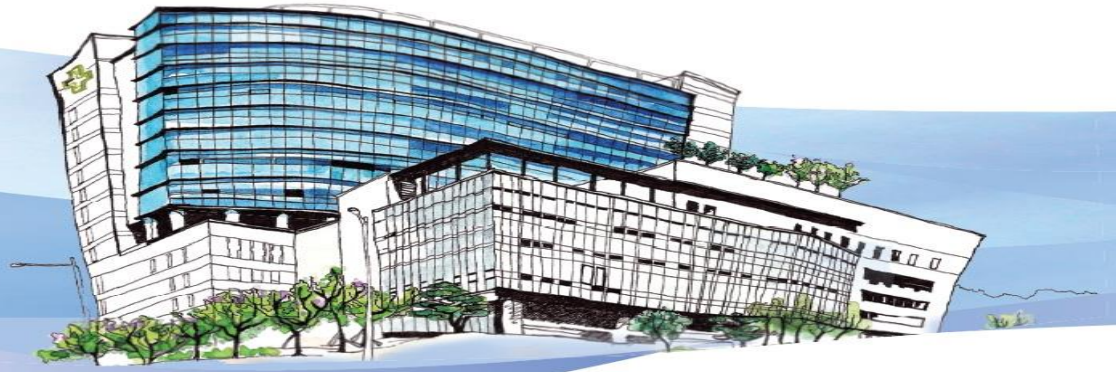


# Respiratory Review 2024

## : Interstitial Lung Diseases

해운대백병원

이재하

INJE UNIVERSITY
HAEUNDAE PAIK HOSPITAL

# Contents

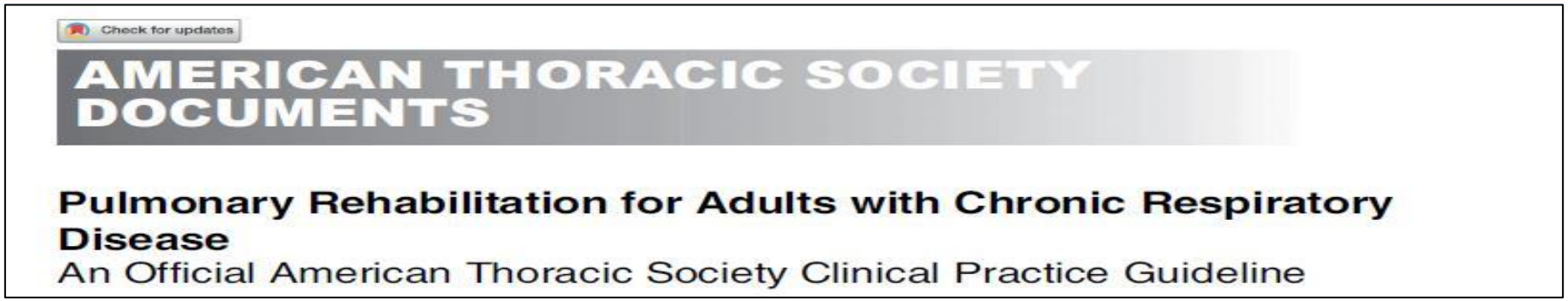
# Digital Health Care in ILD

- Home monitoring: Home spirometry / Drug safety, adherence, collection of patient-centered outcomes
- Wearable device (monitoring and therapy)
- Digital therapeutics: Cognitive therapy for fatigue in Sarcoidosis / Supporting self-management for ILDs

- Telerehabilitation in ILDs

*PLOS Digit Health* 3(1): e0000318
*Lancet Respir Med* 2023;11:265-72

# Pulmonary Rehabilitation (center or tele)




❖ For adults with interstitial lung disease, we recommend participation in pulmonary rehabilitation
(strong recommendation, moderate-quality evidence).

❖ For adults with stable chronic respiratory disease, we recommend offering the choice of center-based pulmonary rehabilitation or telerehabilitation
(strong recommendation, moderate quality evidence).



*AJRCCM* 2023; 208 (4): e7-26

# Center-based pulmonary rehabilitation in ILD

Cochrane Library

Cochrane Database of Systematic Reviews

**Pulmonary rehabilitation for interstitial lung disease (Review)**

- Exercise capacity
- Health-related quality of life
- Dyspnea
- Health care use
- Mortality
- Acute exacerbation



*Cochrane Database Syst Rev* 2021;2:CD006322

# Center-based pulmonary rehabilitation in ILD

- PR improved 6MWD after PR compared with control (MD: 40.07m)
- Improvement in 6MWD was maintained at 6-12 month follow-up (wider CI, not IPF)
- HRQoL improved after PR (Total SGRQ, MD: -9.29)
- Dyspnea (mMRC scale) improved both at the end of PR (SMD: -0.36) and at 6-12 months follow-up (SMD: - 0.29)



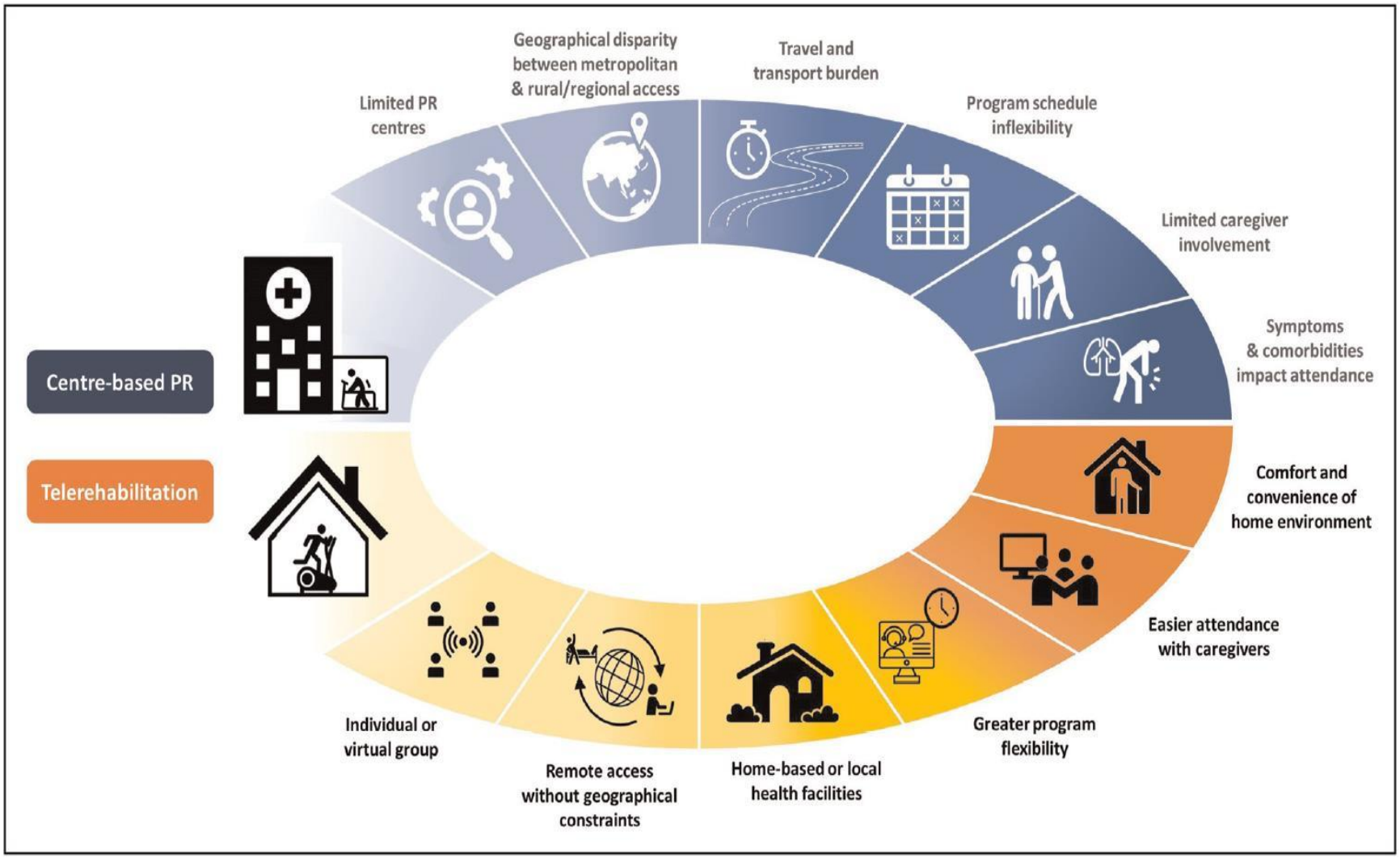
*Cochrane Database Syst Rev* 2021;2:CD006322

# Telerehabilitation

- Limitations of center-based PR programs
- Insufficient number of programs and staff
- Poor referral rates
- Patient-related barriers to attendance with transport, cost, and comorbidities problems

- Telerehabilitation may provide a PR option for patients who cannot otherwise attend a center-based program
- The technological modalities – telephone calls, a purposed-designed website, telephone support, and videoconferencing

# Telerehabilitation



# Telerehabilitation

: A post hoc analysis of digital therapeutics for PR

*Article*

## Efficacy of Digital Therapeutics for Pulmonary Rehabilitation: A Multi-Center, Randomized Controlled Trial

Chul Kim [1,†], Hee-Eun Choi [2,3,†], Chin Kook Rhee [4], Jun Hyeong Song [1] and Jae Ha Lee [5,*]

- A prospective, parallel-group, randomized controlled trial at multi-centers
- Clinical trials for approval of medical device by the Korean Ministry of Food and Drug Safety
- 84 patients (COPD, BOOP, Lung cancer, ILDs)

# Telerehabilitation
## : A post hoc analysis of digital therapeutics for PR

- A prospective, parallel-group, randomized controlled trial at multi-centers
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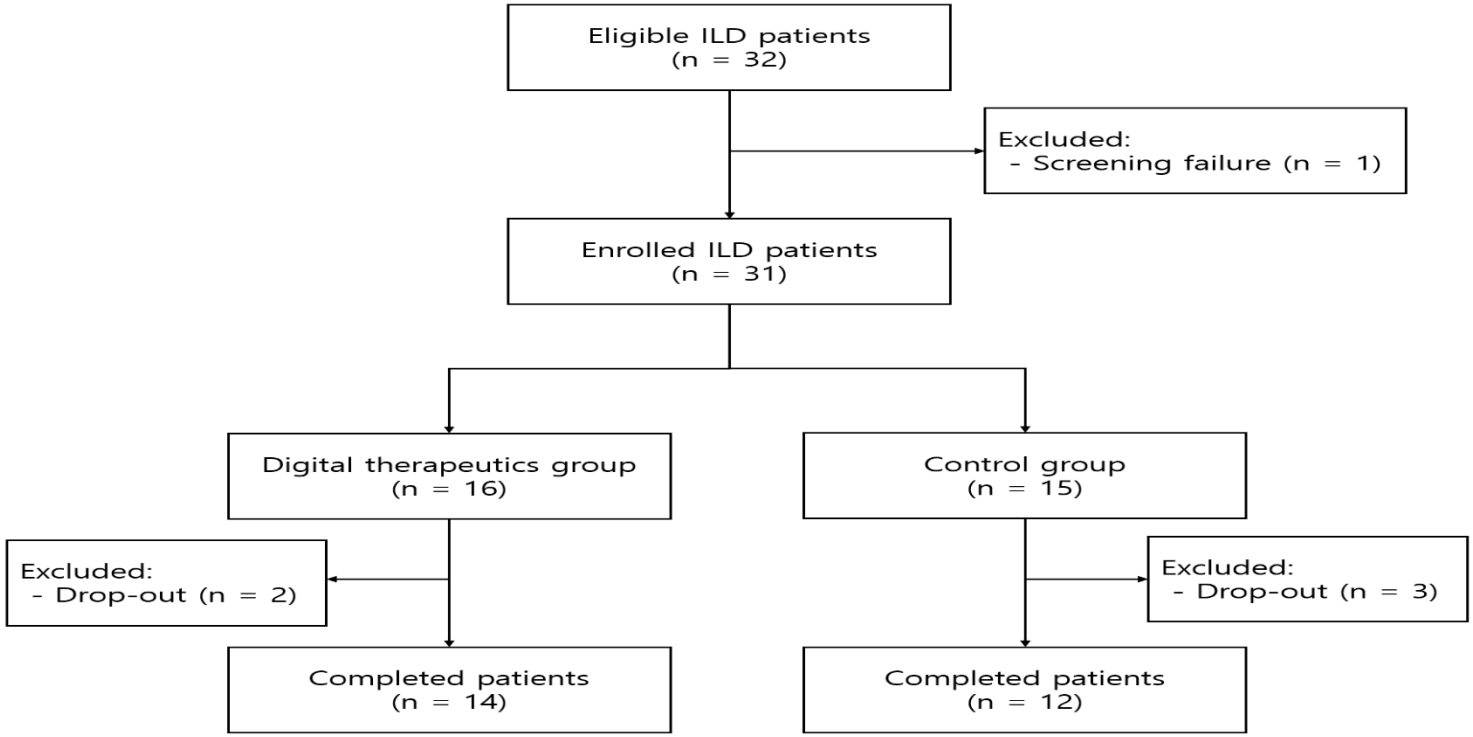

