New trials in ILDs

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Conflict of interests disclosures

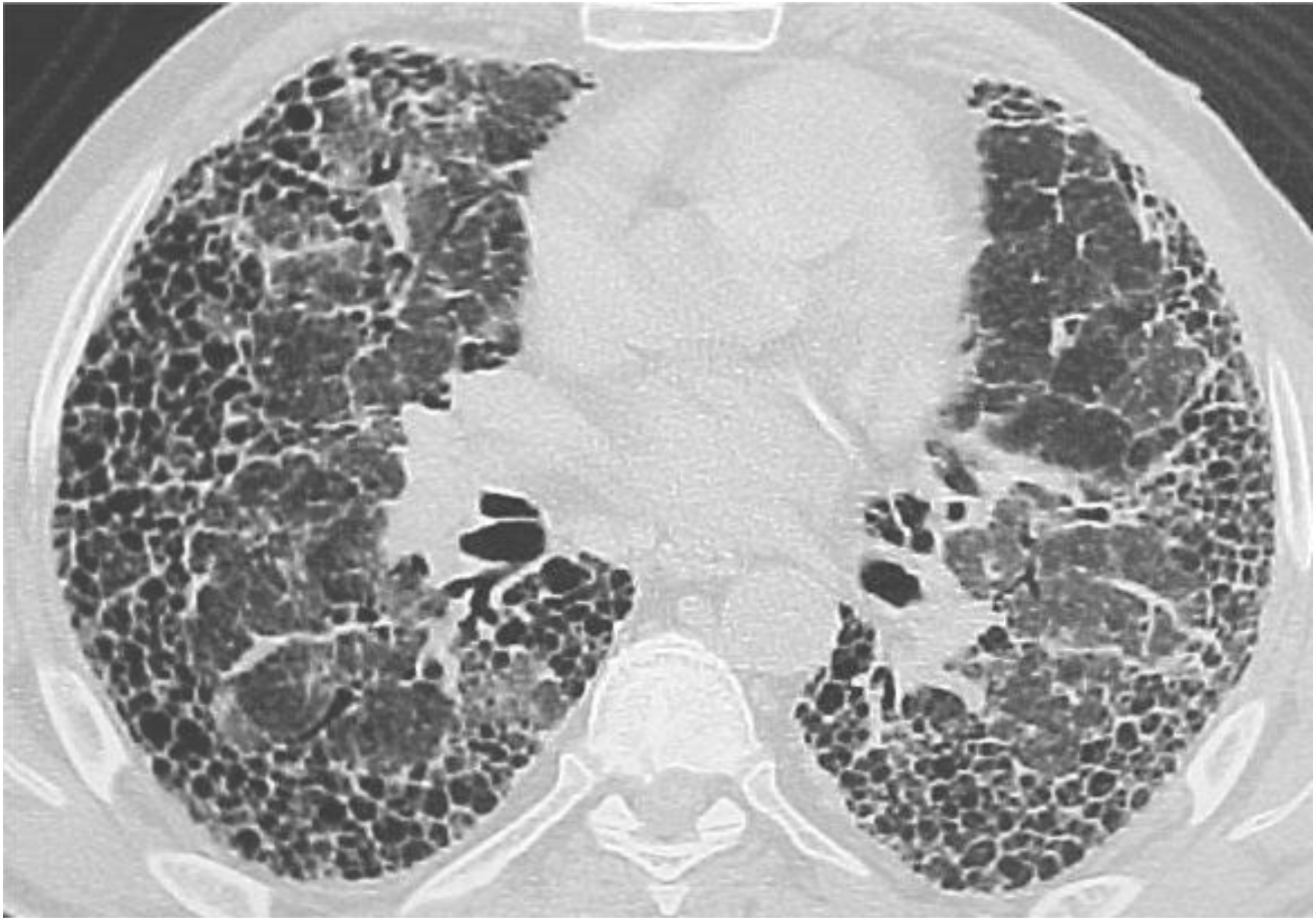
Actelion

Boehringer Ingelheim

Roche

IPF

A phase IIb, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and intermediate or high probability of group 3 pulmonary hypertension



Rationale

- PH is common in patients with IPF, and its prevalence increases with disease severity
- PH is a major contributor to morbidity and mortality in patients with advanced IPF, and it has an adverse impact on survival
- There are currently no approved therapies for PH secondary to lung disease (Group 3 PH), including PH secondary to IPF
- Phase II and III clinical trials in IPF, including pirfenidone trials, have generally excluded patients with advanced disease and/or PH
- Patients with PH secondary to advanced IPF therefore represent a group with a high unmet medical need

