LAM: what's new after ERS guidelines

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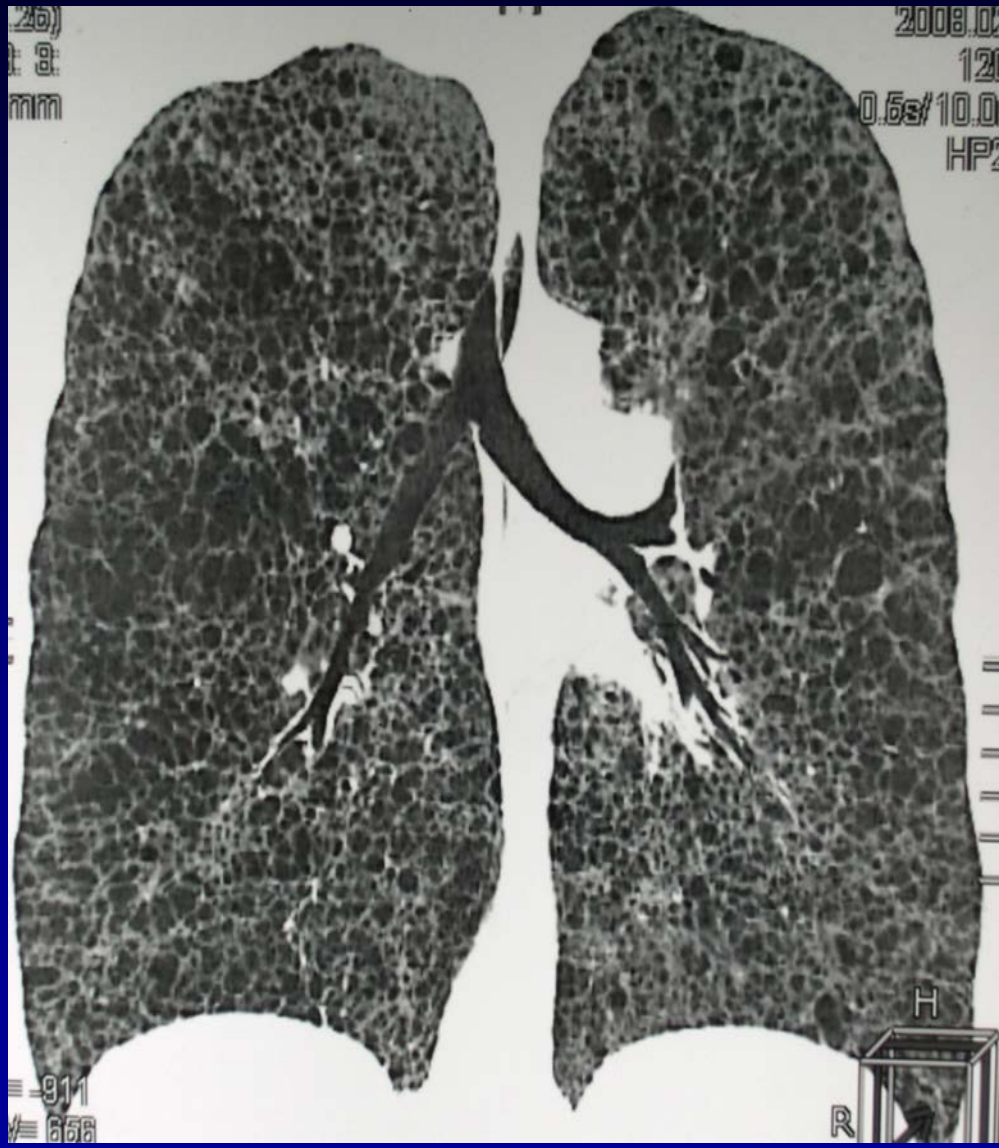
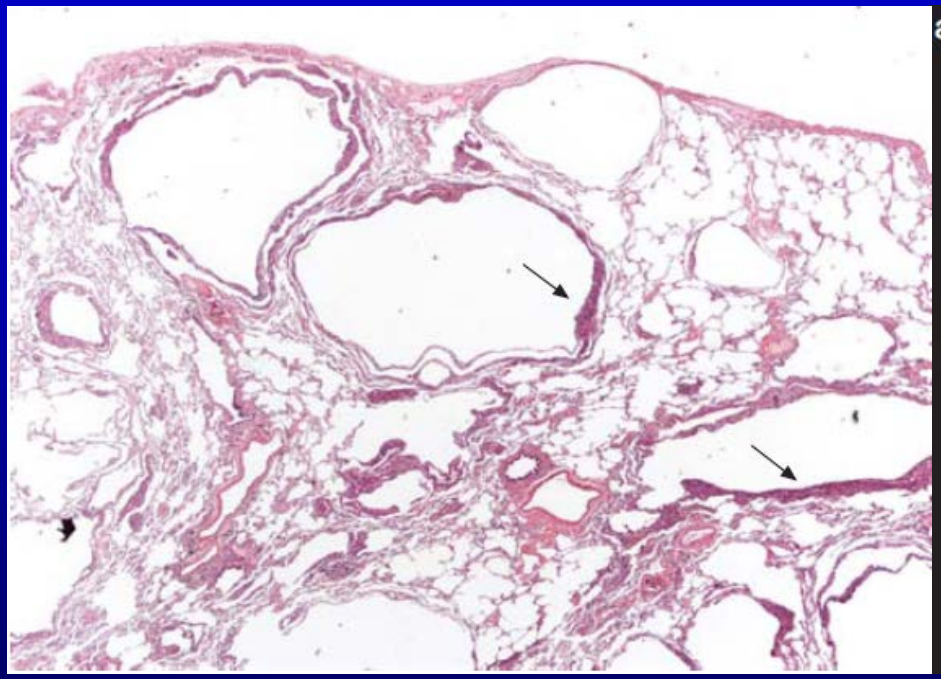
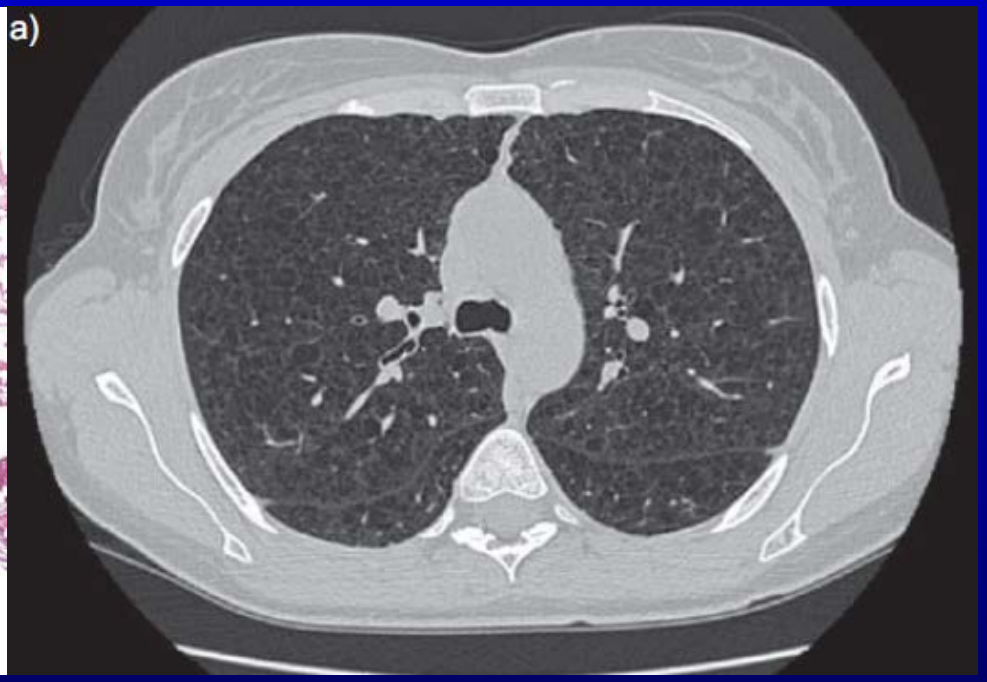


25th Panhellenic Thoracic Congress Athen
26th June 2016

Lymphangioleiomyomatosis (LAM)





Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder affecting predominantly young females in their reproductive years. It is characterised by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumours(e.g. angiomyolipomas)