# Baseline characteristics of patients with ILD

| Variables | Total (n=26) | Digital therapeutic group (n=14) | Control group (n=12) |
|---|---|---|---|
| Age, years | 67 (62.3 - 68.8) | 65 (62.0 - 68.0) | 68 (65.8 - 70.8) |
| Male | 22 (84.6%) | 11 (78.6%) | 11 (91.7%) |
| BMI, $kg/m^2$ | 23.5 (22.0 - 27.8) | 23.1 (23.1 - 27.0) | 24.6 (20.9 - 28.3) |
| Ever smoker | 17 (65.4%) | 11 (78.6%) | 6 (50.0%) |
| IPF | 16 (61.5%) | 6 (42.9%) | 10 (83.3%) |
| PFT, FVC, % predicted | 66.5 (62.3 - 77.0) | 73.5 (62.5 - 78.8) | 65.5 (62.5 - 71.3) |
| PFT, DLco, % predicted | 61 (51.5 - 66.0) | 55.5 (50.3 - 63.8) | 65 (59.0 - 77.5) |
| 6MWT, distance, m | 514 (481 - 540) | 518 (491 - 558) | 503 (479 - 540) |
| 6MWT, Baseline $SpO_2$, % | 97 (96.0 - 99.0) | 98.5 (96.0 - 99.8) | 97 (95.5 - 98.0) |
| 6MWT, Nadir $SpO_2$, % | 89 (84.5 - 94.0) | 91 (83.3 - 94.8) | 87 (85.5 - 93.3) |

# Comparison of 6MWD over eight weeks

| 6MWD, m | Total (n=26) | Digital therapeutic group (n=14) | Control group (n=12) | *P*-value |
|---|---|---|---|---|
| Baseline | 514 (481 - 540) | 518 (491 - 558) | 503 (479 - 540) | .299 |
| After 8 weeks | 569 (512 - 609) | 608 (587 - 627) | 503 (480 - 545) | <.001 |
| Change in 8 weeks | 34 (4.5 - 78.8) | 78.5 (45.0 - 98.3) | 1.5 (-3.8 - 12.0) | <.001 |

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| Change in 8 weeks | 34 (4.5 - 78.8) | 78.5 (45.0 - 98.3) | 1.5 (-3.8 - 12.0) | <.001 |

# Changes of QOL over eight weeks

| SGRQ | Total (n=26) | Digital therapeutic group (n=14) | Control group (n=12) | *P*-value |
|---|---|---|---|---|
| Baseline | 23.3 (18.2 - 32.0) | 24.6 (19.2 – 31.3) | 21.7 ( 17.6 – 32.6) | .676 |
| After 4 weeks | 21.9 (18.2 - 31.2) | 21.5 (17.6 – 27.0) | 24.3 (20.1-34.8) | .231 |
| Change in 4 weeks | -0.1 (-4.2 - 1.9) | -3.6 (-4.9 - -0.4) | 2.0 (-0 – 4.5) | .001 |
| After 8 weeks | 22.7 (18.2 - 32.2) | 18.6 ( 13.3 – 24.0) | 28.6 (21.7 – 36.3) | .009 |
| Change in 8 weeks | -0.2 (-5.7 - 3.2) | -5.1 (-11.9 - -1.2) | 3.6 ( 1.7 – 8.3) | <.001 |

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| SGRQ | Total (n=26) | Digital therapeutic group (n=14) | Control group (n=12) | *P*-value |
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# Telerehabilitation

- 의료기 GMP 인증, 혁신의료기기 선정
- 의료품목 허가
- 보험수가 제정 절차 예정 (2024년)

- Key challenges – financial and cost barriers, validity and reliability, better quality, algorithm, and platforms control
- Specific PR program and methods for ILDs
- Research for Long term effects

# Learning and importance from SSc-ILD

- Typical feature of CTD-ILD
- High prevalence of lung involvement in SSc
- High morbidities and mortality
- Early involvement and risk for ILD development
- Risk of renal crisis d/t corticosteroid
- Evidence from previous RCTs

# Treatment of SSc-ILD (PPF)

| ATS SSc-ILD CLINICAL PRACTICE GUIDELINE SUMMARY | | |
|---|---|---|
| *THERAPY* | *QUALITY OF EVIDENCE** | *RECOMMENDATION*** |
| Mycophenolate | *Very Low* | *Strong in Favor* |
| Cyclophosphamide | *Low* | *Conditional in Favor* |
| Rituximab | *Very Low* | *Conditional in Favor* |
| Tocilizumab | *Very Low* | *Conditional in Favor* |
| Nintedanib | *Very Low* | *Conditional in Favor* |
| Nintedanib Plus Mycophenolate | *Very Low* | *Conditional in Favor* |
| Pirfenidone | *Very Low* | *Research Recommendation* |
| Pirfenidone Plus Mycophenolate | *Very Low* | *Research Recommendation* |

# Treatment of SSc-ILD (PPF)

| ATS SSc-ILD CLINICAL PRACTICE GUIDELINE SUMMARY | | |
|---|---|---|
| *THERAPY* | *QUALITY OF EVIDENCE** | *RECOMMENDATION*** |
| Mycophenolate | • Impairs T and B cell proliferation<br>• Cyclophosphamide (previous standard treatment) d/t SLS I<br>• SLS II<br>• Improved FVC and DLco at 12 or 24 months (no difference with CYC)<br>• Quality of Life (TDI score) and mRSS<br>• Fewer adverse events<br>• SSc 제외 CTD-ILD에서도 급여기준 확대 | |
| Cyclophosphamide | | |
| Rituximab | | |
| Tocilizumab | | |
| Nintedanib | | |
| Nintedanib Plus Mycophenolate | | |
| Pirfenidone | | |
| Pirfenidone Plus Mycophenolate | | |

# Treatment of SSc-ILD (PPF)

| ATS SSc-ILD CLINICAL PRACTICE GUIDELINE SUMMARY | | |
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| Mycophenolate | *Very Low* | *Strong in Favor* |
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|---|---|---|
| *THERAPY* | *QUALITY OF EVIDENCE** | *RECOMMENDATION*** |
| Mycophenolate | *Very Low* | *Strong in Favor* |
| Cyclophosphamide | *Low* | *Conditional in Favor* |
| Rituximab | | |
| Tocilizumab | | |
| Nintedanib | | |
| Nintedanib Plus Mycophenolate | | |
| Pirfenidone | *Very Low* | *Research Recommendation* |
| Pirfenidone Plus Mycophenolate | *Very Low* | *Research Recommendation* |

- CD20 monoclonal antibody → B cell depletion
- A key part in the pathogenesis of SSc
- A lack of corticosteroid role in B cell depletion

# Rituximab vs Cyclophosphamide : RECITAL study

- A randomized, double-blind, phase 2b trial from 2014 to 2020
- Severe or progressive ILD (scleroderma, inflammatory myositis, or MCTD)
- Primary endpoint: Rate of change in FVC at 24 weeks
- Secondary endpoint: FVC at 48 weeks, 6MWD, dyspnea, QoL

| | Cyclophosphamide group (n=48) | Rituximab group (n=49) |
|---|---|---|
| Age, years | 56·7 (11·6) | 56·6 (11·4) |
| Sex | | |
| Female | 35 (73%) | 31 (63%) |
| Male | 13 (27%) | 18 (37%) |



*Lancet Respir Med* 2023;11:45-54

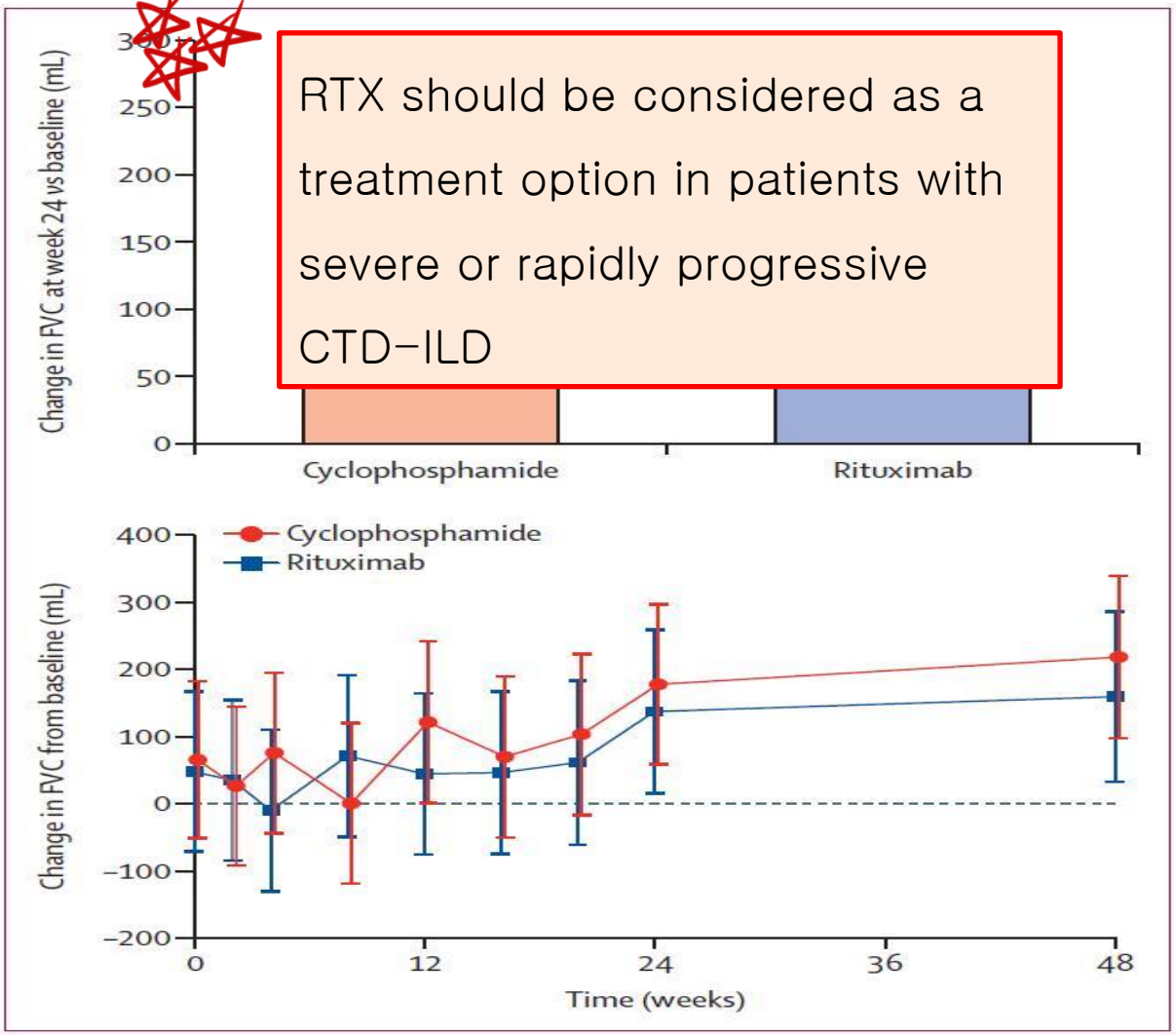
# Rituximab vs Cyclophosphamide : RECITAL study

| | Cyclophosphamide group (n=48) | Rituximab group (n=49) |
|---|---|---|
| Age, years | 56·7 (11·6) | 56·6 (11·4) |
| Sex | | |
| Female | 35 (73%) | 31 (63%) |
| Male | 13 (27%) | 18 (37%) |
| Years since onset of connective tissue disease | 4·8 (6·2) | 4·5 (7·6) |
| FVC, L | 2·23 (0·85) | 2·25 (0·77) |
| FVC, % of predicted | 71% (20) | 68% (17) |
| $DL_{CO}$, mL/min per kPa | 3·35 (1·42), n=46 | 3·46 (1·33), n=45 |
| $DL_{CO}$, % of predicted | 40% (14), n=46 | 40% (14), n=45 |
| $SpO_2$ on room air, % | 96% (2) | 97% (2) |
| 6 min walk distance, m | 363 (111) | 356 (126) |