Rationale

STEP-IPF: RCT, sildenafil studied in 180 patients with advanced IPF (DLCO< 35%), failed to meet its primary endpoint of ≥20% improvement in 6MWD; secondary endpoints such as DLCO, dyspnoea, SaO2 and QoL achieved statistical significance

- A subgroup of patients with RV systolic dysfunction treated with sildenafil experienced a 99 m lower decline in 6MWD and improved QoL compared with those who received placebo

Study design

- Patients with advanced IPF and intermediate or high probability of Group 3 PH who are on pirfenidone in a range dose of 1602-2403 mg/day with demonstrated tolerability
- 176 patients to be enrolled
- Randomization 1:1

Key inclusion criteria

For the purpose of this study, patients have to present with:

Advanced IPF

(defined as a measurable %DLCO≤40% at screening)

AND

Intermediate or high probability of Group 3 PH

(defined as a mPAP≥ 20 mmHg with PAWP≤15 mmHg) on a previous RHC of acceptable quality

OR

In the absence of a previous RHC, patients with ECHO intermediate or high probability of PH, as defined by the 2015 ESC/ERS guidelines (peak TRV ≥ 2.9 m/s), will be considered eligible for the study

Primary endpoint

- The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:
  - Relevant decline in 6MWD of at least 15% from baseline, respiratory –related non-elective hospitalization, or all cause mortality

Efficacy and Safety of Nintedanib When Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment

Nintedanib and sildenafil

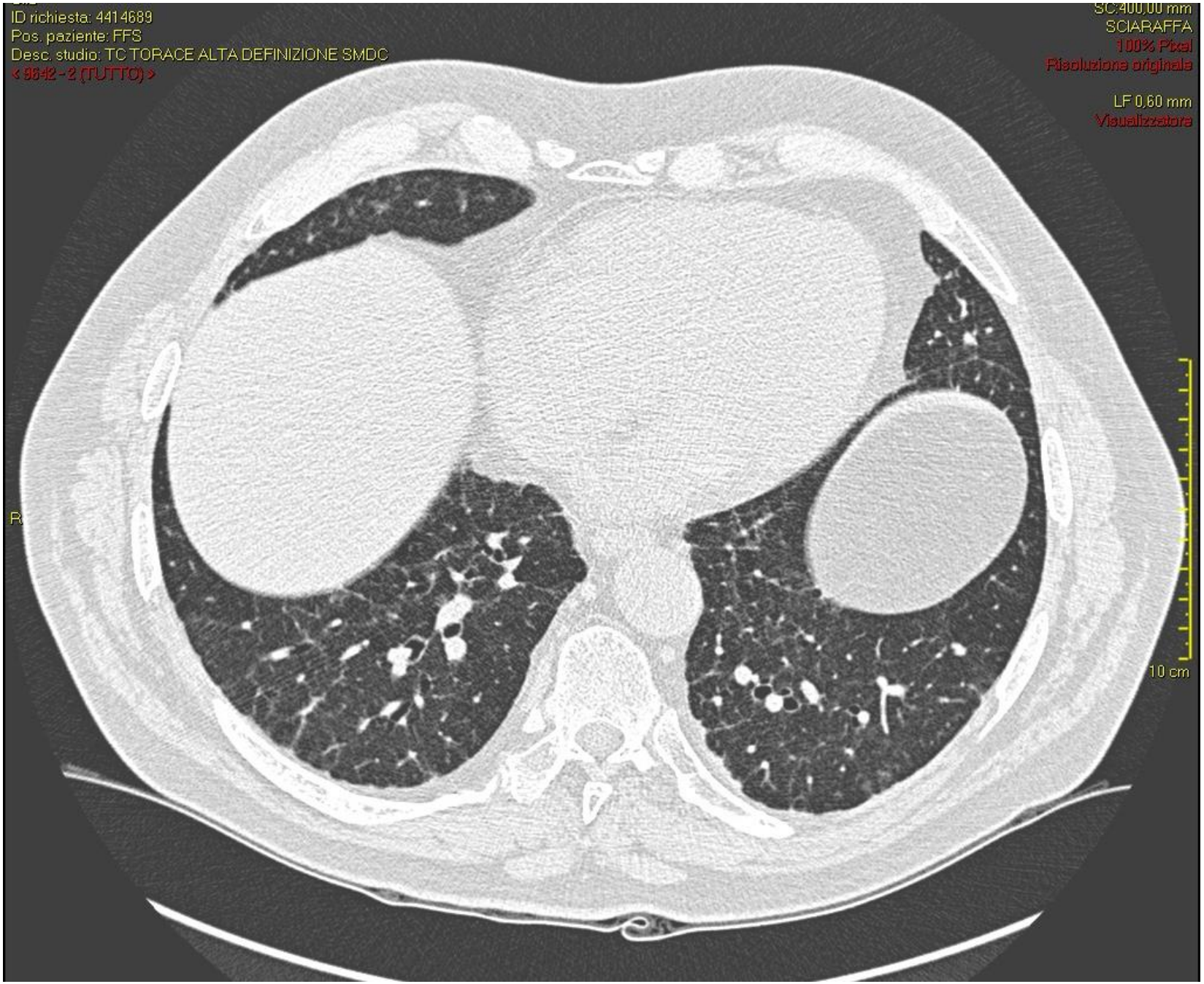
- A 24-week, double-blind randomized parallel group study evaluating the **efficacy and safety** of oral nintedanib co-administered with oral sildenafil
- Clinical phase: III b
- **Objective:** To assess efficacy and safety of concomitant treatment with nintedanib and sildenafil in IPF patients with advanced lung **function impairment**

