>• Loose clusters of epithelioid cells and/or multinucleated giant cells ± intracytoplasmic inclusions<br>• Situated in peribronchiolar interstitium, terminal air spaces, and/or organizing pneumonia (Masson bodies)<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates | Both of the following features (*1* and *2* from first column) in at least one biopsy site:<br>1. Cellular interstitial pneumonia<br>• Bronchiolocentric (airway-centered)<br>• Cellular NSIP-like pattern<br>• Lymphocyte-predominant<br>2. Cellular bronchiolitis<br>• Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers<br>• ±Organizing pneumonia pattern with Masson bodies<br>• ±Foamy macrophages in terminal air spaces<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates | At least one biopsy site showing one of the following:<br>• *1* or *2* from the first column<br>• Selected IIP patterns<br>○ Cellular NSIP pattern<br>○ Organizing pneumonia pattern<br>○ Peribronchiolar metaplasia *without* other features to suggest fibrotic HP<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates |

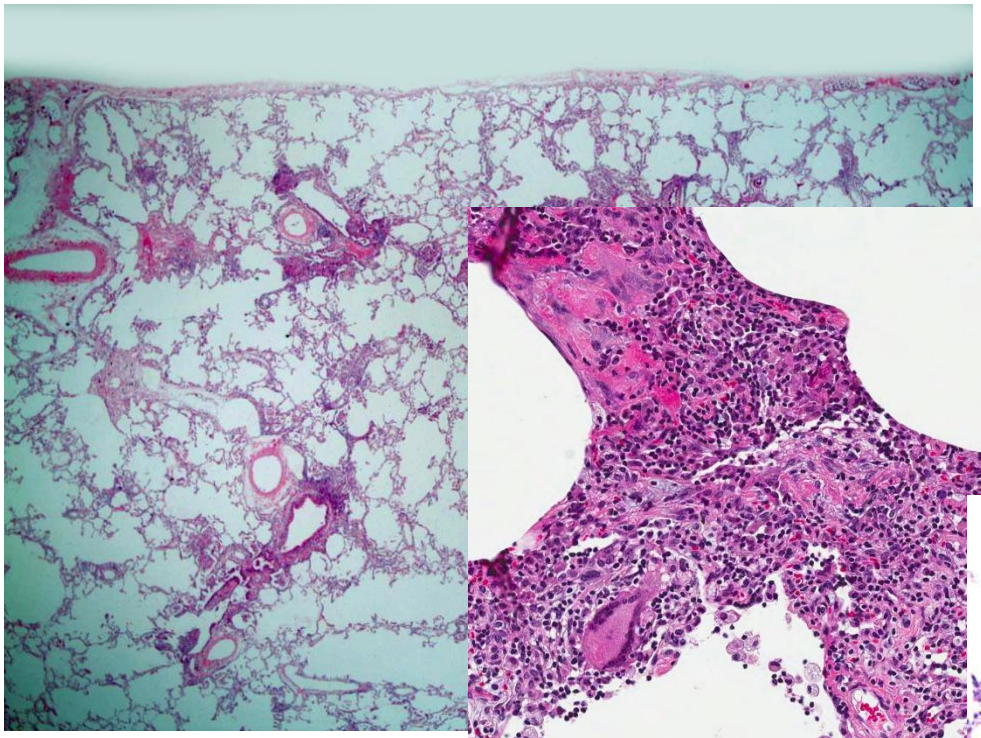
Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