*Lancet Respir Med* 2023;11:45-54

# Rituximab vs Cyclophosphamide : RECITAL study

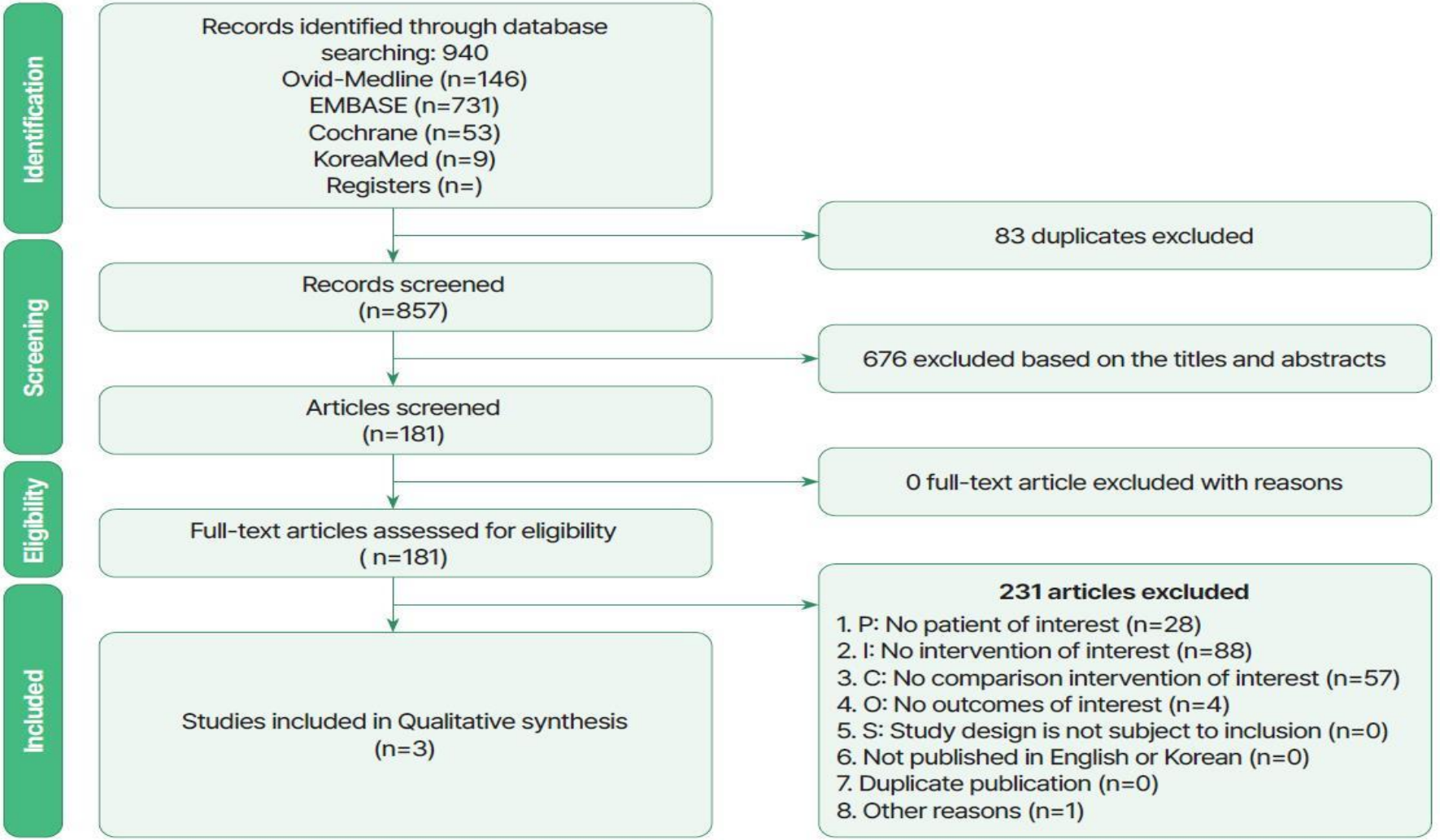



- Improvement of quality of life (K-BILD)
- No significant difference in secondary endpoints
- Lower steroid exposure and fewer adverse events in RTX