Nintedanib and sildenafil

- 300 patients to be included, ≥ 40 years and with DLCO ≤ 35%
- Randomization 1:1
- Nintedanib 150 mg bid with the possibility to reduce to 100 mg bid to manage adverse events or placebo and sildenafil 20 mg tid
- 24 weeks of randomized treatment
- **Primary Endpoint**: Change from baseline in SGRQ total score at week 12

Unclassificable “ILD”

Multicenter, international, double-blind, two arm, randomized, placebo-controlled, phase II trial of pirfenidone in patients with unclassifiable progressive fibrosing ILD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Background

- Unclassifiable ILD represents a heterogeneous collection of undiagnosed fibrosing ILDs, which have a prognosis between IPF and other non-IPF fibrosing
- Owing to the heterogeneous nature of the disease, the choice of pharmacotherapy for unclassifiable ILD is unquestionably complex
- Treatment usage is complicated by both a lack of direct evidence in this patient population and by clinical data that indicate that different therapeutic strategies need to be employed in patients with IPF compared with patients with other fibrotic ILDs

This trial will evaluate the efficacy and safety of pirfenidone in patients with fibrosing interstitial lung disease (ILD) who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary team (MDT) review (**“unclassifiable” ILD**).

Clinical phase: II

- **Efficacy objective:** rate of decline in FVC measured in ml by daily handheld spirometer over the 24-week double-blind treatment period

- 250 patients will be randomized in a 1:1 ratio, on a double-blind basis using a stratified algorithm, to receive either pirfenidone (801 mg TID) or placebo. The randomized patients will be stratified by concomitant MMF treatment (yes/no), the presence/absence of interstitial pneumonia with autoimmune features (IPAF) as defined by the MDT

Inclusion criteria

- Age 18–85 years
- Progressive disease as considered by the investigator using the following definition: Patient deterioration within the last 6 months, which is defined as:
  - A rate of decline in FVC >5% OR
  - Significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes
- Extent of fibrosis >10% on high-resolution computed tomography (HRCT; visual scoring) within the last 12 months
- FVC ≥45% of predicted value
- Diffusing capacity of the lung for carbon monoxide (DLco) ≥30% of predicted value .
- 6-minute walk distance (6MWD) ≥150 meters

A Double Blind, Randomized, Placebo-controlled Trial Evaluating the Efficacy and Safety of Nintedanib Over 52 Weeks in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

- The aim of the is to investigate the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD.

- There is currently no efficacious treatment available for PF-ILD.

- This study is recruiting partecipants (start Jan 2017)

Primary Outcome Measures:

- Annual rate of decline in Forced Vital Capacity

Secondary Outcome Measures:

- Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score
- Time to first acute ILD exacerbation or death over 52 weeks
- Time to death over 52 weeks
- Time to death due to respiratory cause over 52 weeks
- Time to progression (defined as a equal or more than 10 percent absolute decline in Forced Vital Capacity (FVC) percent pred) or death over 52 weeks
- Proportion of patients with a relative decline from baseline in Forced Vital Capacity (FVC) percent pred of more than 10 percent at week 52
- Proportion of patients with a relative decline from baseline in Forced Vital Capacity (FVC) percent pred of more than 5 percent at week 52
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52 [Time Frame: 52 weeks]
  Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52

Acute Exacerbation of IPF

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a major event of IPF with an annual incidence between 5 and 10% and is responsible for the death of one third of IPF patients. When AE-IPF occurs, it is associated with poor survival with an overall mortality at 3 months upper of 50%. To date, no treatment has been proved to be effective in AE-IPF

Phase III Clinical Study of ART-123 for the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis: a Multicenter Randomized Placebo-controlled Double-blind Study to Assess the Efficacy and Safety of ART-12