Diagnosis – ERS guidelines

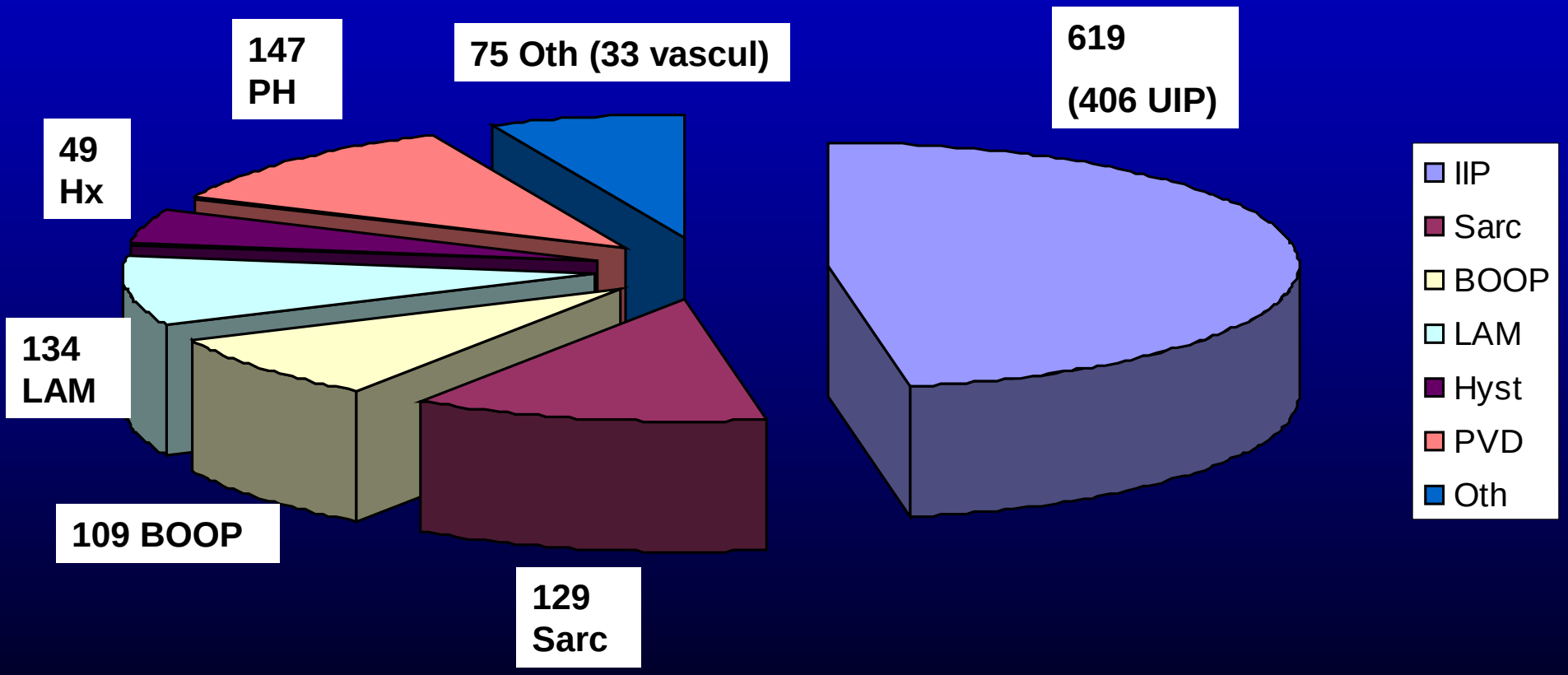
Definite LAM	characteristic lung HRCT + any of the following - angiomyolipoma - thoracic or abdominal chylous effusion, - lymphangioleiomyoma - biopsy-proven lymph node involved by LAM - TSC
Probable LAM	characteristic lung HRTC + compatible clinical history compatible lung HRTC + angiomyolipoma or chylous effusion
Possible LAM	characteristic or compatible lung HRTC alone

Characteristic HRCT: multiple (more than 10) thin-walled round well-defined air-filled cysts with no other significant pulmonary involvement (with the exception of MMPH in TSC)

Compatible HRTC: few (more than two and fewer than 10) typical cysts

Johnson SR et al, ERJ 2010

Rare Lung Diseases
Ospedale San Giuseppe Experience (2001- 2016)
Tot. 1262 pts



Biomarkers

Serum VEGF-D

Vascular endothelial growth factors C (VEGF-C) and D (VEGF-D) are ligands for the lymphatic growth factor receptor VEGFR-2 and VEGFR-3/Flt-4 that induce formation of lymphatics and promote the spread of tumor cells to lymph nodes in mouse models and in humans.

Serum levels of VEGF-D, but not VEGF-C, are elevated in patients with S-LAM in comparison with normal controls.

Biomarkers: VEGF-D

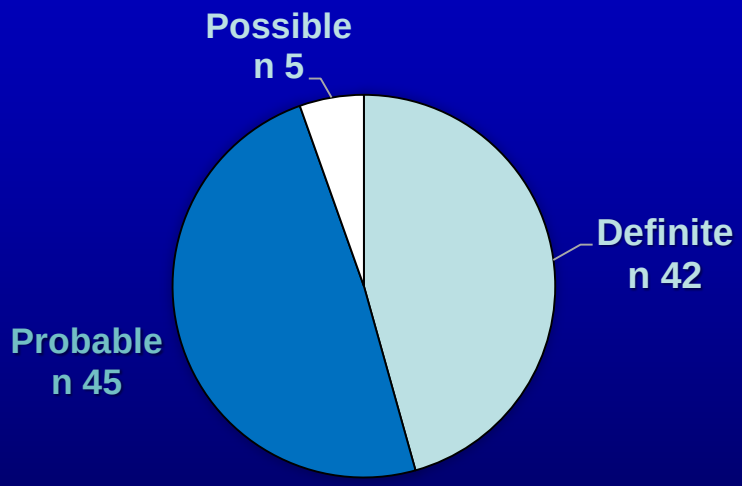
2006	Seyama K et al.	VEGF-D is increased in serum of patients with LAM
2008	Young et al.	VEGF-D serum levels are higher in LAM than in similar cystic or chylous lung diseases
2010	Young et al.	VEGF-D level higher than 800 pg/mL in a woman with typical changes on high-resolution CT scan is diagnostically specific for LAM, and identifies LAM in women with TSC
2010	**VEGF-D serum level has been used as diagnostic criteria in MILES trial**	
	VEGF-D serum level has been used as diagnostic criteria in everolimus trial	
2013	**The results of an analysis of data from the MILES trial confirm that VEGF-D is a useful biomarker that correlates with disease severity and treatment response** (Young LR, Lancet Respir Med 2013)	