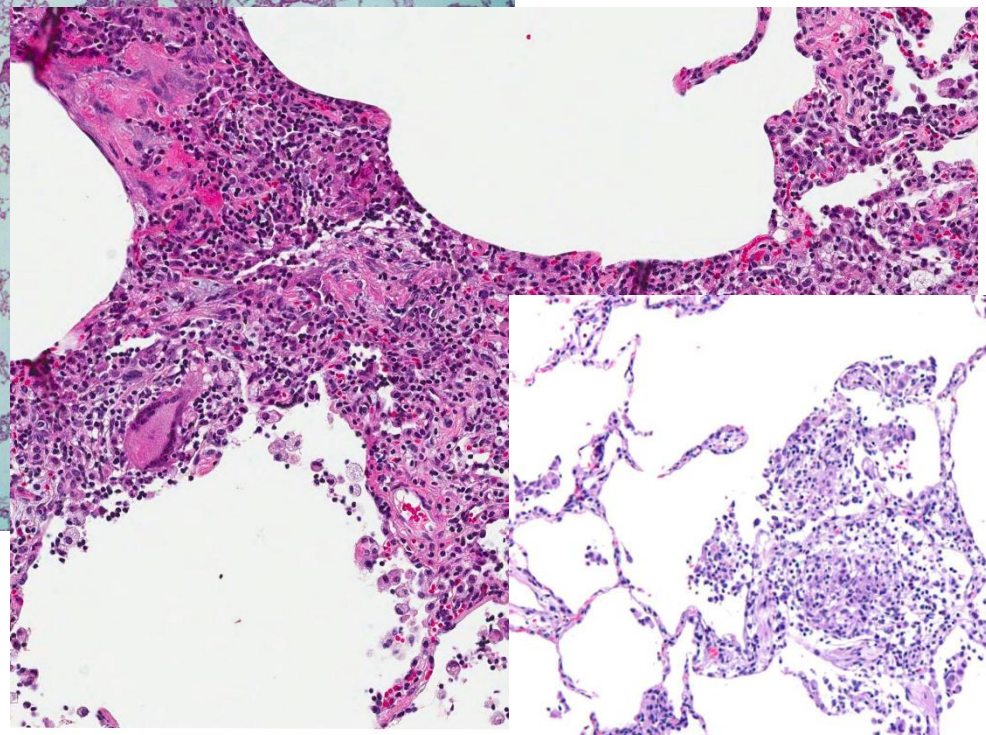
# Histopathologic Criteria (Fibrotic HP)

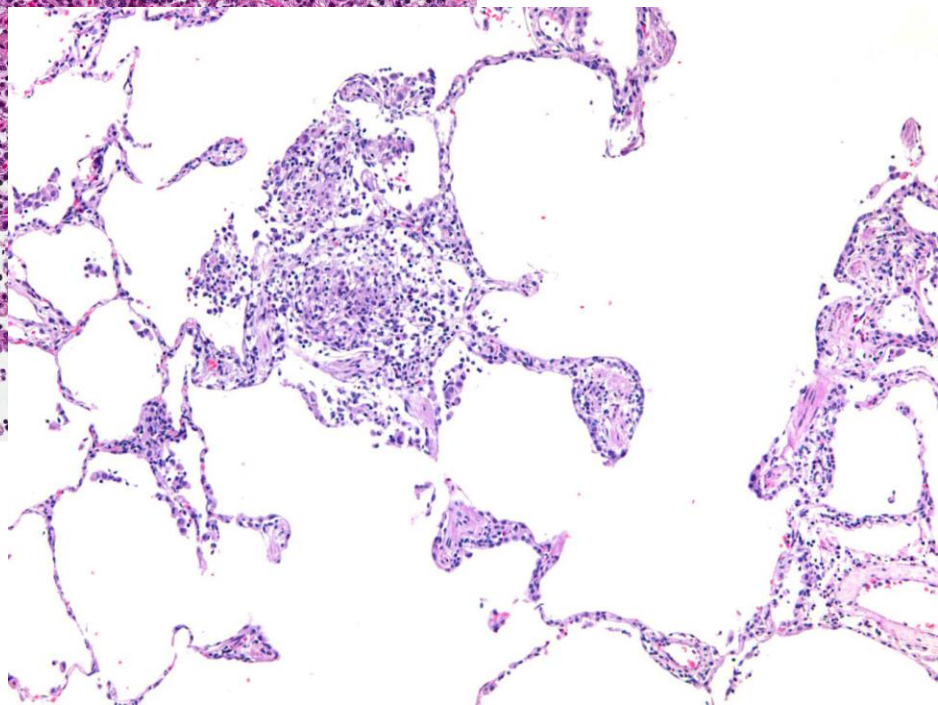
| HP | Probable HP | Indeterminate for HP |
|---|---|---|
| **Fibrotic HP**[‡]<br>Typical histopathological features of fibrotic HP; *1* or *2 and 3* in at least one biopsy site:<br>1. Chronic fibrosing interstitial pneumonia<br>• Architectural distortion, fibroblast foci ± subpleural honeycombing<br>• Fibrotic NSIP-like[§] pattern<br>2. Airway-centered fibrosis<br>• ±Peribronchiolar metaplasia<br>• ±Bridging fibrosis[‖]<br>3. Poorly formed nonnecrotizing granulomas[†]<br>±Cellular interstitial pneumonia<br>±Cellular bronchiolitis<br>±Organizing pneumonia pattern<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates | Both of the following features (*1* or *2* from first column) in at least one biopsy site:<br>1. Chronic fibrosing interstitial pneumonia<br>• Architectural distortion, fibroblast foci ± subpleural honeycombing<br>• Fibrotic NSIP-like pattern<br>2. Airway-centered fibrosis<br>• ±Peribronchiolar metaplasia<br>• ±Bridging fibrosis[‖]<br>±Cellular interstitial pneumonia<br>±Organizing pneumonia pattern<br>±Cellular bronchiolitis<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates | Either one of the following features in at least one biopsy site:<br>1. Chronic fibrosing interstitial pneumonia<br>• Architectural distortion, fibroblast foci ± honeycombing<br>• Fibrotic NSIP-like pattern<br>±Cellular interstitial pneumonia<br>±Cellular bronchiolitis<br>±Organizing pneumonia pattern<br>*and*<br>Absence of features in any biopsy site to suggest an alternative diagnosis<br>• Plasma cells > lymphs<br>• Extensive lymphoid hyperplasia<br>• Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas<br>• Aspirated particulates |

Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

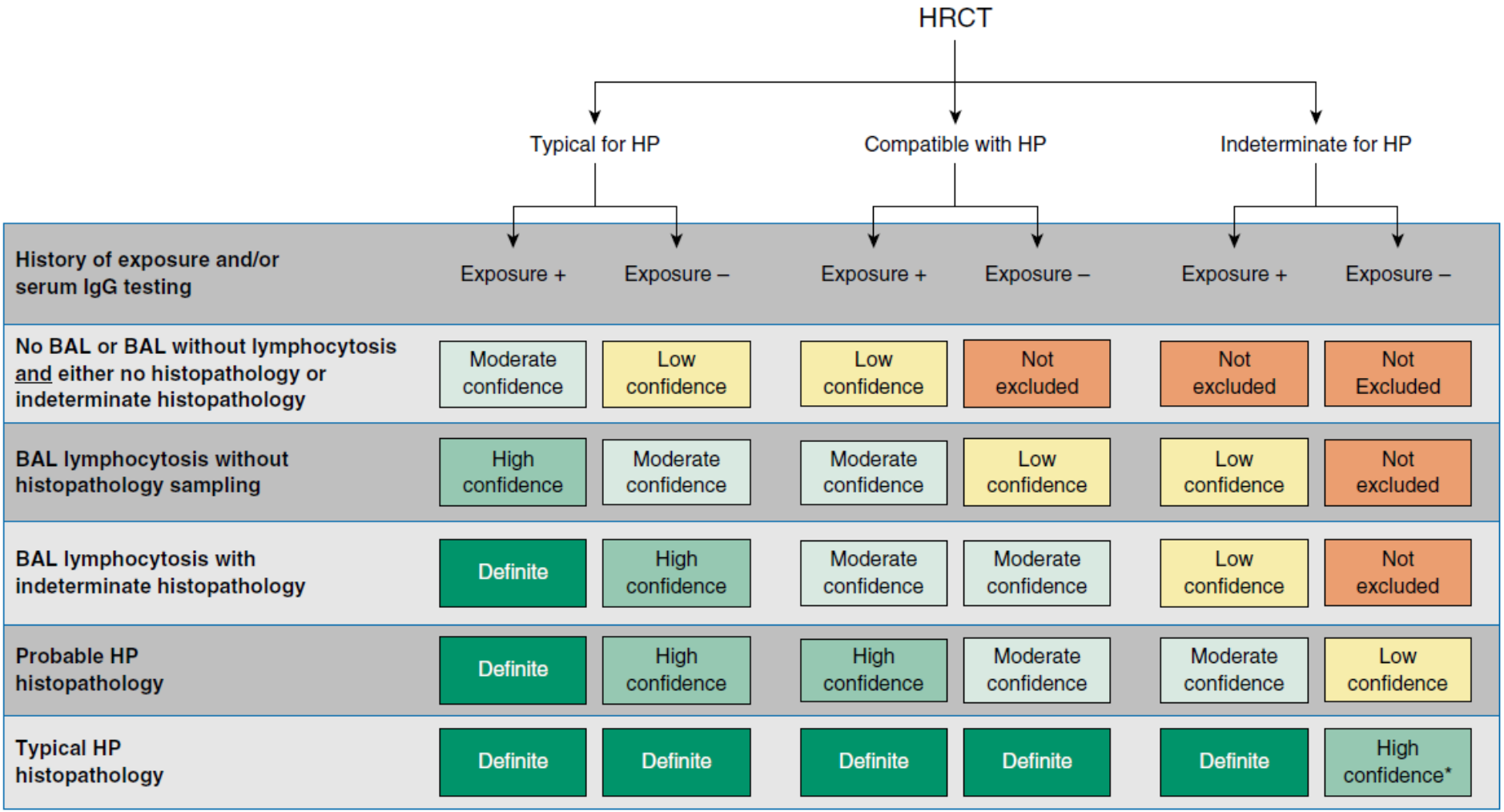
# Histopathologic Criteria (Nonfibrotic HP)