- The purpose of this study is to assess the efficacy and safety of the intravenous drip infusion of ART-123 (a Recombinant human soluble thrombomodulin) in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF) in a multicenter, double-blind, randomized, placebo-controlled, parallel group comparison study, and to confirm its superiority over placebo

- This study is currently recruiting participants

- Study Start Date:May 2016
- Estimated Study Completion Date:March 2018

Primary Outcome Measures: Survival rate on Day 90

Secondary Outcome Measures:

- Overall survival [Time Frame: 180 days after the start of investigational product administration in the last subject]
- Survival time up to Day 90 [Time Frame: 90days]
- Coagulation tests [Time Frame: 4 days, 7 days, 15days, 28 days, 60 days, 90 days]

Cyclophosphamide Added to Corticosteroid in the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis: a Placebo-controlled Randomized Trial

The efficacy of cyclophosphamide (CYC) on survival has been suggested, mainly by retrospective series and needs to be confirmed.

Patients will be randomly assigned to receive Intravenous Cyclophosphamide (CYC), 600 mg/m² (adapted to age and renal function, maximal dose of 1.2 g) at Day 0, Day 15, M1, M2 or placebo in association to corticosteroids

This study is recruiting partecipants

Actual Study Start Date: December 2015Estimated Study Completion Date: December 2018Estimated Primary Completion Date: December 2018

(Final data collection date for primary outcome measure)

Primary Outcome Measures:

"Early" survival [Time Frame: 3 months]All cause of mortality at 3 months.

Secondary Outcome Measures:

- Overall Survival
- Respiratory disease-specific mortality
- Worsening dyspnea or Increase need of supplemental oxygen of more than 3l/min to obtained a SaO2 > 90% or decrease of PaO2 of more than 10 mmHg with the same rate of flow supplemental oxygen or Decrease FVC of more than 10% of predicted value or Decrease diffuse capacity for carbon monoxide (DLCO) of more than 15%
- Prognosis factors of AE-IPF [Time Frame: 3 months]PFTs results before AE-IPF
- Hemorrhagic cystitis (occurence of hematuria on urine dipstick and pelvic pain and/or dysuria should lead to cystoscopy)
- Number of Infectious disease

Chronic Hypersensivity Pneumonia

The Chronic Hypersensitivity Pneumonitis (HP), is a complex syndrome due to a exaggerated immune response caused by inhalation of foreign substances, such as molds, dusts, and organic particles, causing alveoli inflammation and in the chronic forms the disease has high rate of mortality, due to the big number of patients who develop progressive interstitial fibrosis and eventually they curse with respiratory insufficiency who cause the death of the patient

Actually HP has been treated with Prednisone and occasionally with Azathioprine, but unfortunately the treatment with these drugs have not an effective result to treat the interstitial fibrosis.

Pirfenidone for Chronic Hypersensitivity Pneumonitis Treatment

Pirfenidone has been studied over the world for the treatment of Idiophatic Pulmonary Fibrosis (IPF), disease who constitute the most aggressive of the fibrotic diseases of the lung.

Additionally Pirfenidone has been showed potential results in the treatment of fibrotic diseases in other organs, as Liver, Kidney, Hearth, etc. Pirfenidone has been described as a modulator of the fibrotic process due to his action over TGF-beta and MMP´s and also has into-inflammatory actions acting over TNF-alfa and IL-1 and IL-6.

Due to the positive results obtained with Pirfenidone in the treatment of IPF and other kind of organ fibrosis, the investigators propose to evaluate the addition of Pirfenidone to the treatment with Prednisone and Azathioprine in the treatment of patients with Pulmonary Fibrosis secondary to a Chronic Hypersensitivity Pneumonitis.

Patients will be randomly allocated in one of the three arms: placebo /Pirfenidone 1800 mg/ Pirfendone 1200 mg

The study is still recruiting patients

Inclusion Criteria:

- Chronic Hypersensitivity pneumonitis with recent diagnosis confirmed by HRT with or without biopsy

Primary Outcome Measures:

- Forced Vital Capacity (FVC)

Secondary Outcome Measures:

- High Resolution Tomography
- 6 minutes walk distance test
- San George Qty Score, SOBQ and EQ5D Quality Scores
- Pulmonary artery systolic pressure with echocardiogram
- Oxygen desaturation in exercise

LAM

Is LAM a tumor?