VEGF-D

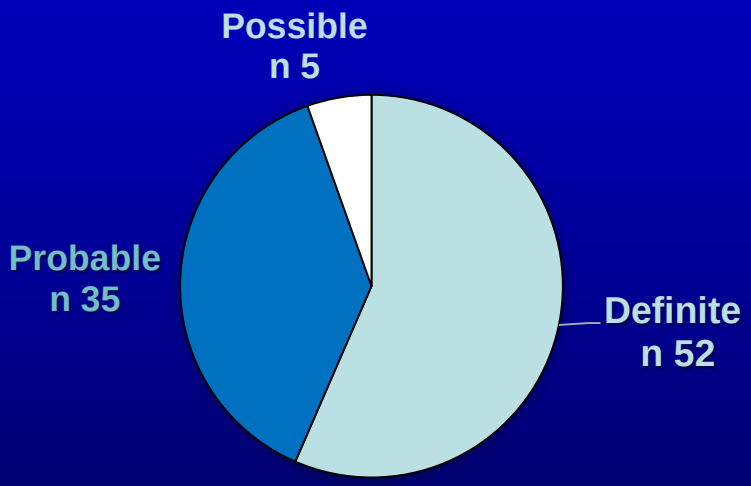
Ospedale San Giuseppe experience

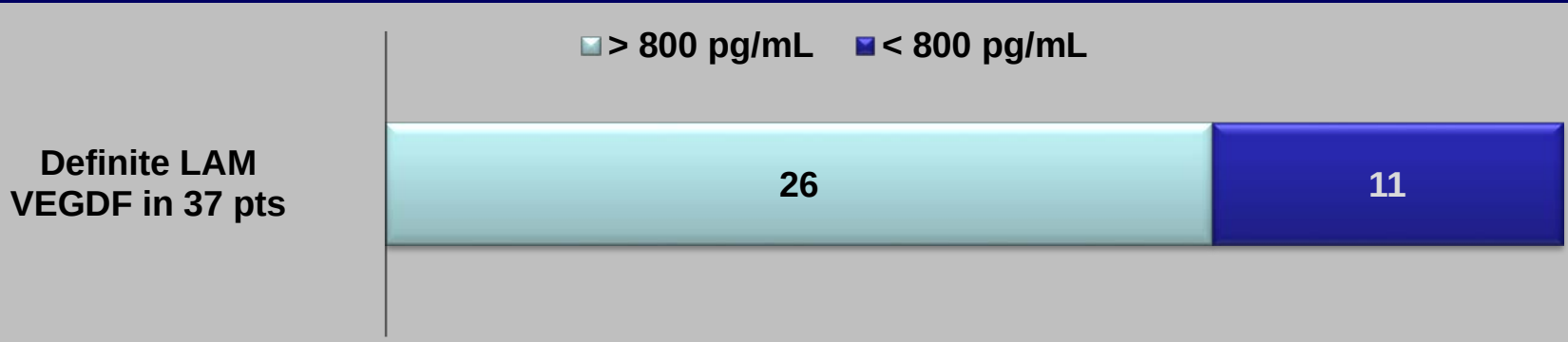
134 patients, 42 with biopsy

GUIDELINES CRITERIA



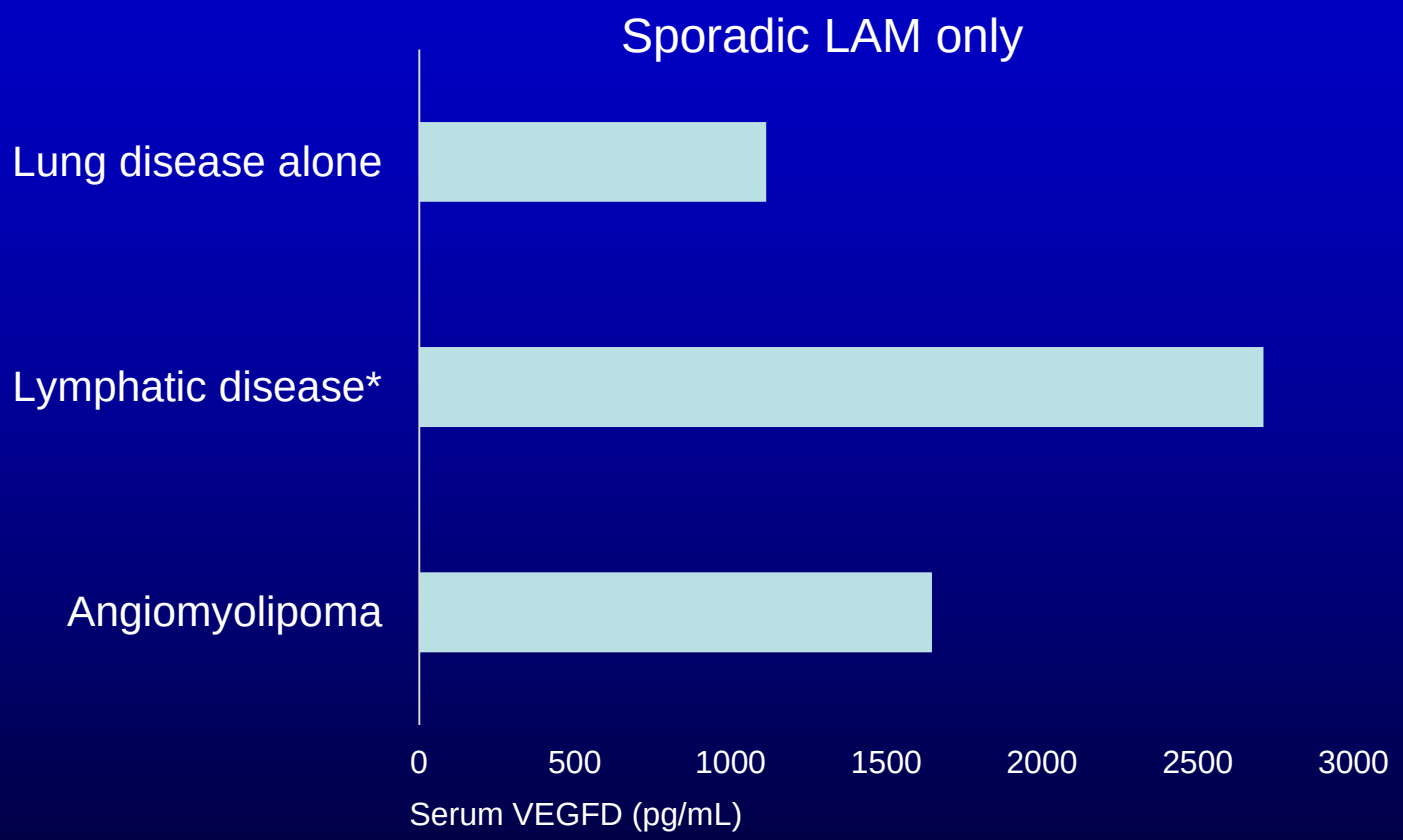
BEYOND GUIDELINES (VEGFD)





VEGF-D

Ospedale San Giuseppe experience



* Chilous effusions, lymph nodes, lymphangioleiomyomas

TSC loss of herozygosis (LOH) in cells from body fluids

Molecular and genetic analysis of disseminated neoplastic cells in lymphangioleiomyomatosis

Denise M. Crooks*, Gustavo Pacheco-Rodriguez*, Rosamma M. DeCastro*, J. Philip McCoy, Jr.†, Ji-an Wang‡, Fumiyuki Kumaki*, Thomas Darling‡, and Joel Moss*§

Crooks et al, PNAS 2004

Sirolimus Decreases Circulating Lymphangioleiomyomatosis Cells in Patients With Lymphangioleiomyomatosis

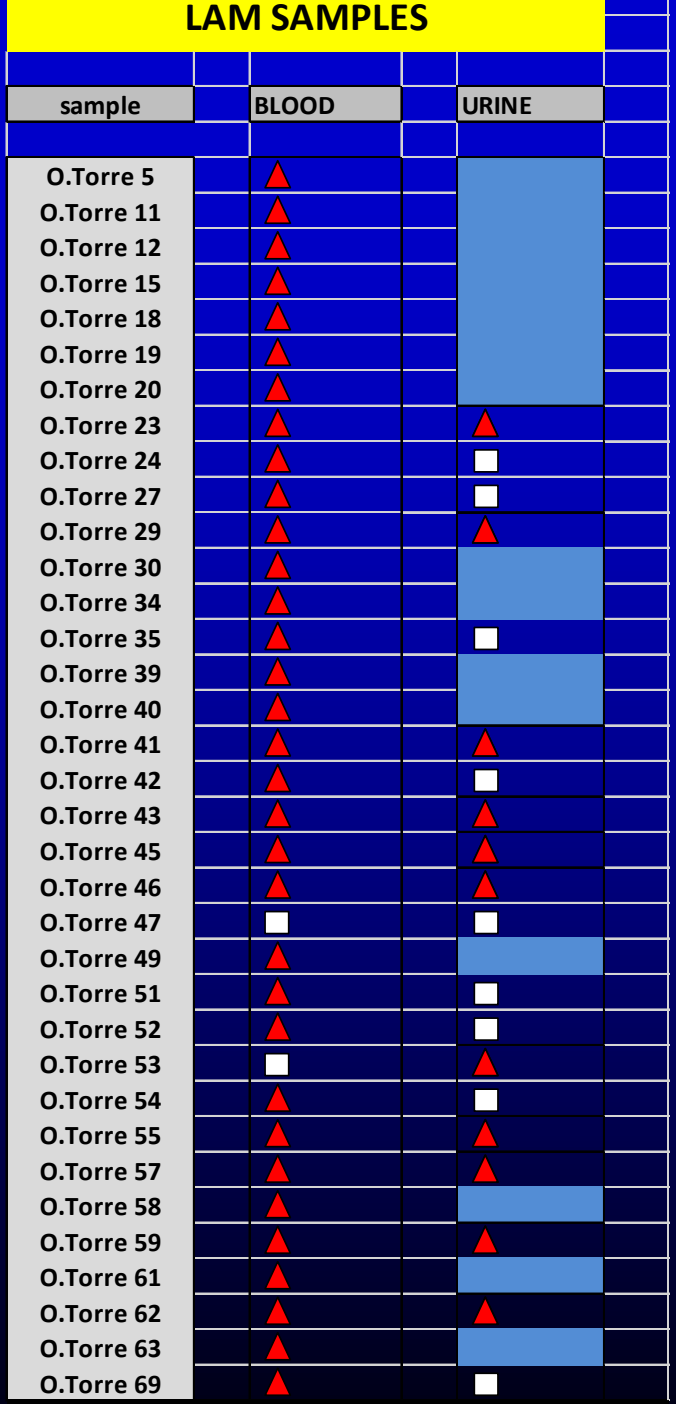
Xiong Cai, PhD; Gustavo Pacheco-Rodriguez, PhD; Mary Haughey, RN, BSN; Leigh Samsel, MS; Suowen Xu, PhD; Hai-Ping Wu, BS; J. Philip McCoy, PhD;

Cai et al, Chest 2014

LAM cells, identified by TSC2 LOH, have been isolated from the blood and other body fluids of LAM patients and they are no longer detectable after treatment with sirolimus

- Link between primary LAM lesions and the process that facilitates dispersion of cells with metastatic potential

- The search for circulating LAM cells in blood or other fluid may identify patients at risk of disease progression or spread and/or the response to potential therapy.