# Diagnosis of HP (Combination of Evaluation)

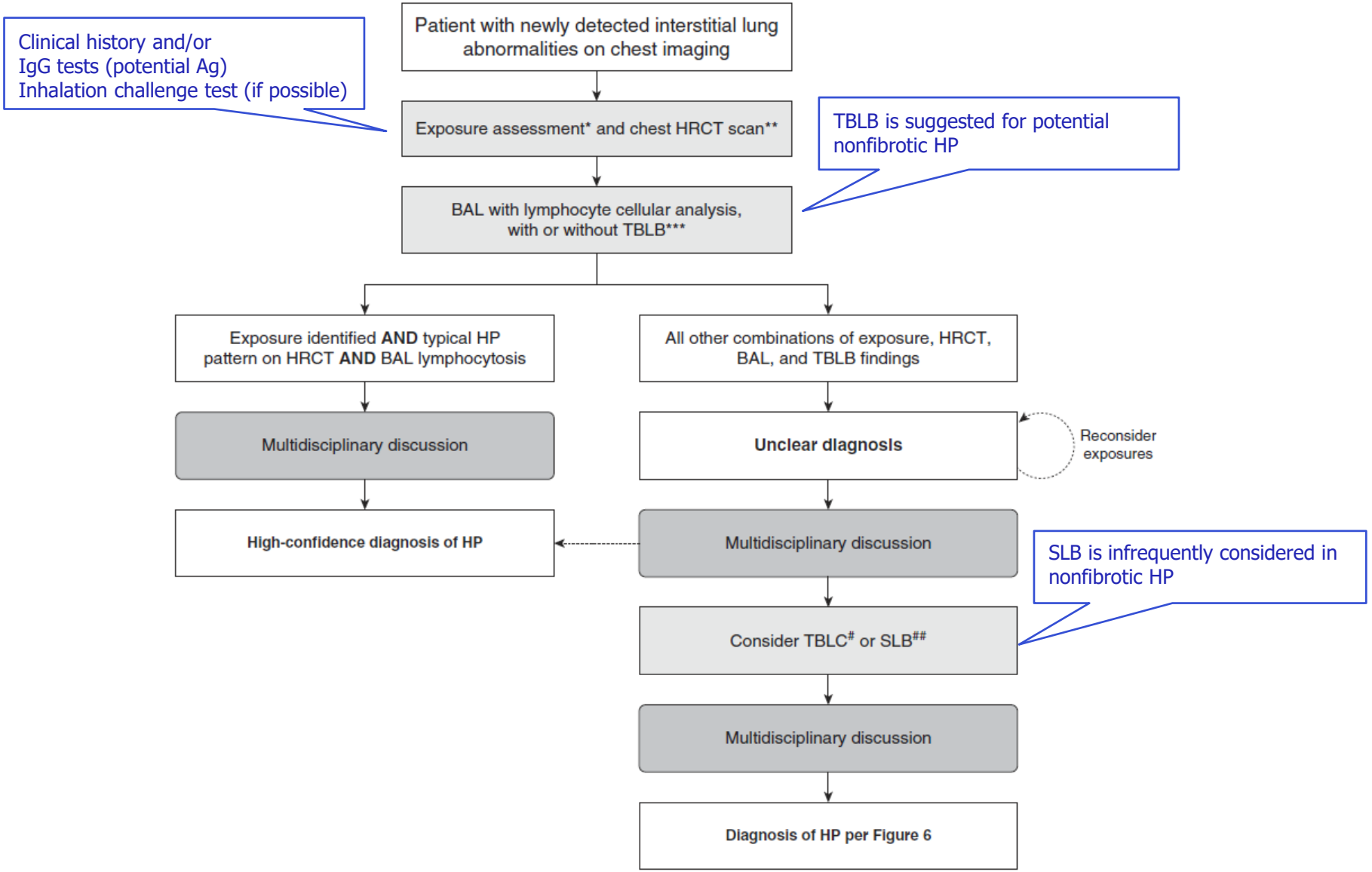



| History of exposure and/or serum IgG testing | Typical for HP: Exposure + | Typical for HP: Exposure – | Compatible with HP: Exposure + | Compatible with HP: Exposure – | Indeterminate for HP: Exposure + | Indeterminate for HP: Exposure – |
|---|---|---|---|---|---|---|
| No BAL or BAL without lymphocytosis and either no histopathology or indeterminate histopathology | Moderate confidence | Low confidence | Low confidence | Not excluded | Not excluded | Not Excluded |
| BAL lymphocytosis without histopathology sampling | High confidence | Moderate confidence | Moderate confidence | Low confidence | Low confidence | Not excluded |
| BAL lymphocytosis with indeterminate histopathology | Definite | High confidence | Moderate confidence | Moderate confidence | Low confidence | Not excluded |
| Probable HP histopathology | Definite | High confidence | High confidence | Moderate confidence | Moderate confidence | Low confidence |
| Typical HP histopathology | Definite | Definite | Definite | Definite | Definite | High confidence* |

All confidence levels are subject to multidisciplinary discussion. *Confidence may increase to "definite" if the pathologist's conclusion persists after reevaluation in the context of additional clinical information or an expert second opinion on histopathology.

Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

# Diagnosis of HP (MDD)




Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