LAM pathogenic mechanisms mirror those of many forms of human cancer

- Mutations
- Inappropriate growth and survival
- Metastasis via blood and lymphatic circulation
- Infiltration
- Tissue destruction
- Sex steroid sensitivity

LAM has been included in PEComas

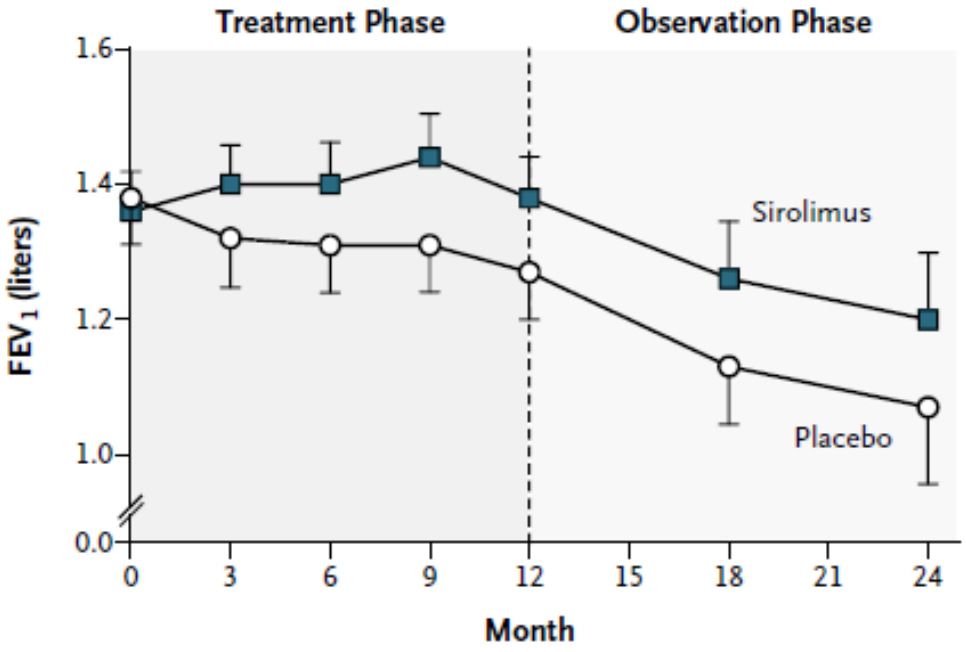
But the source of LAM cells is still unknown
(Uterus? Kidneys? Lymphatics?)

LAM cells show no atypia

Henske EP, McCormack FX AJRCCM 2012
Harari S et al, ERJ 2015

The MILES trial: a milestone

- Stabilization of lung function during the treatment period
- After discontinuation of sirolimus, the decline in lung function resumed and paralleled that in the placebo group



More common adverse effects:
Mouth ulcers, diarrhea, upper respiratory infections, hypercholesterolemia, acneiform rash

McCormack FX et al, NEJM 2011

Sirolimus: current indications

ATS/JRS Guidelines

- Patients with abnormal lung function

  Abnormal lung function: FEV1 less than 70% predicted

  Could elevated RV, reduced DLCO, and exercise induced desaturation been considered as criteria to start treatment?

- Patients whose funtion is declining

  Declining lung function? 90 mL/year?

- Problematic chylous effusions and lymphangioleiomiomas
- Angiomyolipomas?

McCormack FX et al, AJRCCM 2016

LAM treatment

ERS guidelines 2010

- Sirolimus only in clinical trials or on an individual basis
- Intramuscular progesterone may be trialled in patients with a rapid decline in lung function or symptoms
- Other hormonal treatments are not recommended