LOH

Ospedale San Giuseppe experience

▲ LOH

□ ROH

Blood (CD45-/glicoforine-, CD45-/glicoforine+): 94% (33/35)

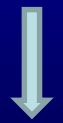
Urine (CD44+/CD9+, CD44+/CD9-): 55%(11/20)

Clinical manifestations

Clinical features

Early clinical findings about LAM were based on small case reports

Clinical papers based on larger numbers of patients drew a new clinical picture



Different clinical phenotypes

Clinical phenotypes

Worse prognosis: dyspnea at presentation (shorter survival)
weight loss (shorter survival)
supplemental oxygen therapy (shorter survival)
reversible obstruction (Faster decline in lung function)
higher VEGF-D (Faster decline in lung function)

Better prognosis: pneumothorax at presentation (longer survival)
older age (Faster decline in of lung function, longer survival)
higher FEV1, DLCO at diagnosis
(Faster decline in lung function)

Taveira–Dasilva AM, Chest 2004
Hayashida M, Repirology 2013
Oprescu N, Lung 2013

Clinical phenotypes

Ospedale San Giuseppe experience 1999-2016

Tot: 134 patients
27 deceased (25 before 2011)

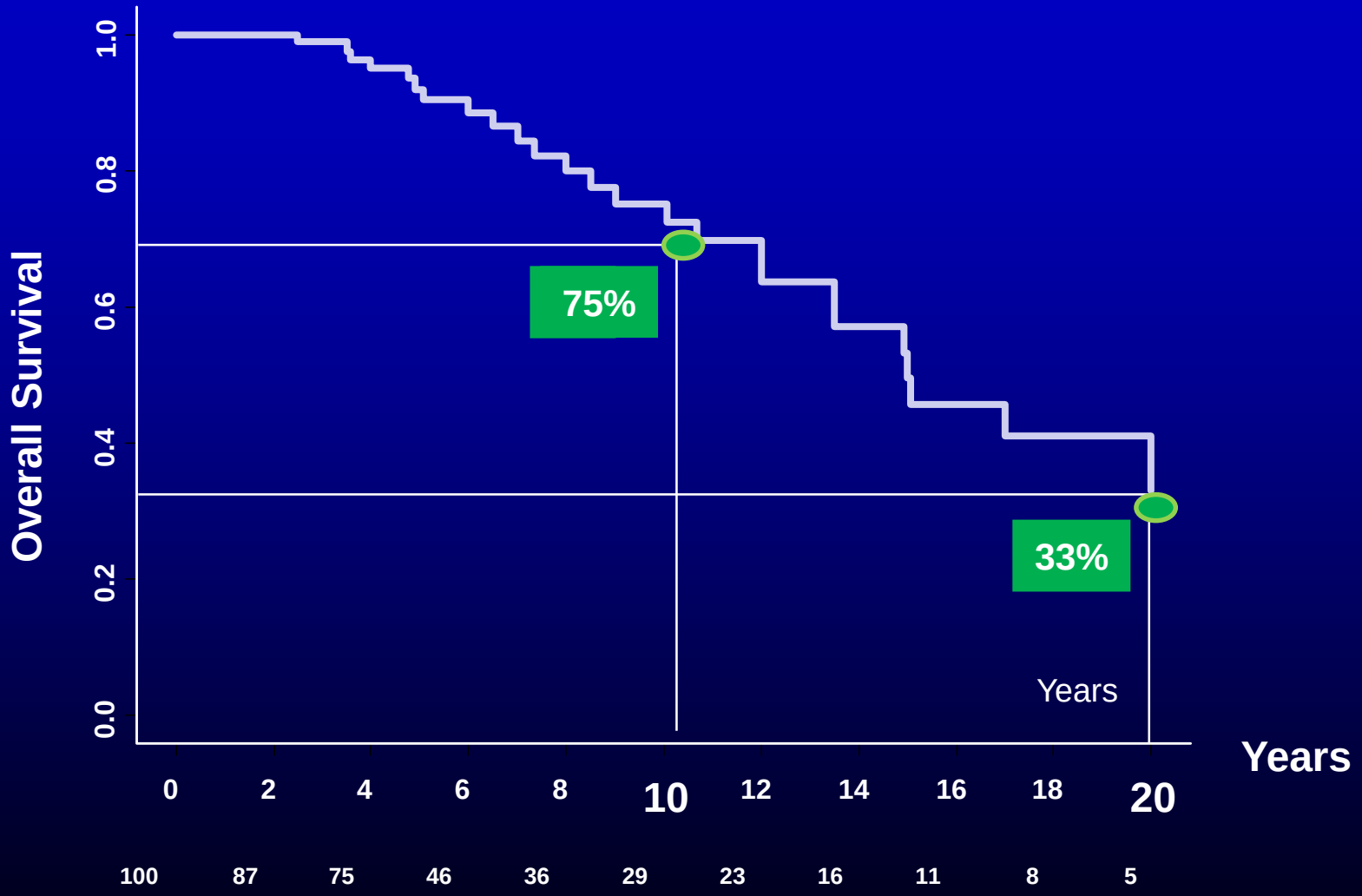
TSC: 24 patients

AML: 45 patients

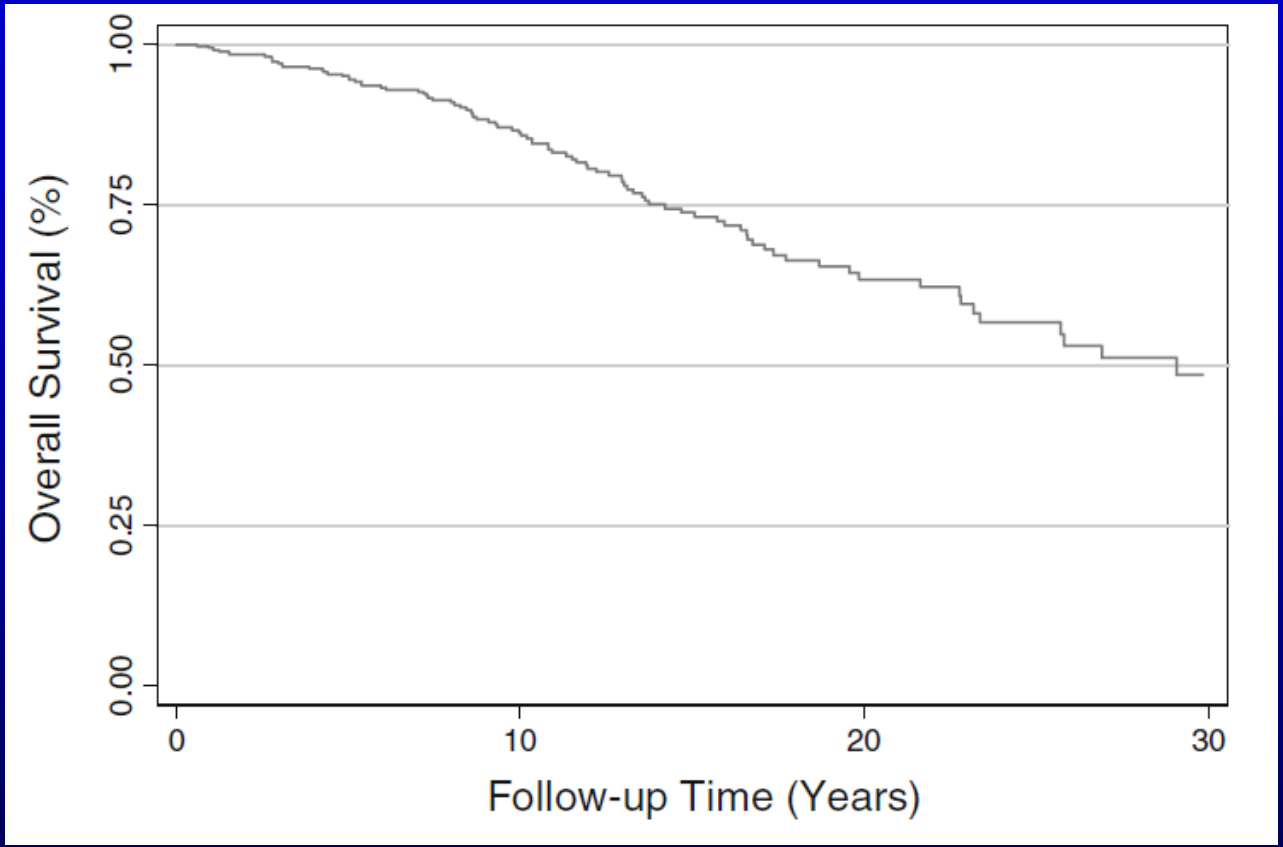
Lymphatic manifestation (including lymphangioleiomyomas) : 23 patients