# Summary of Recommendations for Tests

| | Non-fibrotic HP | Fibrotic HP |
|---|---|---|
| **Questionnaire** | No recommendations for or against (Thorough history for potential exposures and sources) | No recommendations for or against (Thorough history for potential exposures and sources) |
| **Serum IgG testing** | Suggestion (very low confidence) | Suggestion (very low confidence) |
| **BAL Lymphocyte analysis** | Recommendation (very low confidence) | Suggestion (very low confidence) |
| **TBLB** | Suggestion (very low confidence) | No recommendations for or against |
| **TBLC** | No recommendations for or against | Suggestion (very low confidence) |
| **SLB** | Suggestion, only when all other diagnostic testing has not yielded Dx (very low confidence) | Suggestion, only when all other diagnostic testing has not yielded Dx (very low confidence) |

Raghu G *et al. Am J Respir Crit Care Med.* 2020; 202(3)

# Summary (I)

**Diagnosis of ILD**

- Transbronchial cryobiosy in diagnosis of ILD

**Treatment options**

- Inhaled Treprostinil in PH due to ILD
- Tocilizumab in SSc-ILD

**Progressive fibrosing ILD (PF-ILD)**

- Chronic fibrosing ILD with progressive phenotype (IPF, HP, fibrotic NSIP, CTD-ILD etc.)
- Similar clinical course and prognosis with IPF

# Summary (II)

**Interstitial lung abnormality (ILA)**

- Definition and classification of ILA
- Increased risk of lung cancer and lung cancer mortality

**Hypersensitivity pneumonitis (HP)**

- New classification (non-fibrotic vs. fibrotic)
- MDD based on exposure and patterns of HRCT and pathology