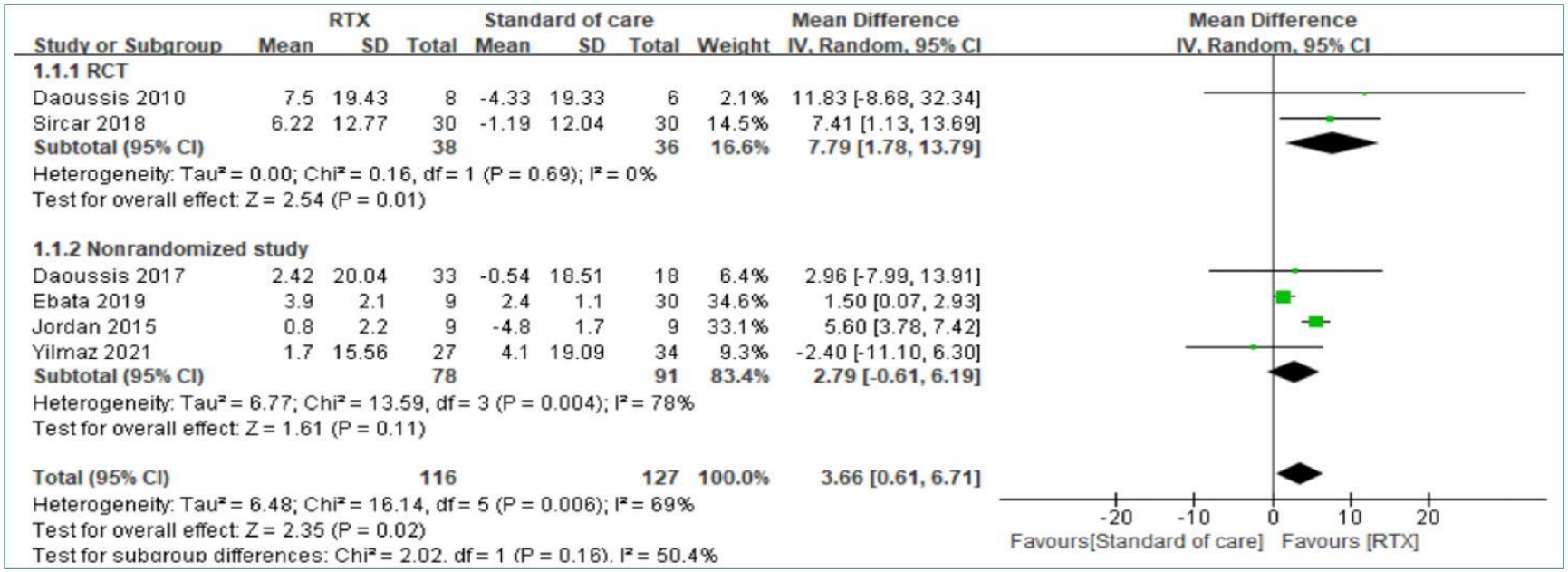


*Lancet Respir Med* 2023;11:45-54

# PICO: Moderate to Severe, therapy: RTX vs Conventional treatment, FVC

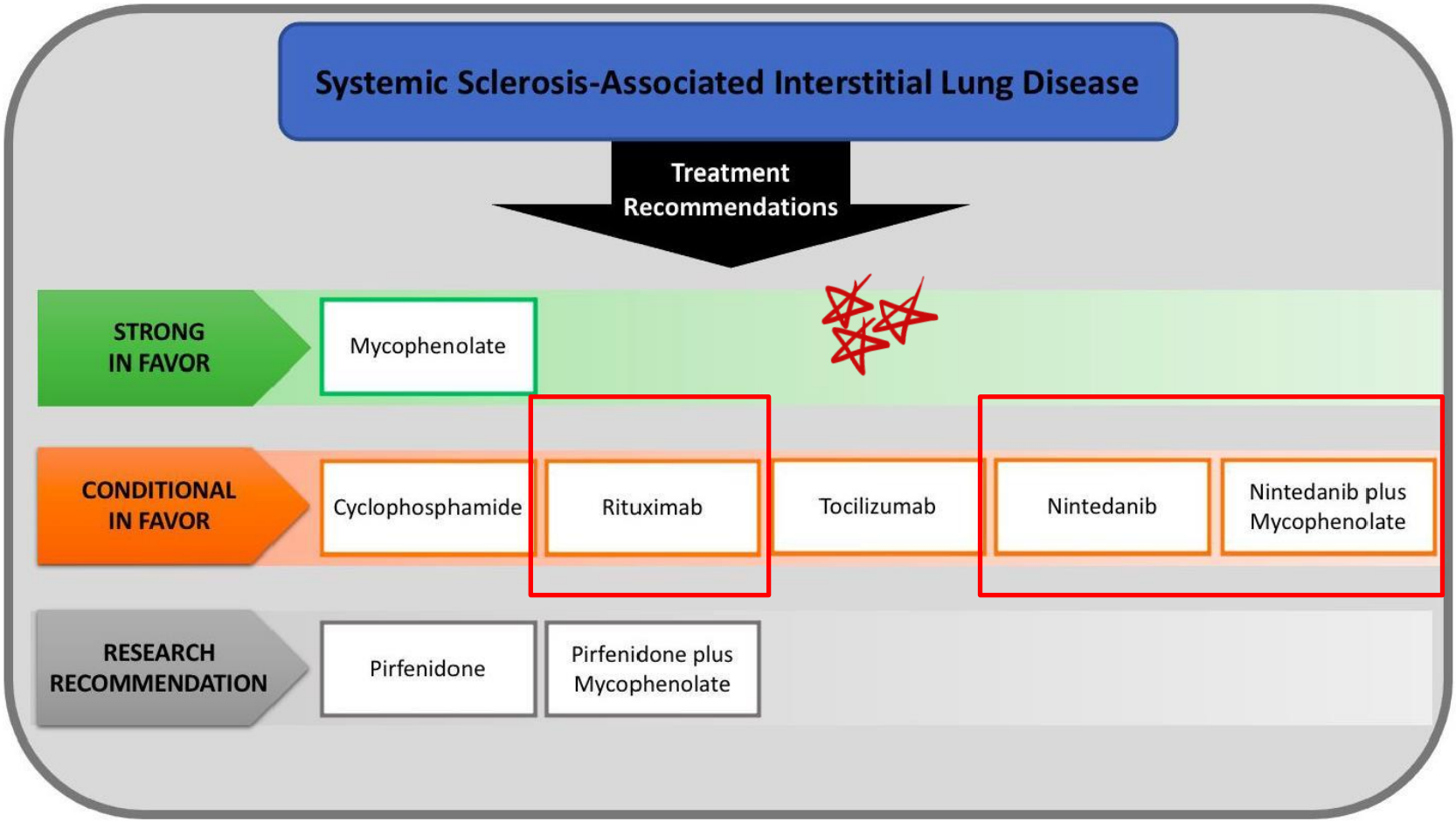


# PICO. 초기 치료에 반응하지 않는 중등도-중증의 전신경화증 연관 간질성폐질환 환자에서 생물학적제제 요법을 고려할 수 있는가?

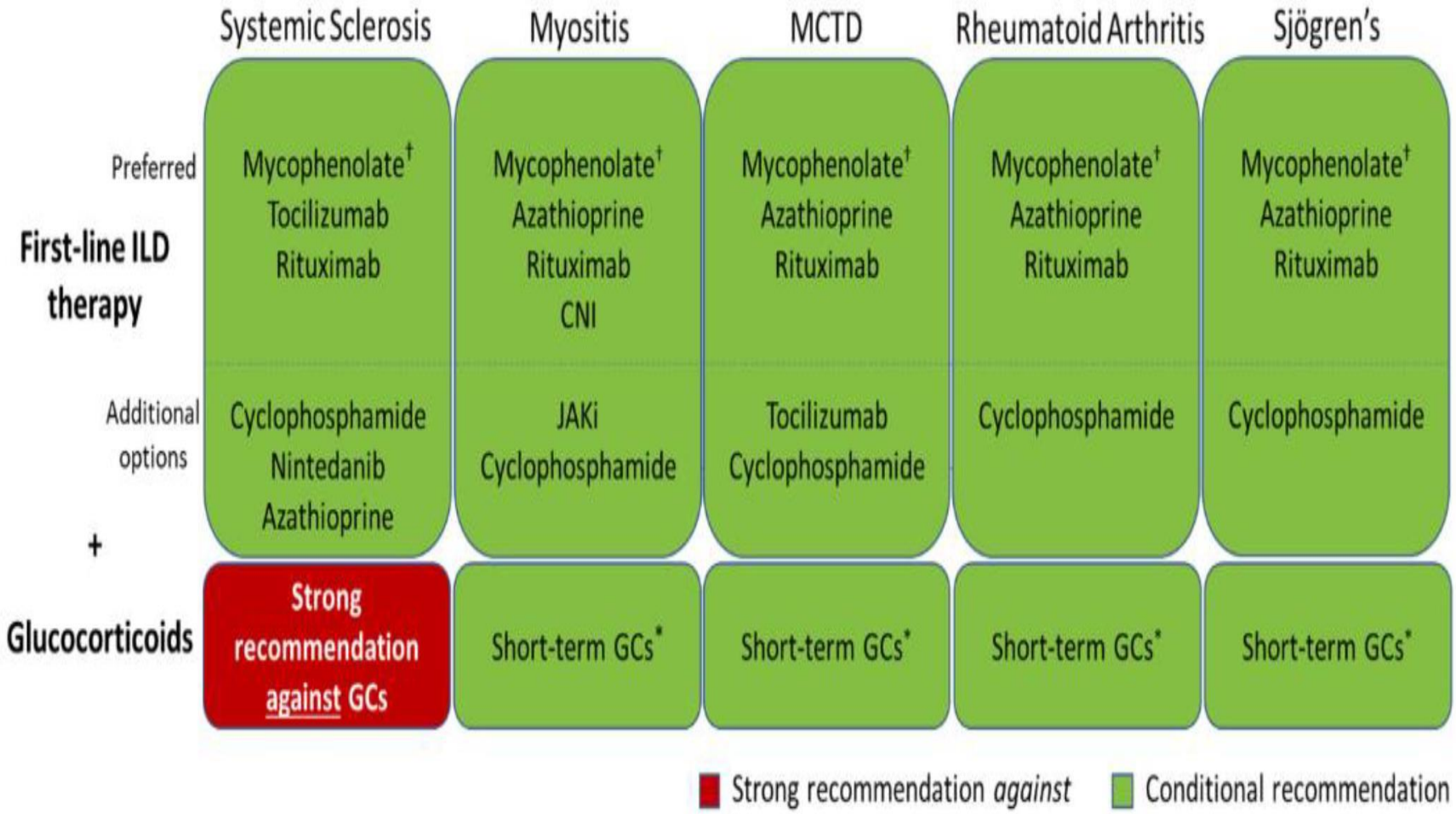



| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | RTX | Conventional treatment | Relative (95% CI) | Absolute (95% CI) | | |
| FVC - RCT | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious[a] | serious[b] | none | 38 | 36 | - | MD **7.79 higher** (1.78 higher to 13.79 higher) | ⨁⨁◯◯ Low | CRITICAL |
| FVC - Nonrandomized study | | | | | | | | | | | | |
| 4 | observational studies | not serious | serious[c] | serious[d] | serious[e] | none | 78 | 91 | - | MD **2.79 higher** (0.61 lower to 6.19 higher) | ⨁◯◯◯ Very low | CRITICAL |

# Treatment of SSc-ILD (PPF)



# ACR guideline of CTD-ILD



# Similarities in pathogenesis of lung fibrosis between IPF and other types of PPF

**IPF** **PPF**

- It is theorized that there are underlying similarities between the pathogenesis of lung fibrosis in IPF and other types of PPF
- Therefore, it is plausible that antifibrotic agents may have utility in slowing disease progression in non-IPF types of PPF just as it has been shown to do in IPF
- In order to be able to provide guidance on whether patients with non-IPF PPF should be treated with antifibrotic medications…

**Similarities**

- We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (Conditional recommendation, Low quality evidence)
- Need for further studies – better identifying at risk of progressive and irreversible fibrotic phenotype
  When to treat and sequence of antifibrotics in relation to immunosuppressants

# Effect of antifibrotics on symptoms in PPF

INBUILD trial - Main secondary end points: K-BILD

Overall population: 0.55 (nintedanib) vs -0.79, Difference (HR): 1.34 (-0.31 to 2.98)

The Living with Pulmonary Fibrosis questionnaire

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
M. WIJSENBEEK ET AL.

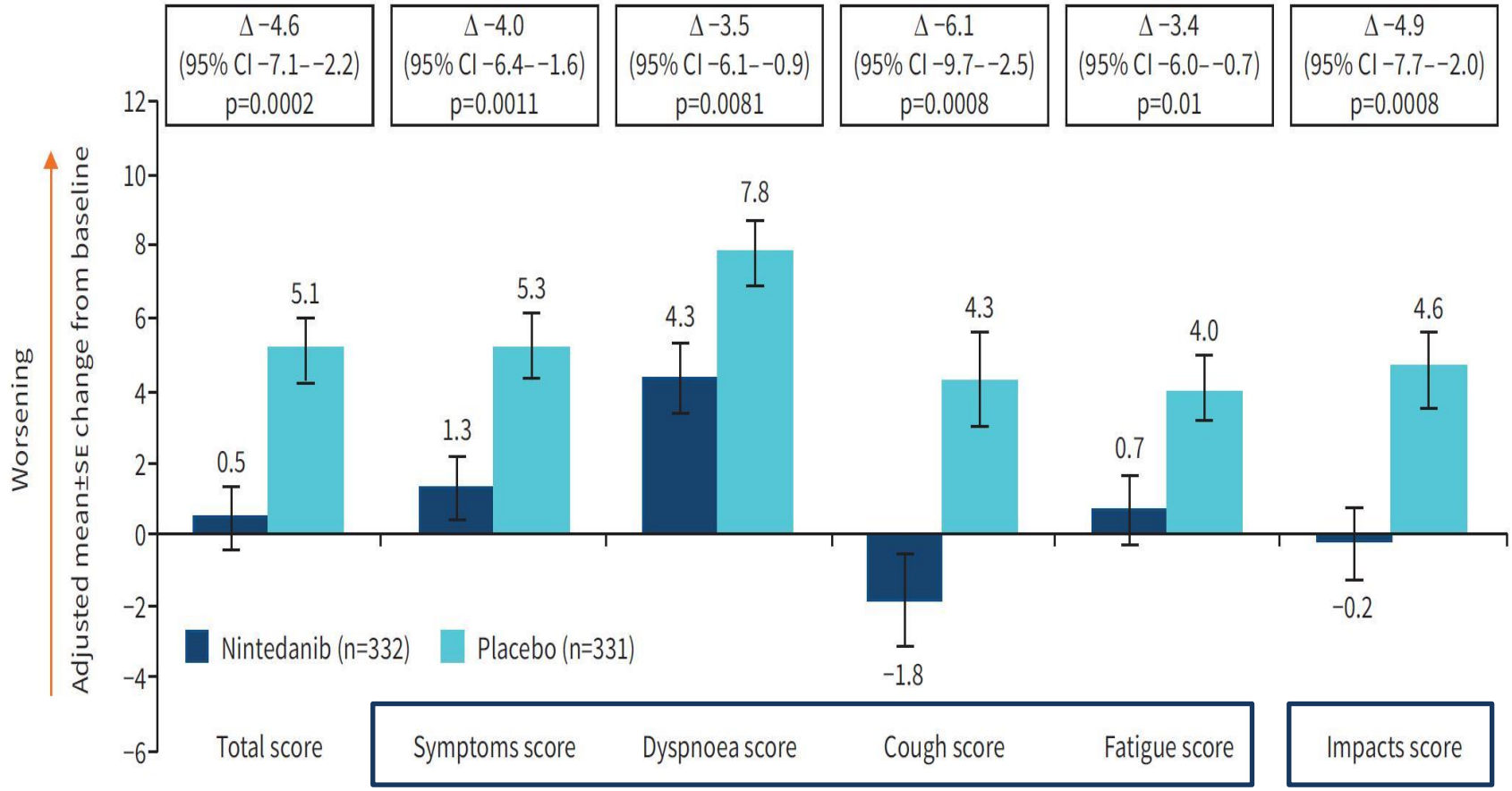
## Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

Marlies Wijsenbeek[1], Jeffrey J. Swigris[2], Yoshikazu Inoue[3], Michael Kreuter[4,5], Toby M. Maher[6,7], Takafumi Suda[8], Michael Baldwin[9], Heiko Mueller[10], Klaus B. Rohr[9] and Kevin R. Flaherty[11] on behalf of the INBUILD Trial Investigators



*ERJ* 2024; 63:2300752

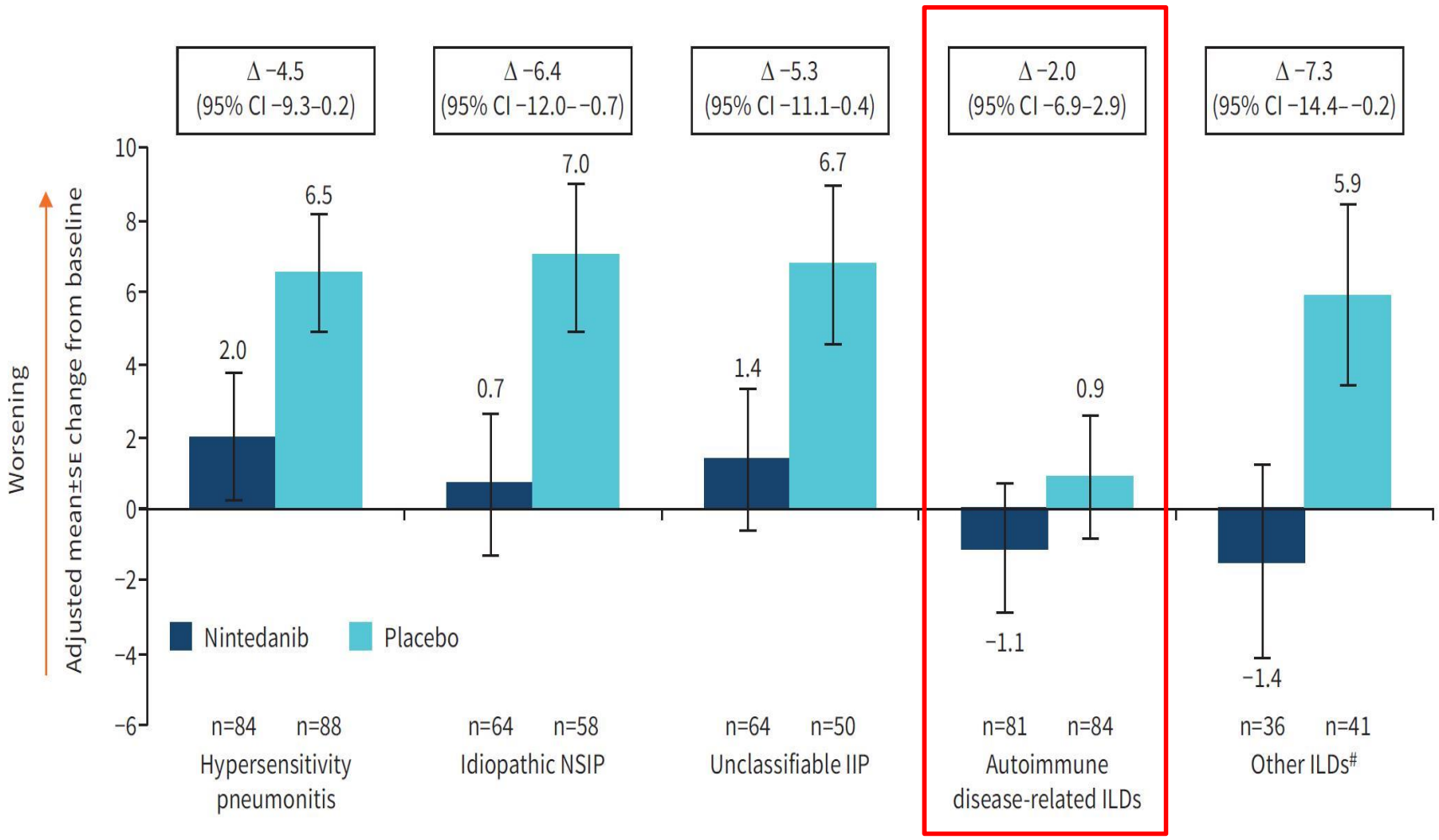
# Effect of antifibrotics on symptoms in PPF