Overall survival in 100 patients

Ospedale San Giuseppe experience 1999-2014



Survival



The median transplant-free survival for the overall cohort (n = 410) was 29 years from the time of symptoms onset

The estimated 10-year transplant-free survival was 86 %

Oprescu N, Lung 2013

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

But the source of LAM cells is still unknown

(Uterus? Angiomyolipomas? Lymphatics?)

LAM cells show little evidence of proliferation, no atypia

Henske1 EP and McCormack FX, J Clin Invest 2012
McCormack FX, et al. AJRCCM 2012

Treatment

Treatment

The past: hormonal treatment

- ✓ Oophorectomy
- ✓ Anti-estrogen therapy

Controversial effects
No objective evidence of improvement

- ✓ Progesterone

Case reports
Retrospective studies

- ✓ Gonadotrophin-releasing hormone (GnRH) analogues

Case reports
Retrospective studies
A prospective study showing no effects on lung function

Taveira–Dasilva AM, Chest 2004
Harari S, Chest 2008

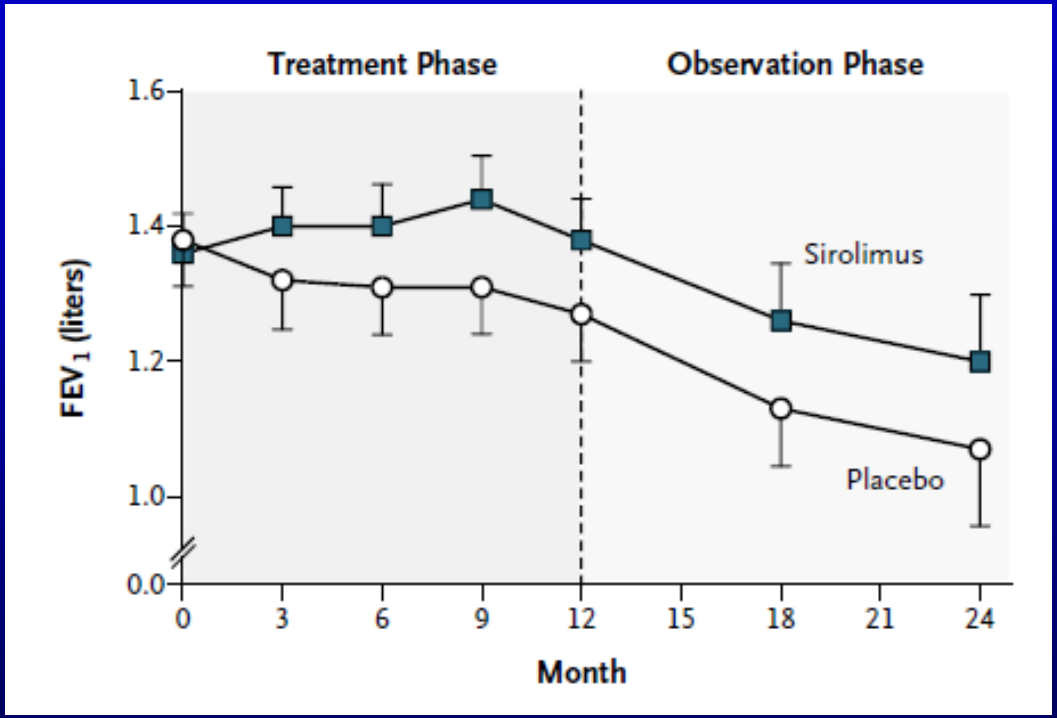
Treatment

mTOR inhibitors

2011	**MILES** (Sirolimus)	Randomised, double-blind, placebo-controlled	Efficacy and safety for sirolimus in LAM
2011	**TESSTAL** (Sirolimus)	Non-randomized, open label trial	Efficacy and Safety rapy for renal angiomyolipmoas in TSC-LAM and S-LAM
2013	**EXIST-1** (Everolimus)	Randomised, double-blind, placebo-controlled	Efficacy and safety in subependymal giant cell astrocytomas
2013	**EXIST -2** (Everolimus)	Randomised, double-blind, placebo-controlled	Angiomyolipoma response in TSC or S-LAM
2015	**RAD001X2201** (Everolimus)	Open-label, within-patient multiple dose escalation in LAM	Efficacy and safety for everolimus in LAM

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, NEJM 2011

The MILES trial: open issues

Patients with pleural effusion were excluded because of the potential effects on pulmonary function

- What about patients with chylous effusions and lymphangioleiomyomas?

MILES trial treatment period was 12 months

Decline of lung function resumes after treatment discontinuation

- What about long-term therapy?

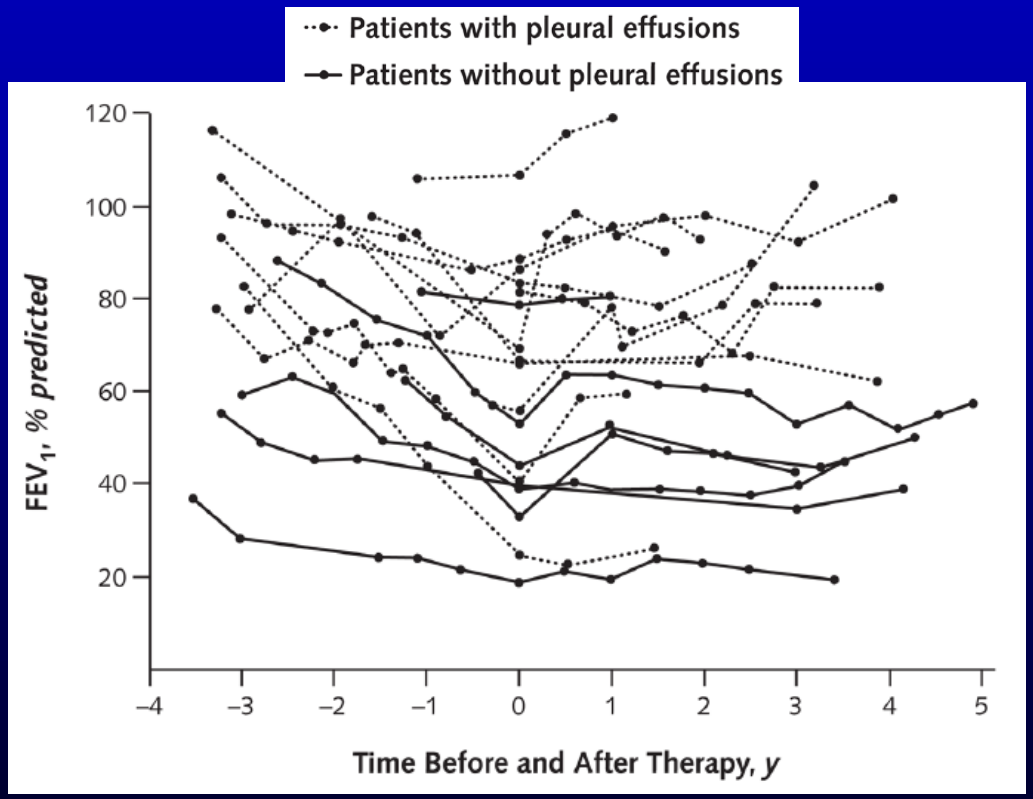
In MILES trial serum levels of sirolimus were mantained between 5 and 15 ng/mL