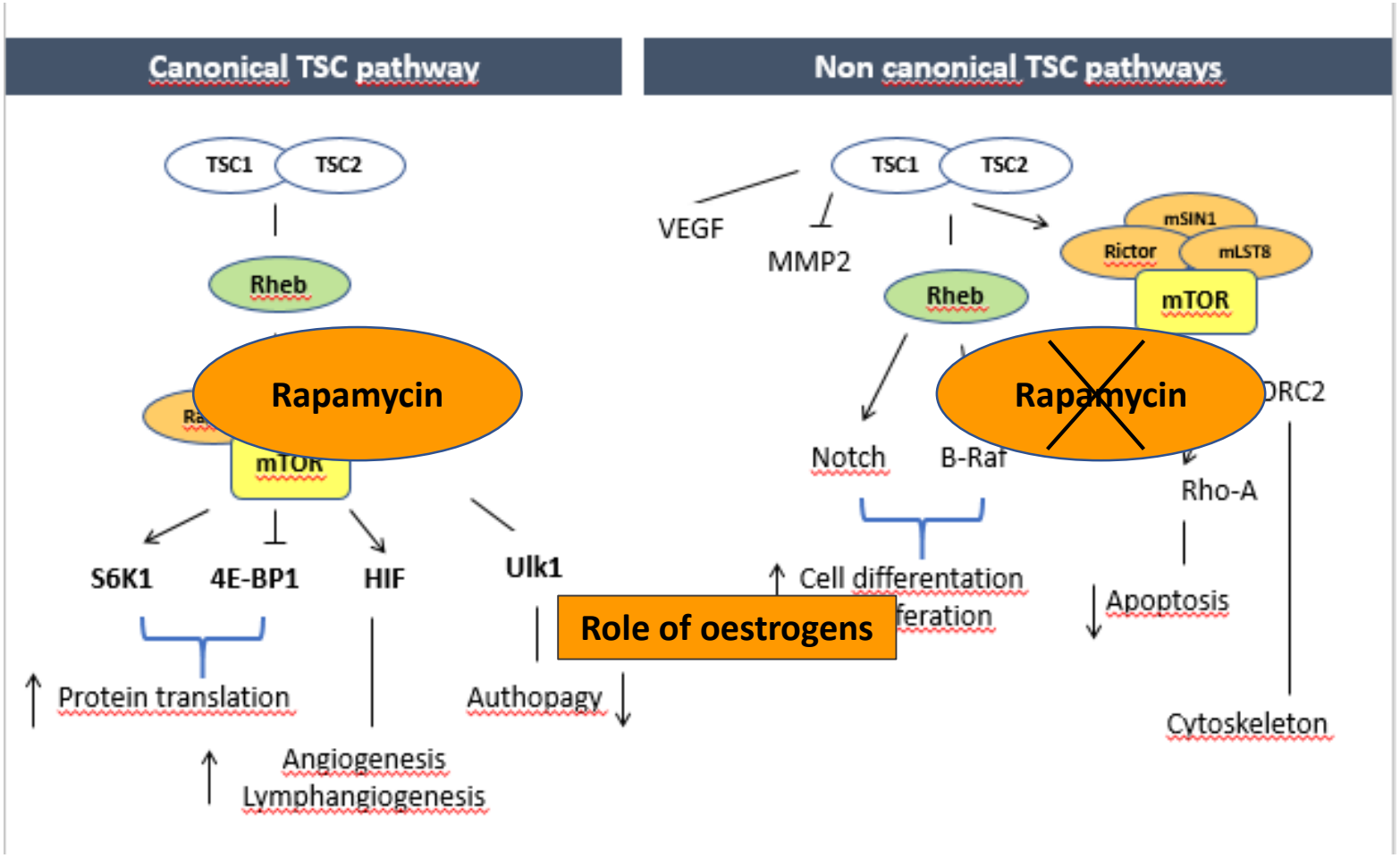
ATS/JRS guidelines 2016

- Sirolimus is recommended
- Hormonal therapy is not recommended
- Doxycycline is not recommended

Johnson SR et al, ERJ 2010
McCormack FX et al, AJRCCM 2016

- mTOR inhibitors are not curative: discontinuation of mTOR inhibitor therapy results in further decline in lung function or return of AMLs to pretherapy tumor size

- Observation of patients not responding or intolerant to mTOR inhibitors



Treatment: the future

- Combination of mTOR and Autophagy inhibition

A safety and tolerability trial of Sirolimus and hydroxychloroquine (200 and 400mg)

24 weeks treatment phase followed by 24 weeks observation phase
Most common adverse events: mucositis, headache, diarrhea
No drug-related SAEs

El-Chemaly S et al, Chest 2017

- Kinase inhibitors

A trial of Saracatinib (SLAM-2), an inhibitor of Src, is ongoing
Involved mechanism: proliferation, motility

- Combination of mTOR inhibition and statins

A retrospective study did not show that simvastatin enhances the beneficial effects of sirolimus therapy

Taveira da Silva et al, Chest 2015

A trial of mTOR inhibitors and simvastin is ongoing

- Estrogen antagonism (a trial of letrozole is waiting for results)
- Inhibition of MMPs and other proteases
- Anti-VEGF therapies

A pilot study of nintedanib for lymphangioleiomyomatosis

Rationale

- Nintedanib was shown to inhibit PDGFR phosphorylation and subsequent protein kinase B (Akt) and extracellular signal-regulated kinase (ERK) 1/2 phosphorylation in lung tissue from mice. PDGFR β is present and active in human and murine TSC lesions

- Akt and ERK 2 can both phosphorylate tuberin resulting in inactivation of hamartin–tuberin complex and consequent activation of mTOR.