*ERJ* 2024; 63:2300752

# Effect of antifibrotics on symptoms in PPF

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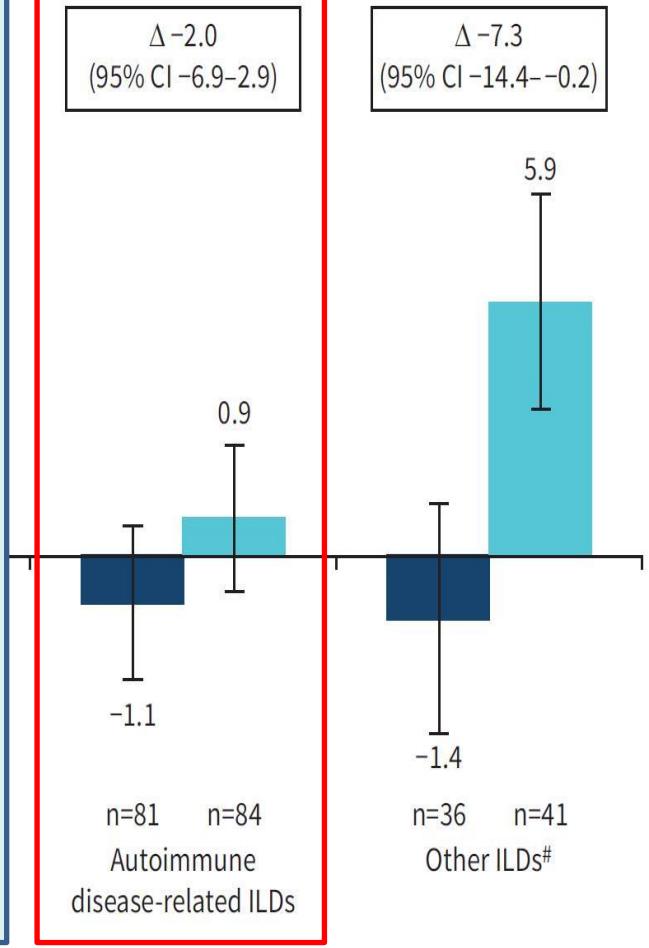
*ERJ* 2024; 63:2300752

# Effect of antifibrotics on symptoms in PPF

- Effect of FVC decline in CTD-ILD
- The impact of extrapulmonary manifestation

- The L-PF vs The K-BILD ?
- Actual mechanism behind the effect of Nintedanib on symptoms?
- Preserving lung function might be beneficial in preventing deterioration in symptoms and patients reported outcomes






*ERJ* 2024; 63:2300752

# Subgroup analysis for effect of Nintedanib in PPF

Adv Ther (2023) 40:5536–5546
https://doi.org/10.1007/s12325-023-02668-x

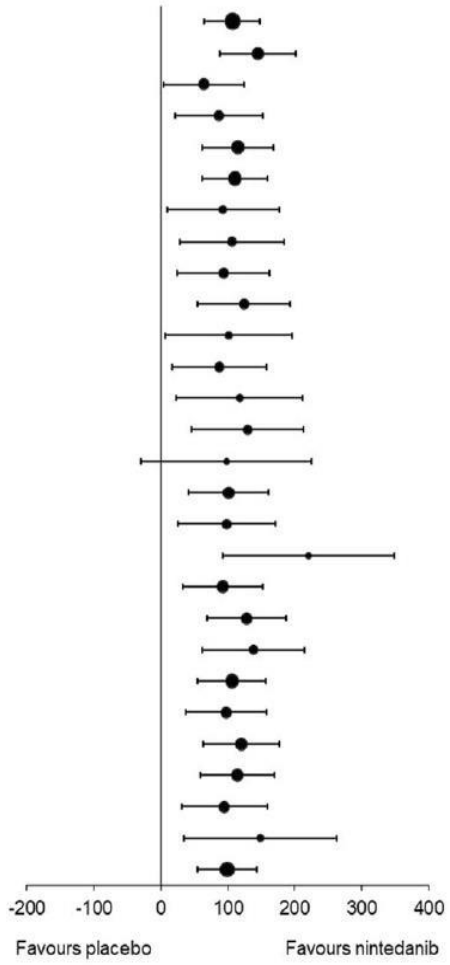
BRIEF REPORT

## Effect of Nintedanib in Patients with Progressive Pulmonary Fibrosis in Subgroups with Differing Baseline Characteristics

- **No difference based on subclassification of ILDs**
- Baseline characteristics
- Sex, Age, Race, BMI
- Time since diagnosis of ILD
- FVC, DLco, GAP
- Drug use: anti-acid, DMARDs

# Subgroup analysis for effect of Nintedanib in PPF

| | | n analysed | | Difference (95% CI) | Treatment-by-subgroup-by-time interaction |
|---|---|---|---|---|---|
| | | Nintedanib | Placebo | | |
| **All subjects** | | 332 | 331 | 107.0 (65.4, 148.5) | |
| **Sex** | Male | 179 | 177 | 145.2 (88.5, 201.9) | $p = 0.06$ |
| | Female | 153 | 154 | 64.2 (3.9, 124.6) | |
| **Age** | <65 years | 139 | 121 | 86.9 (21.5, 152.2) | $p = 0.51$ |
| | ≥65 years | 193 | 210 | 115.1 (61.4, 168.8) | |
| **Race*** | White | 242 | 246 | 110.6 (62.0, 159.2) | $p = 0.77$ |
| | Asian | 84 | 80 | 93.0 (9.3, 176.7) | |
| **Body mass index** | <25 kg/m$^2$ | 90 | 98 | 106.1 (28.3, 184.0) | $p = 0.83$ |
| | ≥25 to <30 kg/m$^2$ | 130 | 112 | 93.7 (24.7, 162.6) | |
| | ≥30 kg/m$^2$ | 111 | 121 | 124.3 (55.4, 193.3) | |
| **Time since diagnosis of ILD** | ≤1 year | 67 | 67 | 101.6 (7.5, 195.6) | $p = 0.89$ |
| | >1 to ≤3 years | 115 | 112 | 87.8 (17.0, 158.5) | |
| | >3 to ≤5 years | 74 | 57 | 117.7 (23.2, 212.1) | |
| | >5 years | 75 | 95 | 129.4 (45.6, 213.1) | |
| **FVC** | ≤50% predicted | 42 | 33 | 98.3 (−28.9, 225.5) | $p = 0.38$ |
| | >50% to ≤70% predicted | 154 | 160 | 101.3 (41.7, 160.9) | |
| | >70% to ≤90% predicted | 104 | 105 | 98.6 (26.1, 171.1) | |
| | >90% predicted | 32 | 33 | 220.8 (92.7, 348.8) | |
| **DLco†** | ≤median (43.3% predicted) | 177 | 150 | 92.4 (32.3, 152.5) | $p = 0.40$ |
| | >median (43.3% predicted) | 149 | 178 | 128.4 (70.1, 186.8) | |
| **CPI** | ≤45 | 82 | 120 | 138.4 (62.7, 214.1) | $p = 0.48$ |
| | >45 | 244 | 208 | 105.9 (55.2, 156.5) | |
| **GAP stage** | I | 142 | 152 | 98.0 (37.6, 158.3) | $p = 0.60$ |
| | II or III | 190 | 179 | 119.8 (63.4, 176.2) | |
| **Anti-acid therapy‡** | Yes | 200 | 180 | 113.9 (58.8, 169.0) | $p = 0.66$ |
| | No | 132 | 151 | 95.2 (31.5, 158.9) | |
| **DMARDs§** | Yes | 43 | 48 | 148.4 (33.9, 262.9) | $p = 0.44$ |
| | No | 289 | 283 | 99.5 (54.8, 144.2) | |