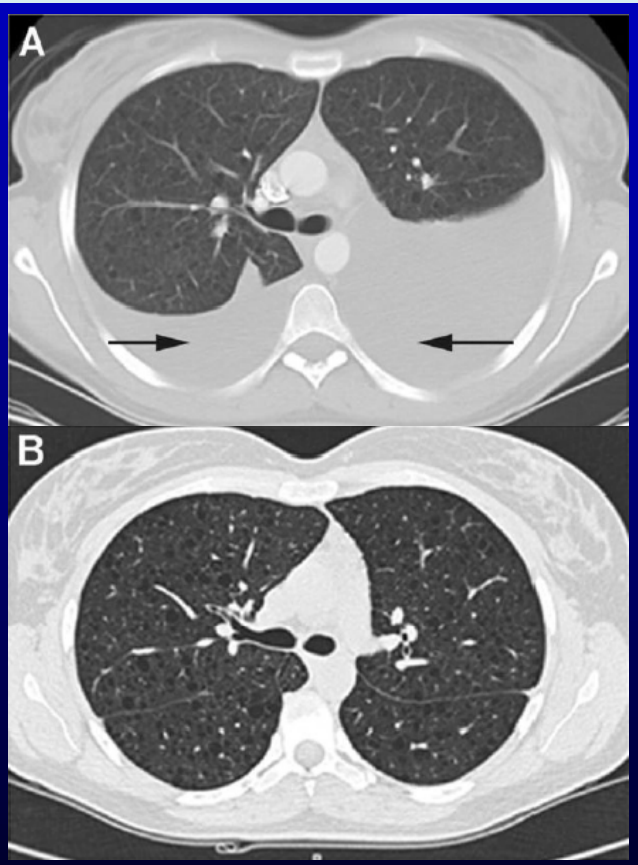
- What about low dose therapy?

- What about non responders, side effects?

Sirolimus: effect on lymphatic disease

An observational study about lung function and the size of chylous effusions and lymphangioleiomyomas before and during sirolimus therapy





Taveira-Dasilva AM, Ann Intern Med. 2011

Sirolimus: long term therapy

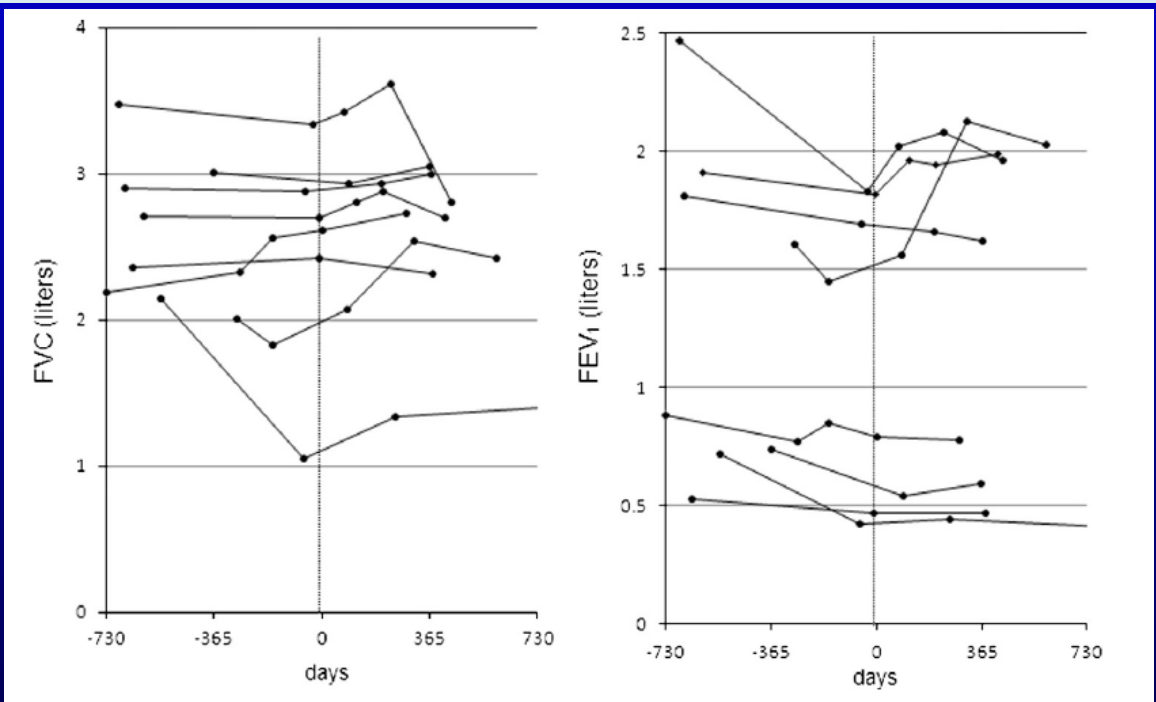
An observational study about sustained effects of Sirolimus on lung function and cystic lung lesions

- A cohort of 38 patients, including patients with lymphatic involvement
- Treatment with sirolimus for a period of about 3.5 years stabilized lung function (decline in FEV1 and DLCO), and changes in lung volume occupied by cysts
- In a subgroup of 12 patients followed for approximately 5 years, the study showed both a reduction in functional decline and changes in cysts
- The prevalence of adverse events associated with sirolimus was high, however most patients were able to continue therapy with only brief interruptions

Yao J, AJRCCM 2014

Sirolimus: low dose therapy

A retrospective, observational study of 15 pts who underwent sirolimus therapy for more than 6 months with serum levels< 5 ng/mL



- Improved annual rates of change in FVC and FEV1 in the 9 patients who were free from chylous effusion
- Chylothorax resolution within 1−5 months of treatment in 6 of 7 cases

Ando K, Respir Invest 2013

Sirolimus: current indications

- Patients with abnormal lung function
- Asymptomatic patients who are declining rapidly
- Symptomatic patients
- Problematic chylous effusions and lymphangioleiomyomas

Everolimus - Study Design

Open-label, within-patient multiple dose escalation

- Everolimus treatment was associated with stability of FVC and improvement in FEV1, relative to baseline
- A trend toward improvement in exercise capacity, with a 47-m mean increase in 6-MWD was also observed
- The adverse event profile of everolimus in our study appears broadly similar to that of sirolimus in the MILES study
  - Stomatitis and headache were the most common adverse events. Most adverse events were experienced at the highest dose level.
  - Five patients withdrew from the study due to six nonserious adverse events, all while on the 10-mg dose

Goldberg HJ, Harari S et al, ERJ 2015

mTOR inhibitors

Ospedale San Giuseppe Experience 1999-2016

54 pts treated with Sirolimus

- 7 pts lost at follow-up
- 2 pts deceased
- 3 pts unable to perform PFTs
- 5 pts < 1 year follow-up

37 pts with > 1 year follow

- mean FEV1 decrease 119 ml/year in pre-treatment period
- mean FEV1 increase 62 ml/year in treatment period

4 pts showed declining lung function after two year treatment period

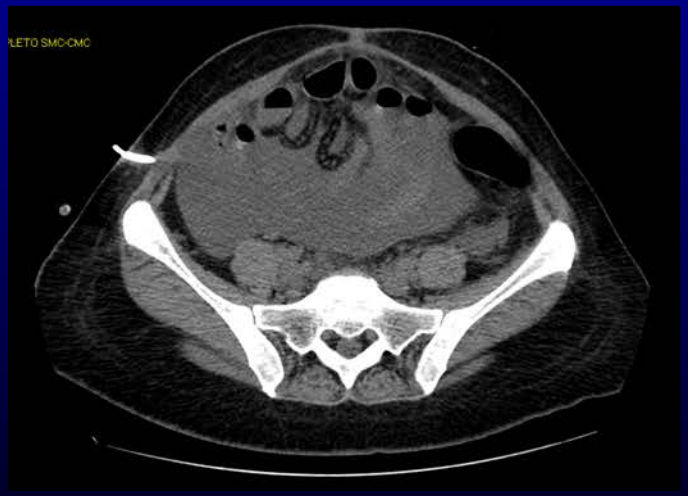
4 pts discontinued the therapy because of adverse events