- The inhibition of VEGF, PDGF and FGF signaling pathways reduces tumor angiogenesis in lung (16). As angiogenesis and lymphangiogenesis are mechanisms involved in dissemination of LAM cells, potential inhibition of angiogenesis by nintedanib may contribute to prevent disease progression in LAM

A pilot study of nintedanib for lymphangioleiomyomatosis

A non-randomized, efficacy, safety, and tolerability trial of nintedanib in sporadic and TSC-associated LAM: a phase II study

Objective To demonstrate the efficacy and safety of nintedanib in the treatment of LAM patients with progressive disease

Study design
Single Group Assignment
Open Label
30 patients (10 patients enrolled already)
12 months treatment period
12 months follow-up

Inclusion criteria:

- Adults with sporadic or TSC associated LAM, classified as ‘‘definite’’ by the ERS criteria or serum VEGFD level >/= 800 pg/ml
- Evidence of a 10% deterioration in FEV1 and /or loss of 80 ml of FEV1 or more in the last year (post bronchodilator) or patients with proven side effects and/or toxicities/ contraindications to sirolimus therapy

A pilot study of nintedanib for lymphangioleiomyomatosis

Primary endpoint:

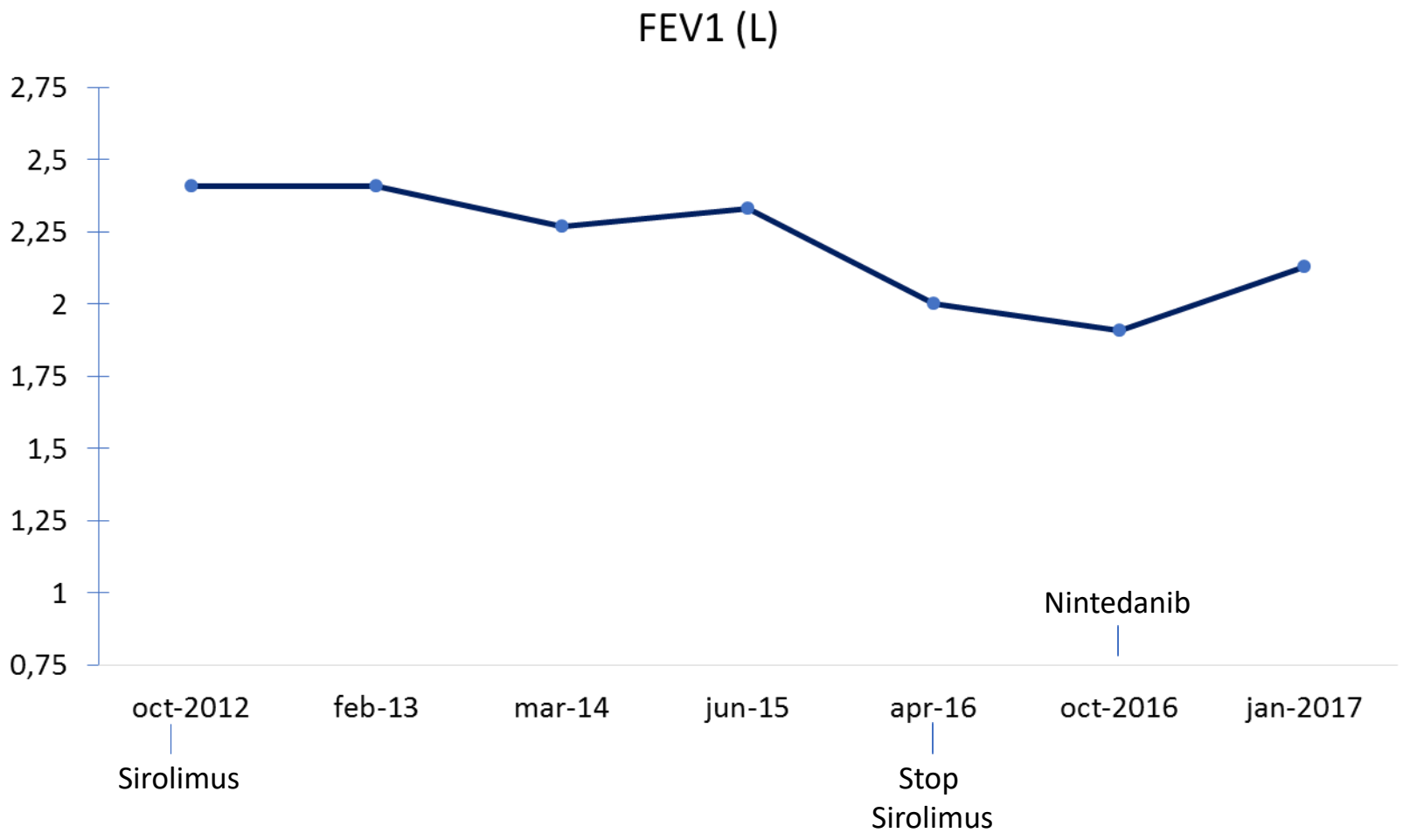
the FEV_1 response, which will be assessed as the change in FEV_1 (FEV_1 slope) in milliliters per month