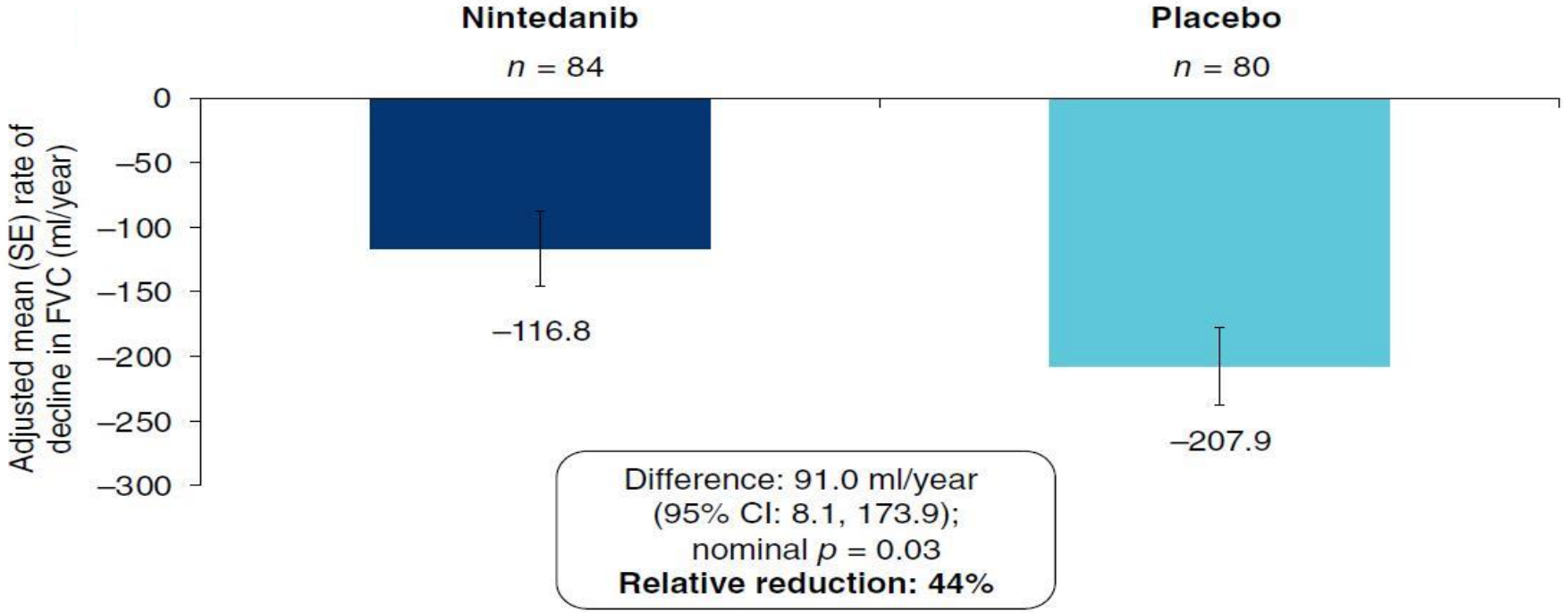


# Subgroup analysis for effect of Nintedanib in PPF

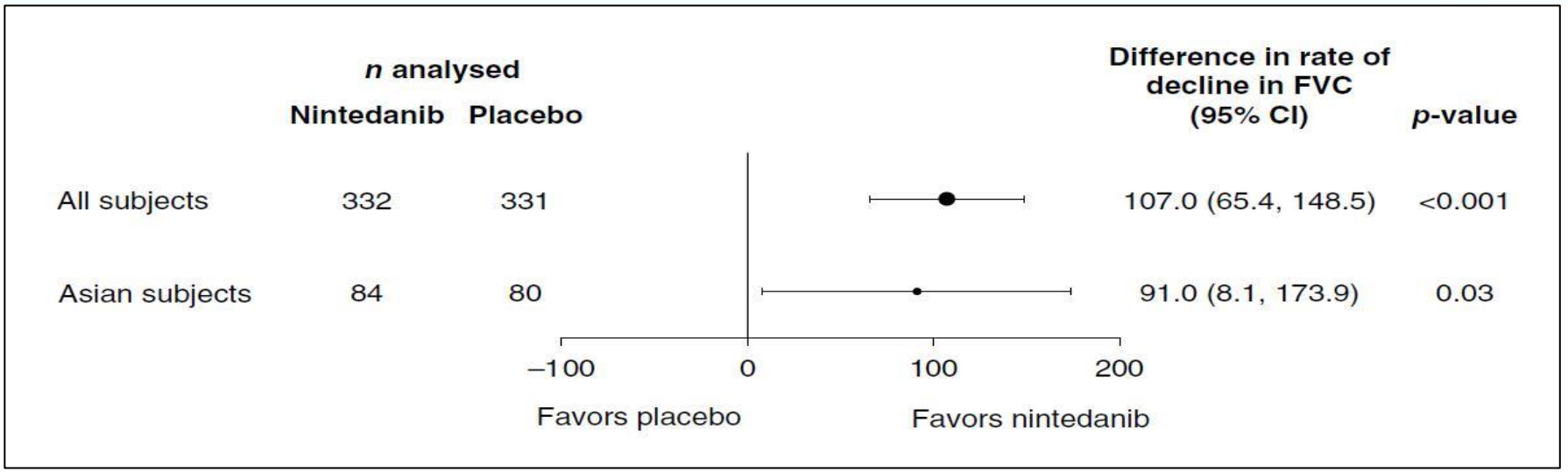
ORIGINAL ARTICLE

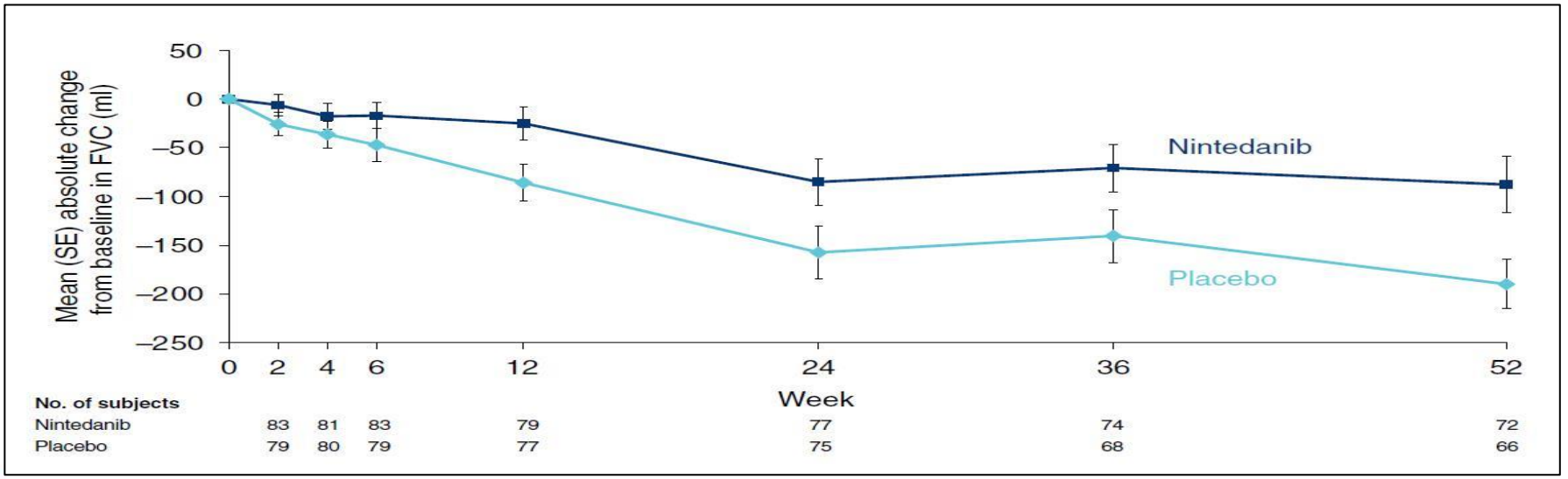
Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

## Nintedanib in Asian patients with progressive fibrosing interstitial lung diseases: Results from the INBUILD trial



# Subgroup analysis for effect of Nintedanib in PPF



# Evidence of nintedanib in PPF

- Reduction of FVC decline (Like IPF)
- Similar effect between ILDs classification

- Effect on symptoms (by absolute change of the Living with Pulmonary Fibrosis)
- Similar effect of reduction of FVC decline in subgroups with differing baseline characteristics (race)

# Antifibrotics in PPF

- When to start or stop
- How to use of corticosteroid or immunosuppressants (extrapulmonary manifestation)
- Pirfenidone?
- Limitations and further research (clinical trials)

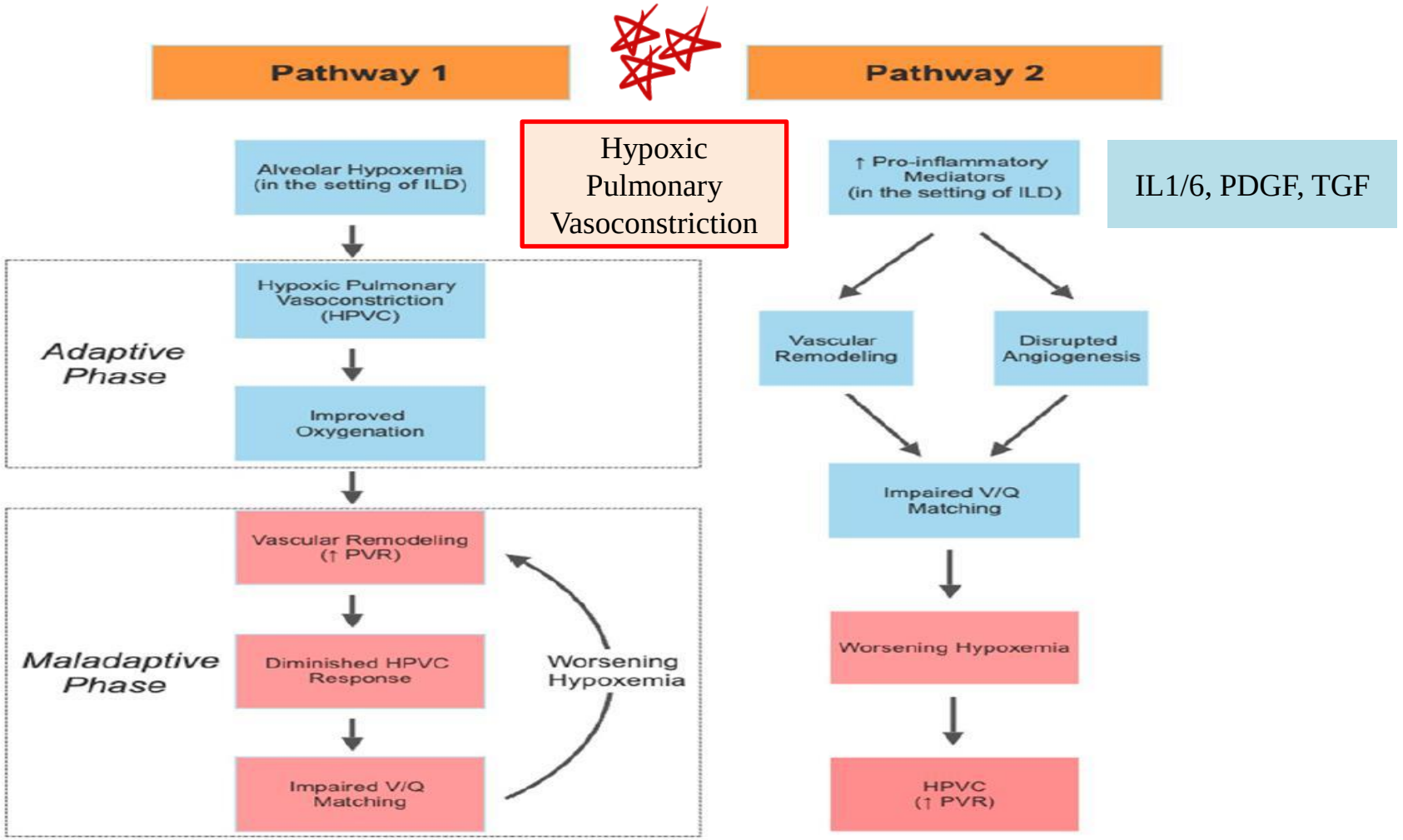
# Pulmonary Hypertension in ILD

- A subset of WHO group 3 (precapillary causes)
- Prevalence of PH-ILD in IPF: 8-86%

→ At diagnosis of IPF: 8-15%, advanced stage: up to 50%, more than 60% of end-stage

- PH-ILD increased morbidity and mortality: decreased functional capacity, more frequent hospitalization, higher supplemental oxygen requirements, reduced QoL

# Proposed pathophysiology in PH-ILD





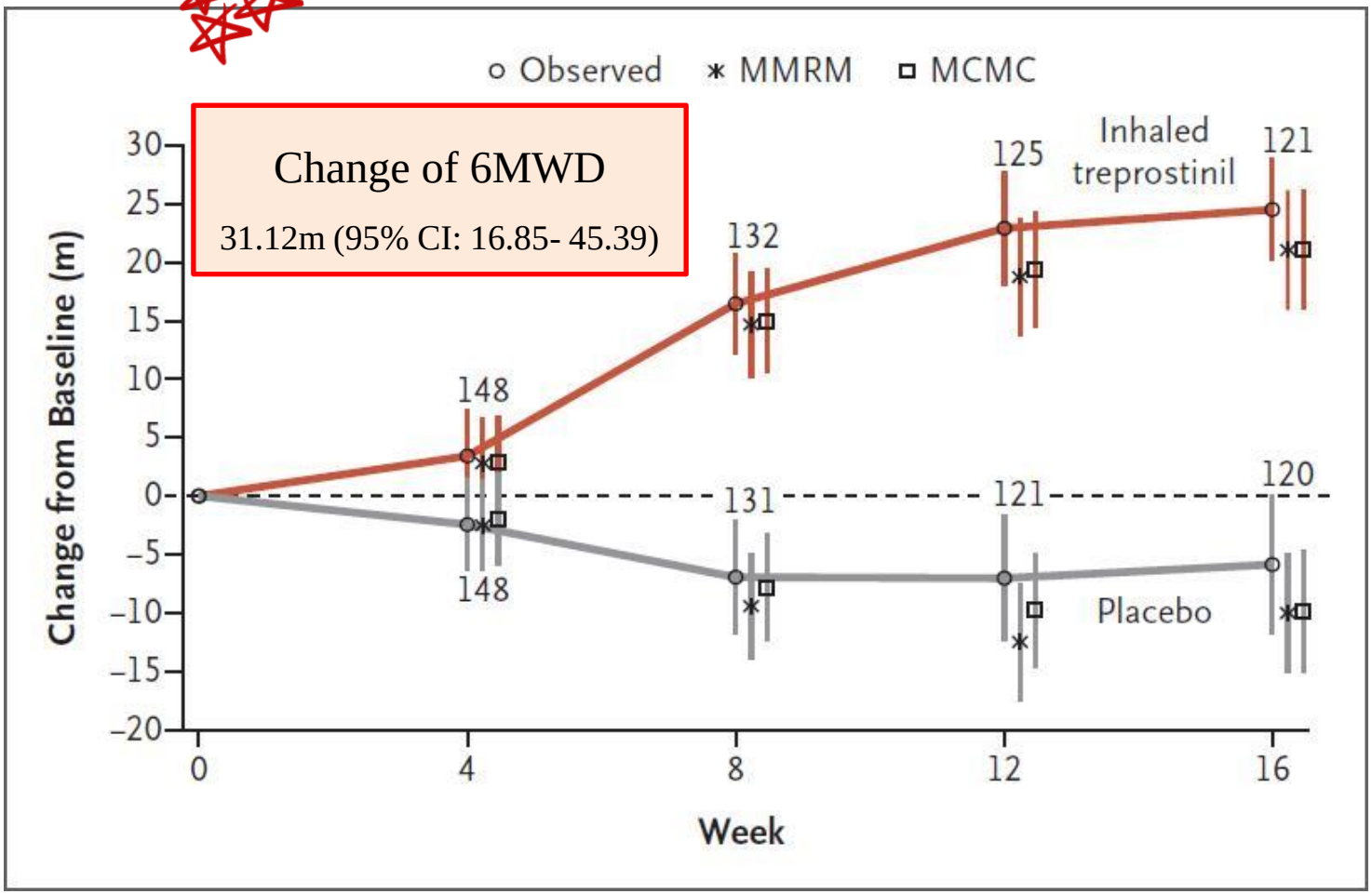

*Cells* 2023; 12, 2394

# PH-ILD: Treatment

Optimal treatment of the underlying lung disease, including long-term $O_2$ therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases

| | |
|---|---|
| Inhaled treprostinil may be considered in patients with PH associated with ILD | IIb |
| The use of ambrisentan is not recommended in patients with PH associated with IPF | III |
| The use of riociguat is not recommended in patients with PH associated with IIP | III |