LAM beyond guidelines

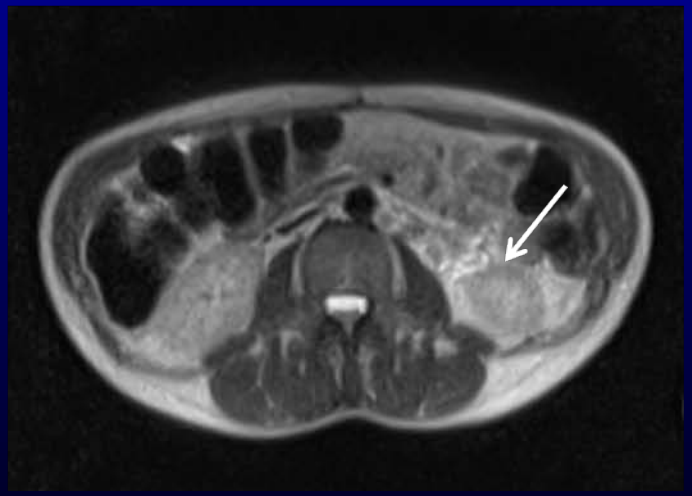
A case report

A 39 years old woman with mild lung disease, a large abdominal lymphangioleiomiomas, and recurrent chylous ascites after every attempt of oral feeding

Before sirolimus



After 3 months of sirolimus (2 mg die)