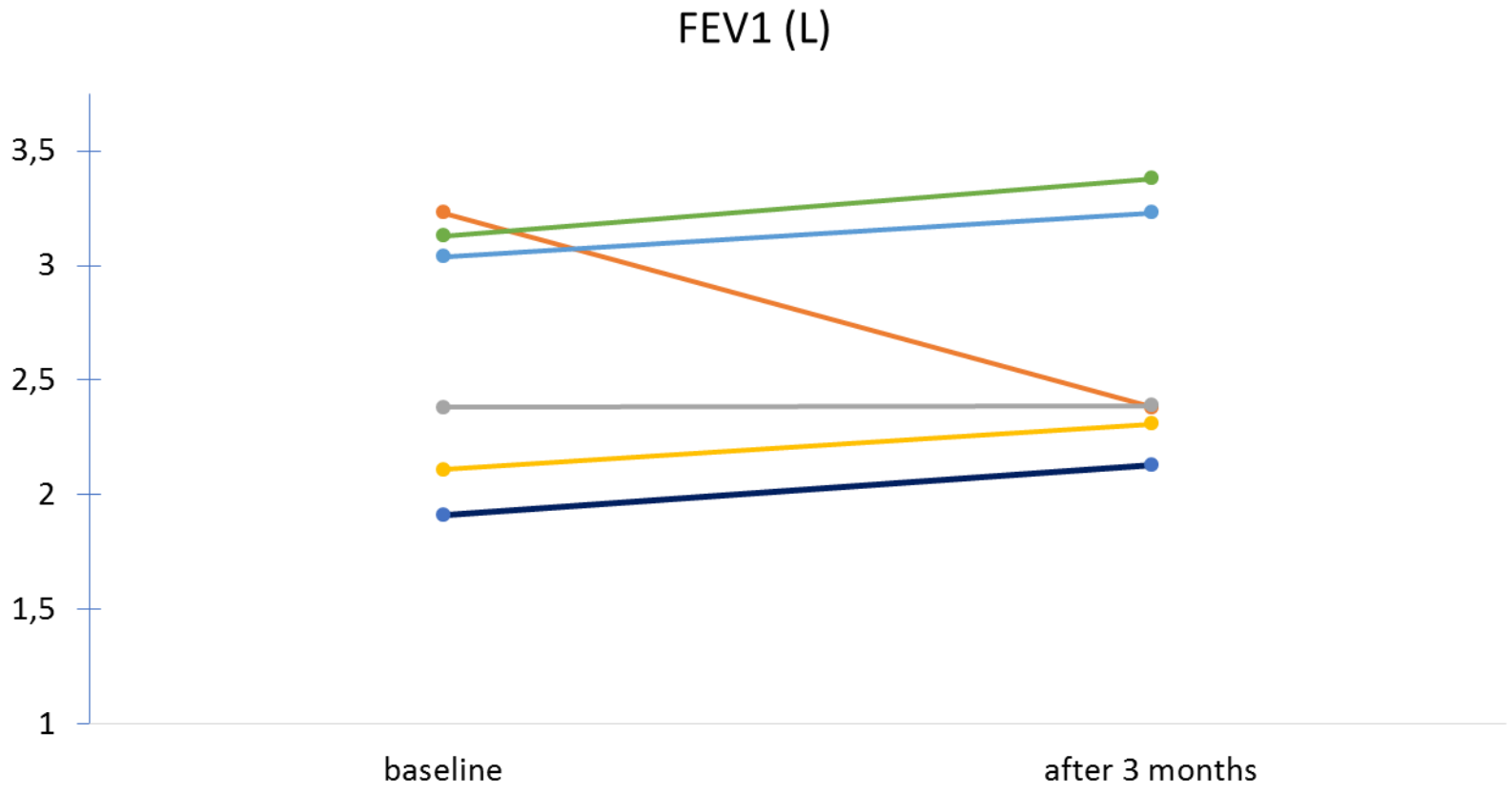
Secondary endpoints:

- The proportion of patients achieving a stabilization of the lung function
- Rate of decline of FVC over the course of the study
- Rate of decline Dlco
- Reduction of size of angiomyolipomas
- Change of VEGFD levels
- Quality of life
- Safety and Tolerability

A 31 years old woman with a biopsy proven LAM started sirolimus in october 2012

After an initial stabilization with therapy, FEV1 started declining





Post-bronchodilator FEV 1 at baseline and after 3 months of treatment in 6 patients