# Inhaled Treprostinil in ILD

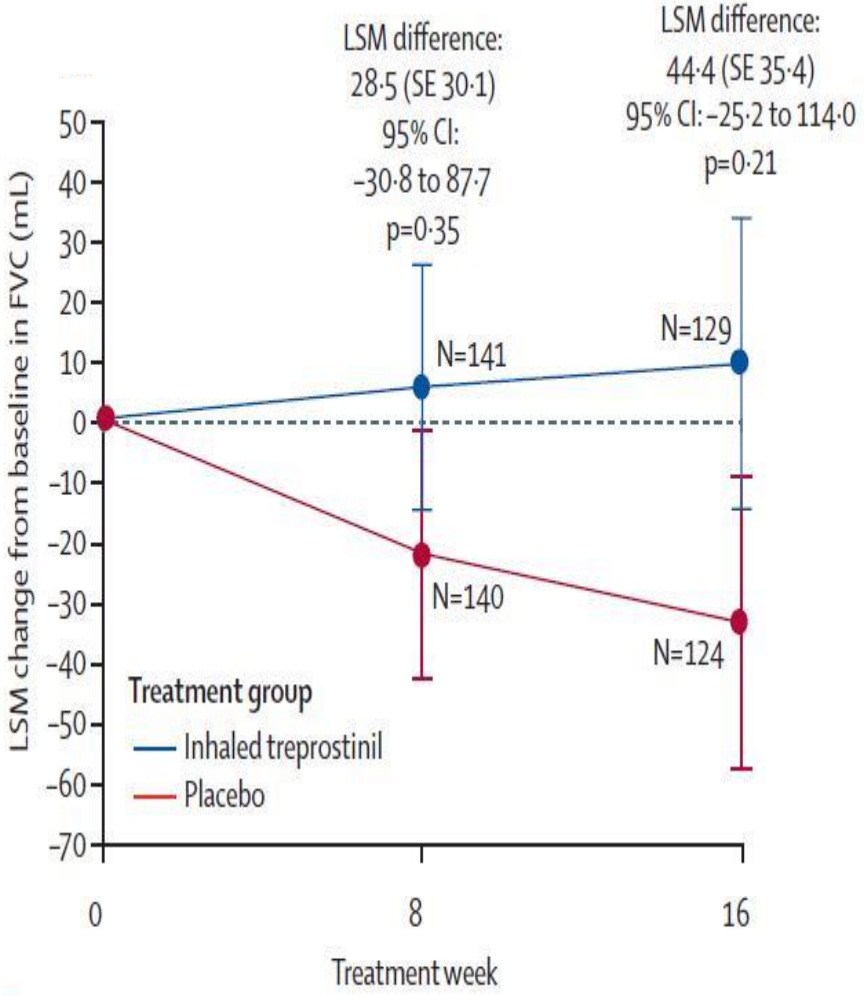




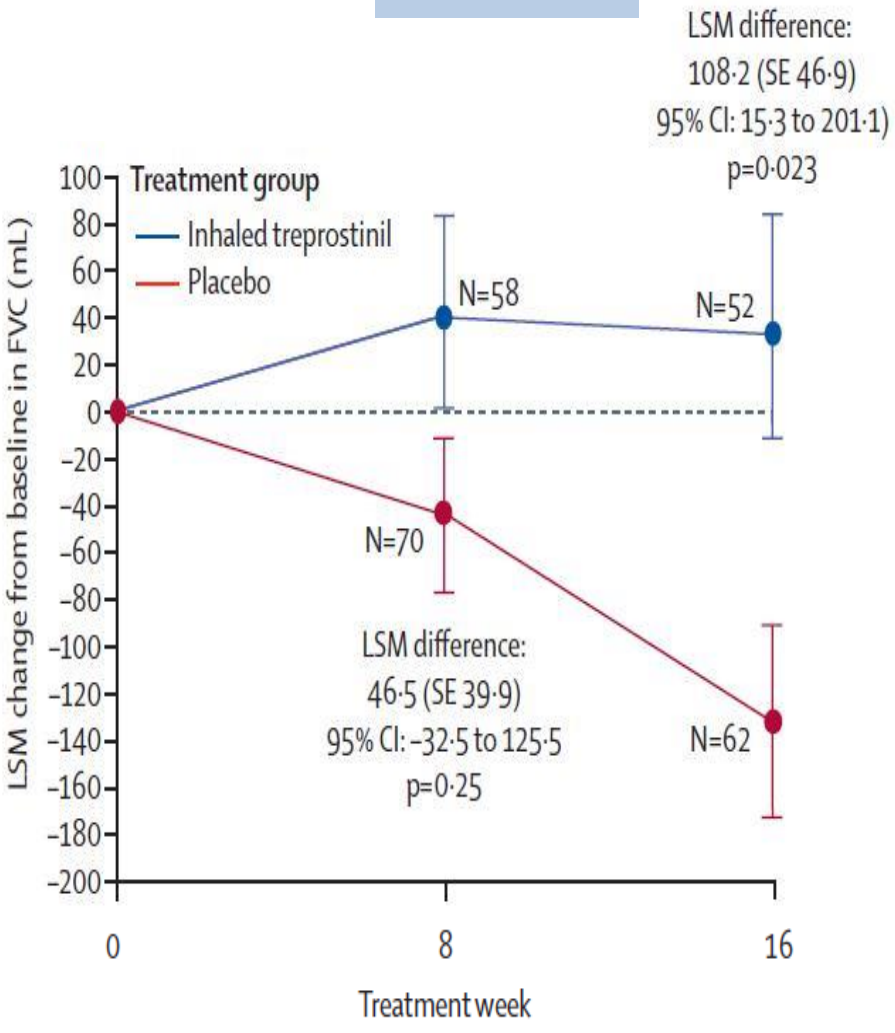

*NEJM* 2021; 384:325-34

# Inhaled Treprostinil in PH-ILD (The INCREASE study)

Overall population




IIP

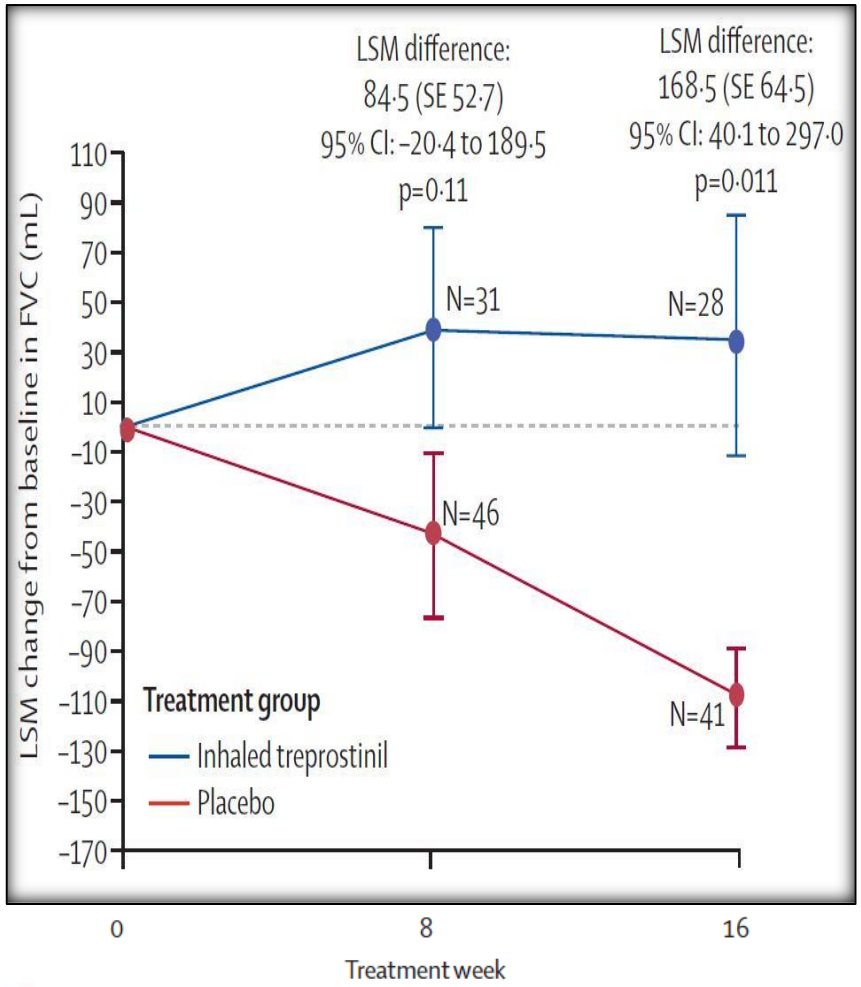




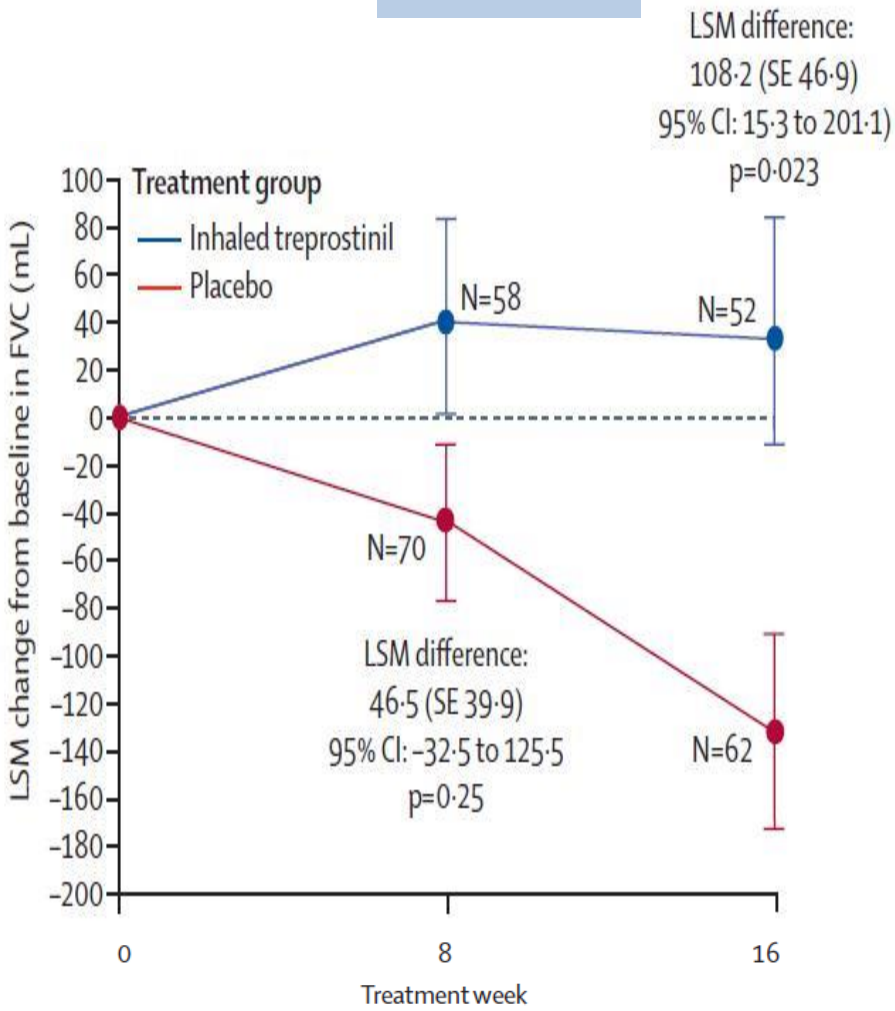

*Lancet Respir Med* 2021;9:1266-74

# Inhaled Treprostinil in PH-ILD (The INCREASE study)

IPF

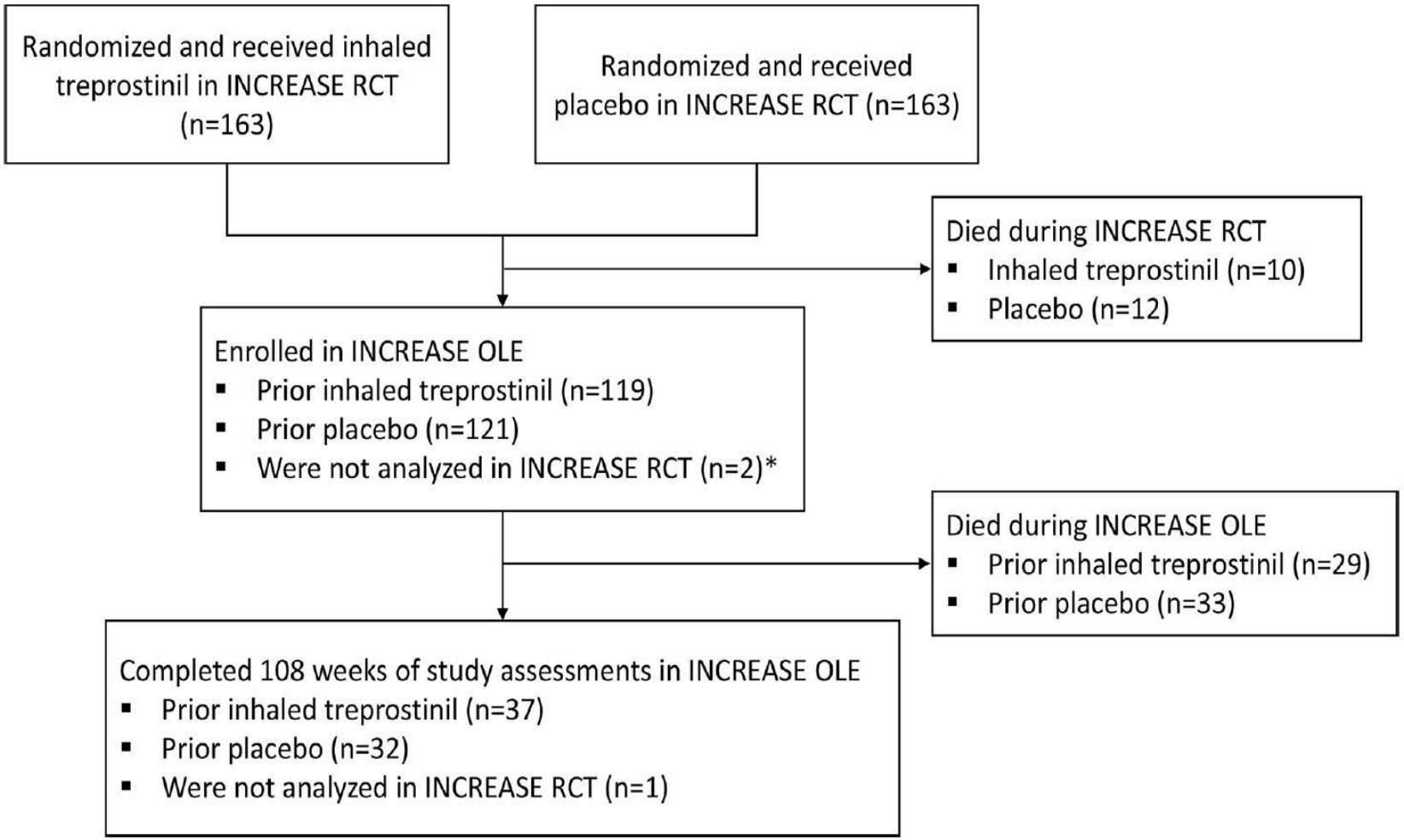



IIP




*Lancet Respir Med* 2021;9:1266-74

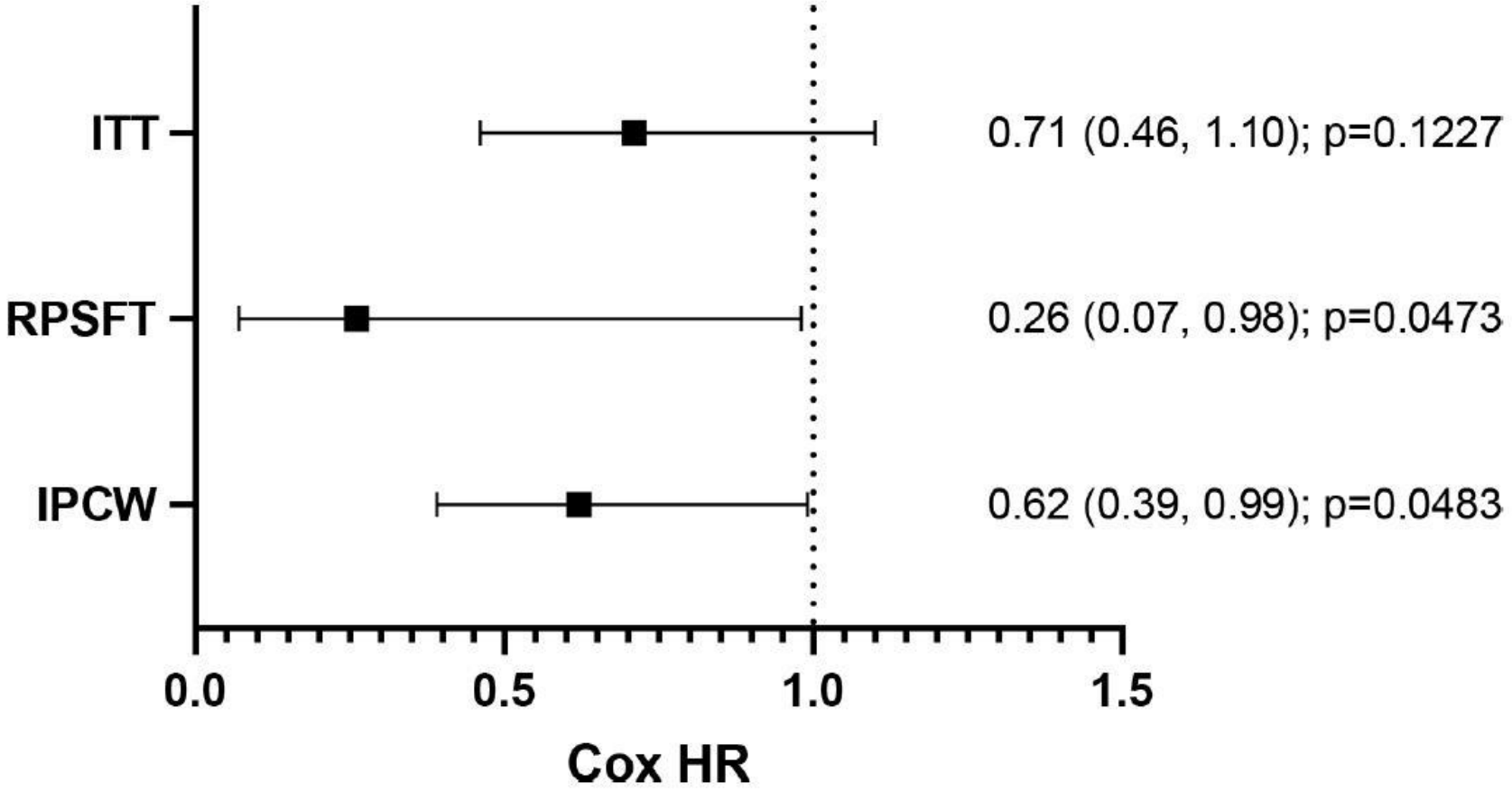
# Survival analysis from the INCREASE study






*Thorax* 2023;0:1-6

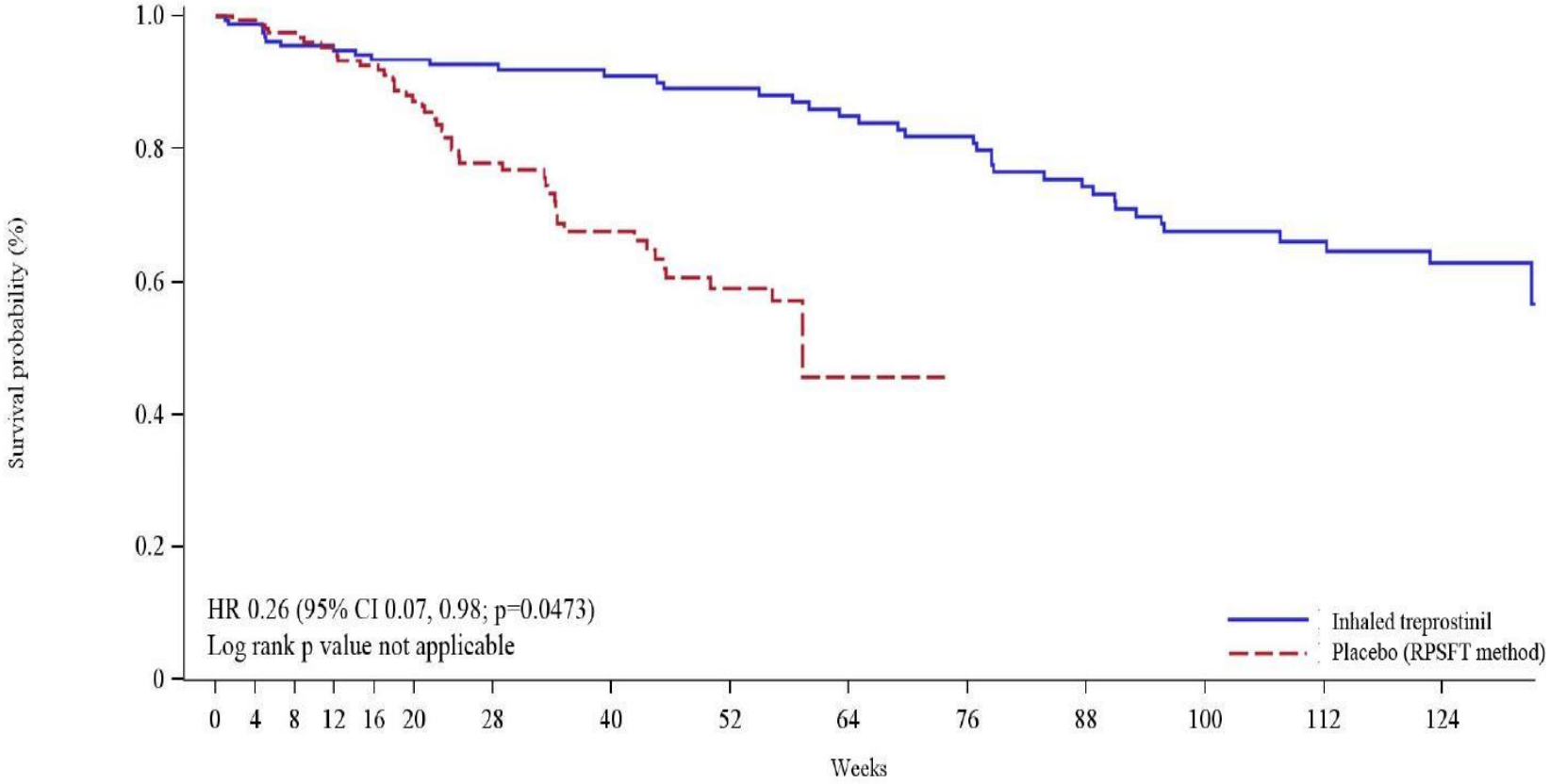
# Survival analysis from the INCREASE study






*Thorax* 2023;0:1-6

# Survival analysis from the INCREASE study



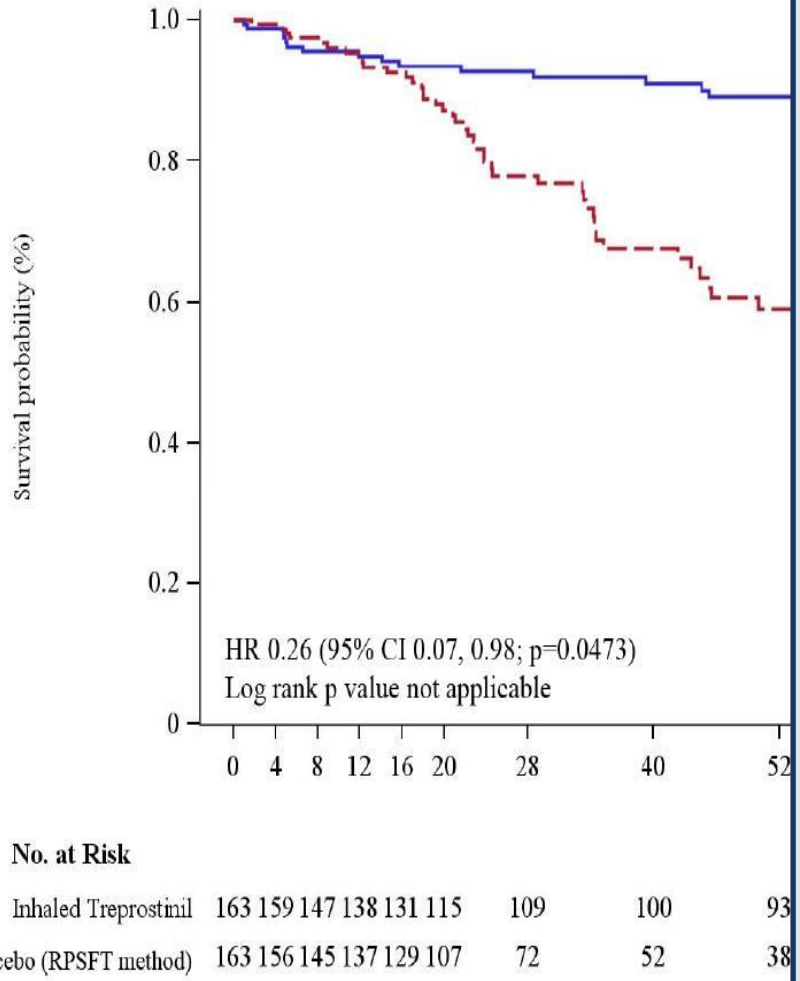

**No. at Risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inhaled Treprostinil | 163 | 159 | 147 | 138 | 131 | 115 | 109 | 100 | 93 | 82 | 77 | 68 | 55 | 45 | 32 |
| Placebo (RPSFT method) | 163 | 156 | 145 | 137 | 129 | 107 | 72 | 52 | 38 | 1 | 0 | | | | |



*Thorax* 2023;0:1-6

# Inhaled treprostinil in PH-ILD




**Conclusion**

- Inhaled treprostinil

→Improved exercise capacity by 6MWD (BNP↓15%)

→ Improvements in FVC vs placebo at 16 weeks (especially IIP and IPF)

→ Well-established statistical methodologies demonstrated a survival benefit

- Active screen and RHC resulting inhaled treprostinil in adequate patients with PH-ILD (For physician)
- 국내사용

*Thorax* 2023;0:1-6

# Summary

- Digital Health Care for ILDs
- Digital Therapeutics for PR in ILDs
- Treatment of CTD-ILD
- Effect of antifibrotics in PPF
- PH-ILD: Role of inhaled treprostinil
- PH-ILD: Screening and patient selection

# 감사합니다