Harari S. et al, Chest in press

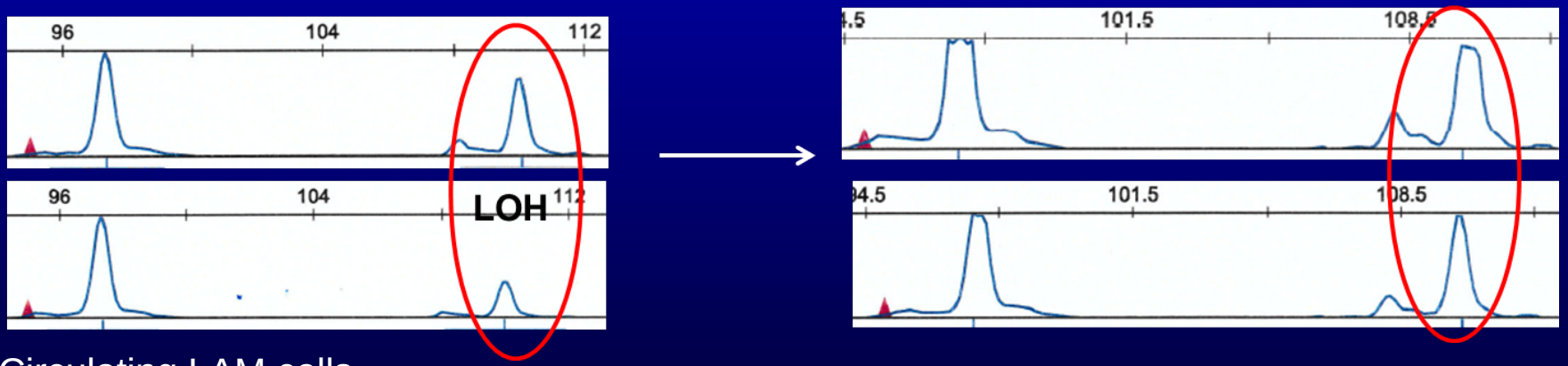
LAM beyond guidelines

A case report

BIOMARKERS

Before sirolimus **After 3 months of sirolimus**

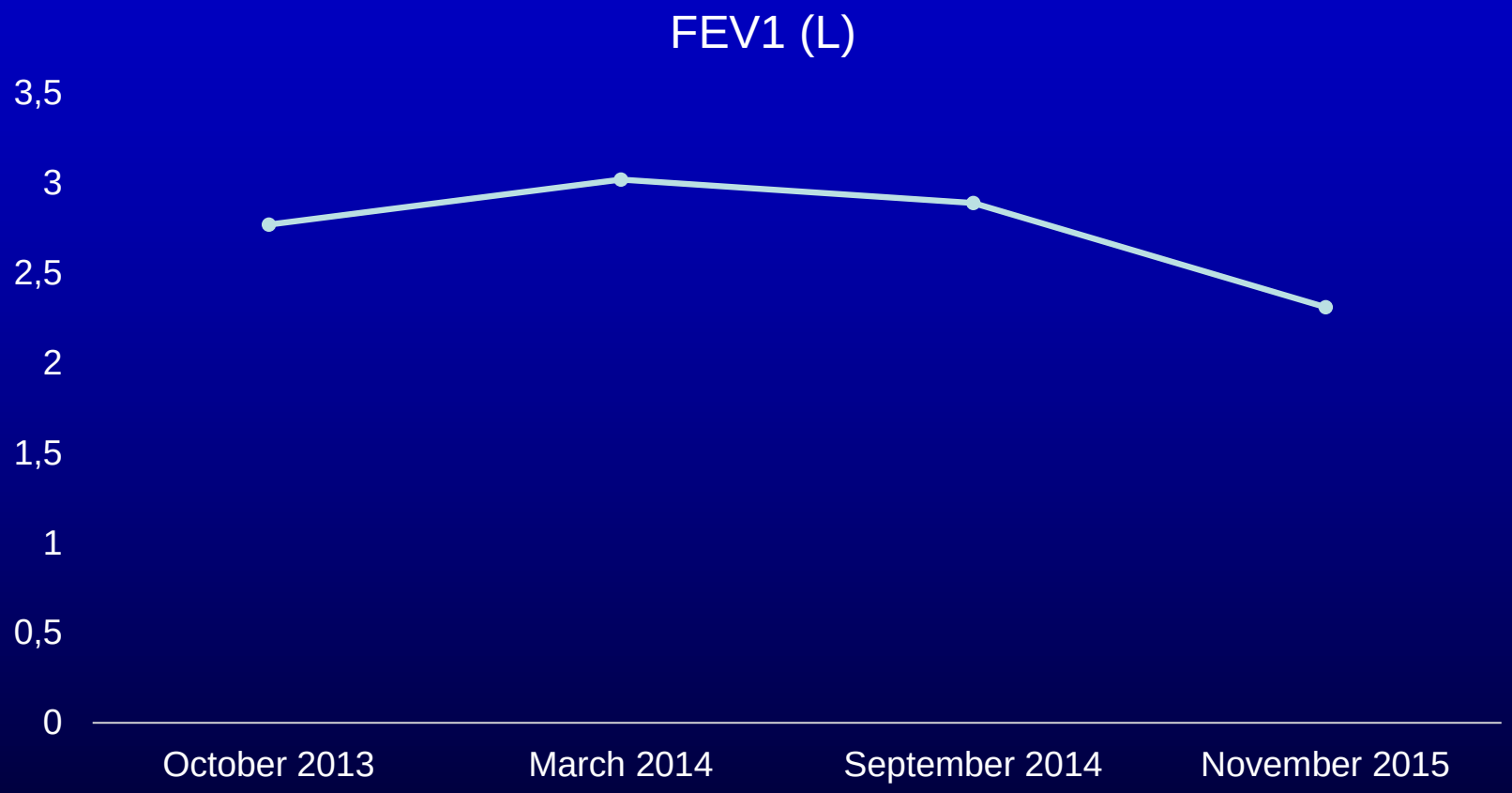
Serum VEGF-D: 4490 pg/mL ⟶ 1 558 pg/mL



Circulating LAM cells

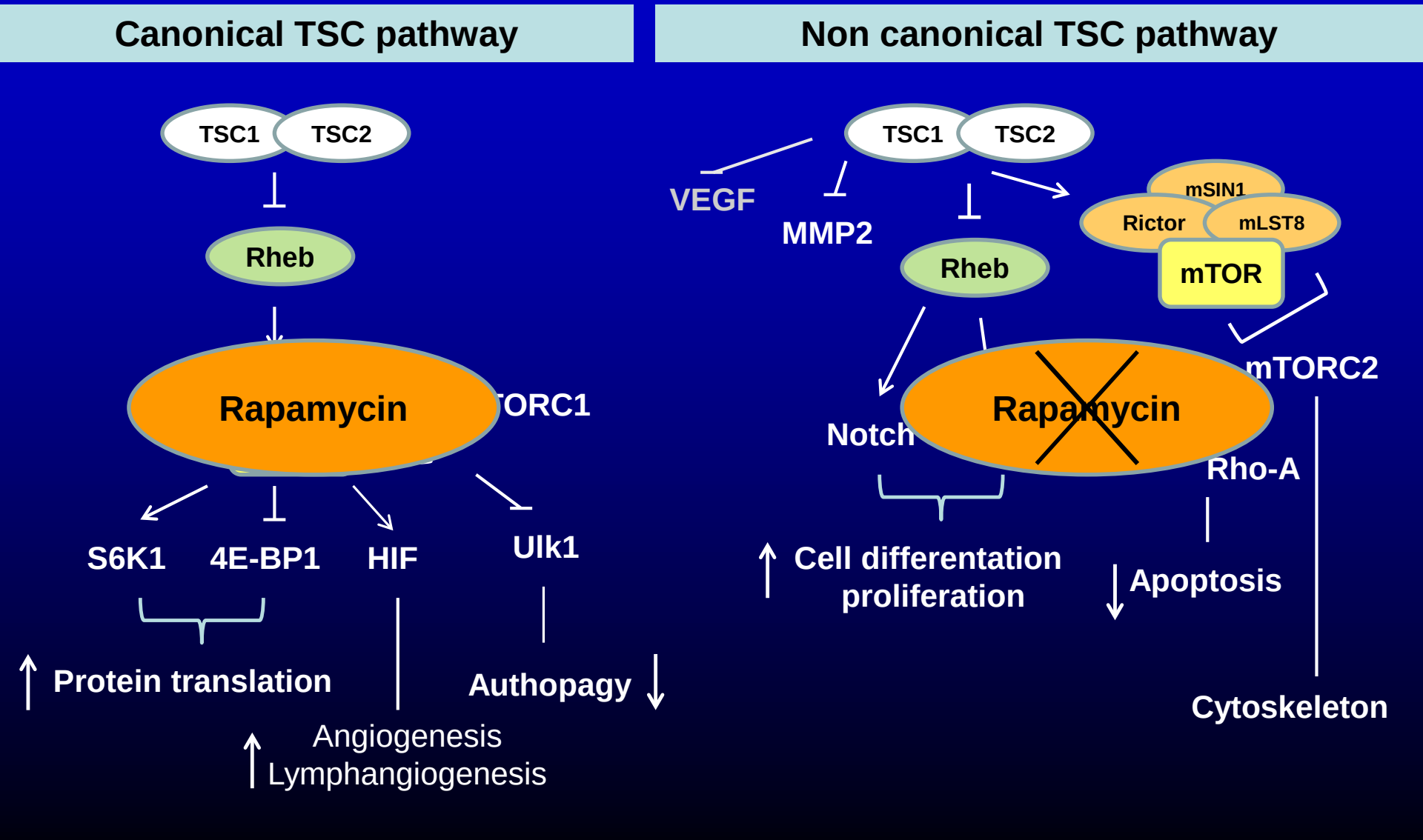
Harari S et al, Chest in press

A 33 years old woman with a biopsy proven LAM started sirolimus in October 2013 for declining lung function (200ml of FEV1 in 6 months)

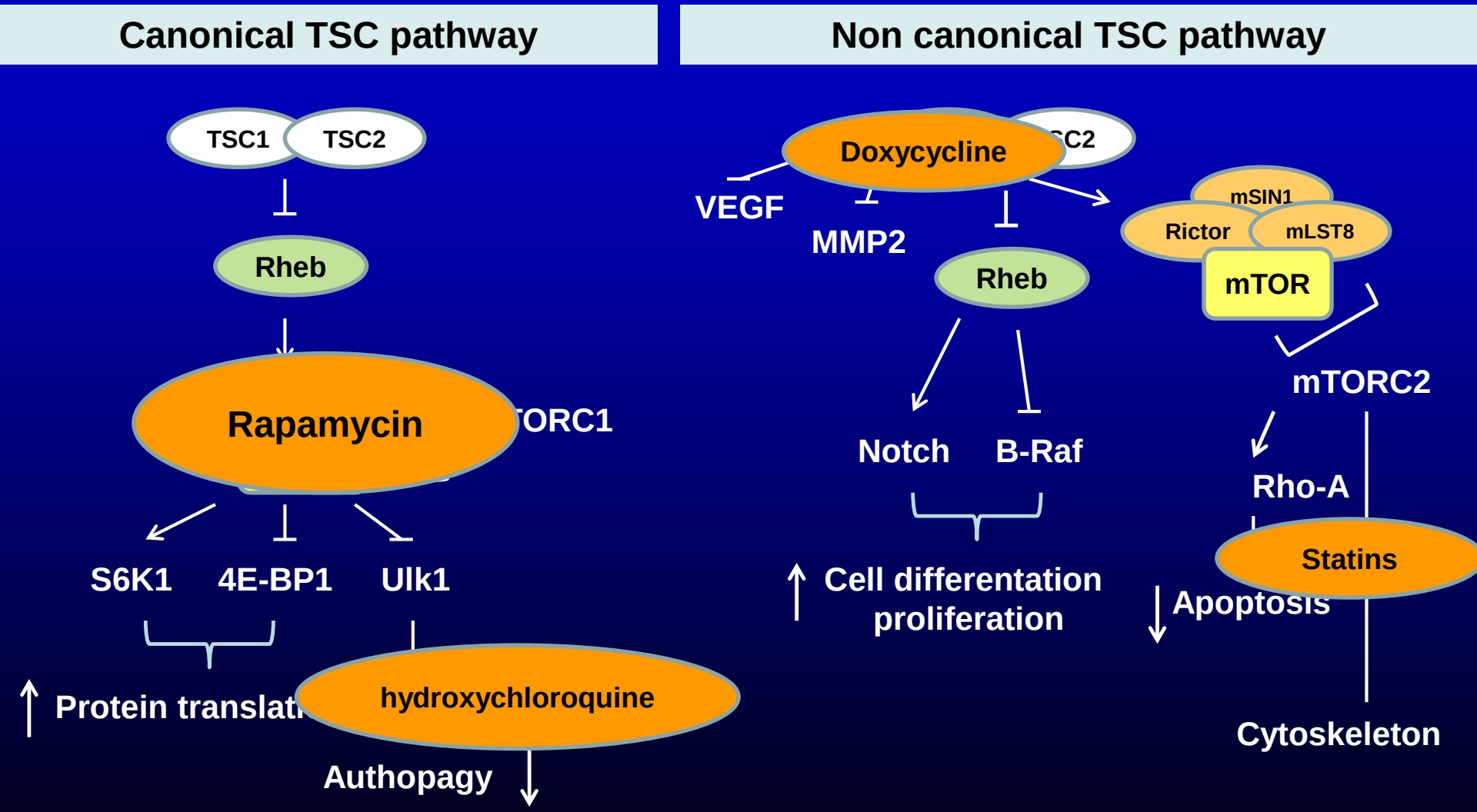


After an initial stabilization with therapy, FEV1 started declining

Pathogenesis and therapy



Treatment


Canonical TSC pathway
Non canonical TSC pathway
TSC1
TSC2
Rheb
Rapamycin
TORC1
S6K1
4E-BP1
Ulk1
Protein translati
hydroxychloroquine
Authopagy
Doxycycline
VEGF
MMP2
Rheb
Notch
B-Raf
Cell differentation
proliferation
mSIN1
Rictor
mLST8
mTOR
mTORC2
Rho-A
Statins
Apoptosis
Cytoskeleton

Treatment: the future

Cell-autonomous therapeutic approaches

Canonical and non-canonical TSC pathways

- Combination of mTOR and Autophagy inhibition:
  A trial of Sirolimus + hydroxychloroquine is ongoing
- Combination of mTOR inhibition and statins:
  A trial of Sirolimus and simvastin is ongoing
- Kinase inhibitors (Saracatinib Phase 1 OL - completed)

Non cell-autonomous therapeutic approaches

- Inhibition of MMPs and other proteases
- Estrogen antagonism (Letrozole phase 2 RCT study - completed)
- Inhibition of LAM cells utilizing melanocyte antigens

Treatment: the future

A pilot study of nintedanib for lymphangioleiomyomatosis

A non-randomized, efficacy, safety, and tolerability trial of nintedanib in sporadic and TSC-associated LAM

Starting Sept 2016 H. San Giuseppe MIlan

Future issues

- Better understanding of pathogenesis
  - Both canonical and Non canonical pathways
  - Role of estrogen
- Development of new biomarkers
- New therapeutic approaches
  - Sirolimus: long-term therapy, optimal mTOR inhibitor dosing

    When is the best moment to start ?
  - Combination therapy targeting different pathways
  - **Alternative therapies to cure and not only to treat the disease**