2019台灣胸腔暨重症加護醫學會夏季會

2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

Lymphangioleiomyomatosis (LAM)

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2019-06-23

Content

- What is LAM?
- Diagnosis
- Management

What is LAM?

- 1 per million people in the whole population
- 3.4–7.8 per million women
- Almost exclusively in women
- Average age at diagnosis : 35 years-old

Eur Respir J 2006; 27: 1056–65

J Clin Invest. 2012;122:3807–16

What is LAM?

- LAM occurs in two settings
  - **TSC-LAM**: in women who has tuberous sclerosis complex

    ※ 30%~40% of women with *tuberous sclerosis complex (TSC)*
  - Sporadic LAM or S-LAM: in women who do not have TSC

    ✓ Non-inherited form of LAM

    ✓ somatic mutations of the *TSC2* gene

Eur Respir J 2006; 27: 1056–65

J Clin Invest. 2012;122:3807–16

Clinical Epidemiology 2015;7:249–57

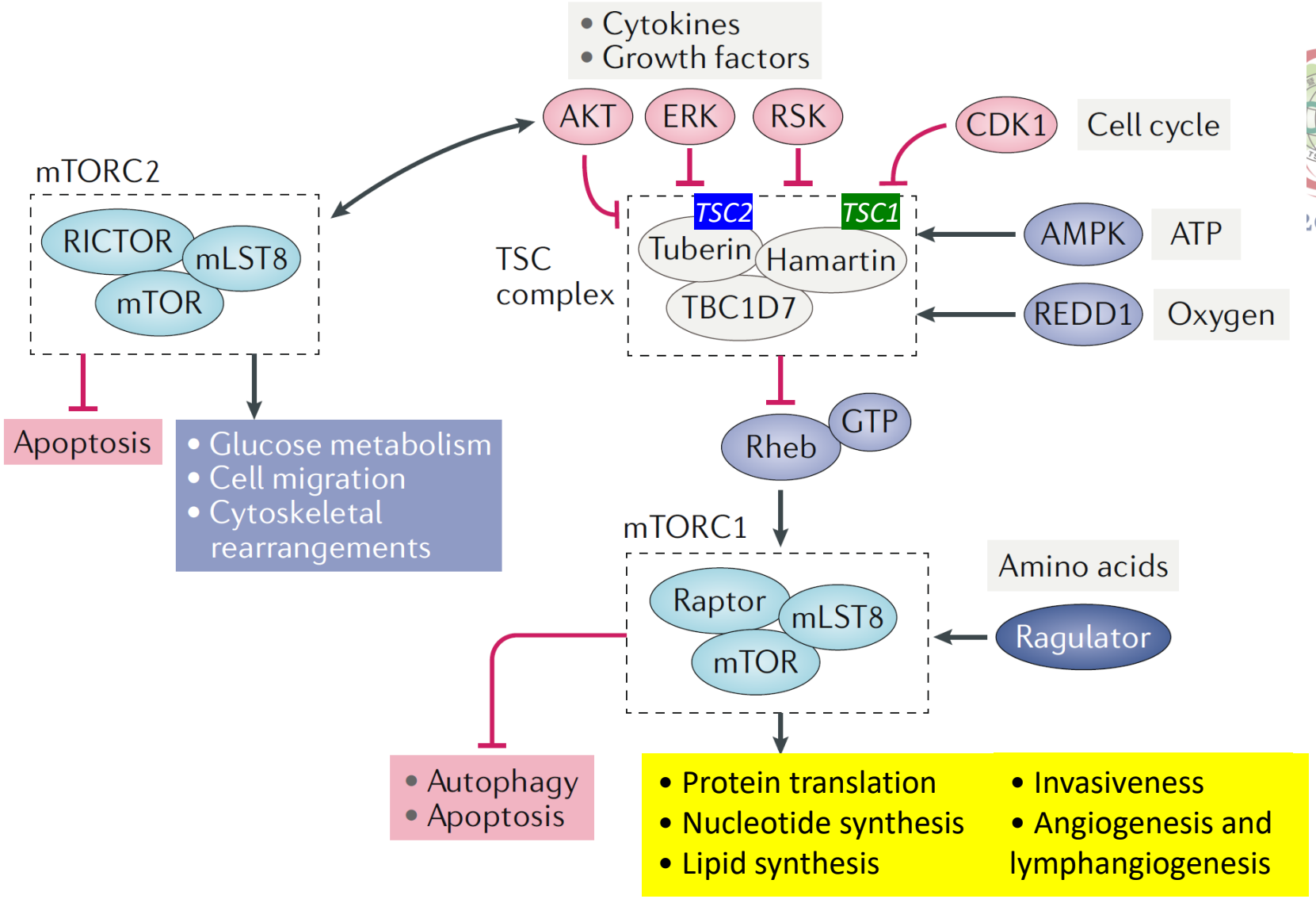
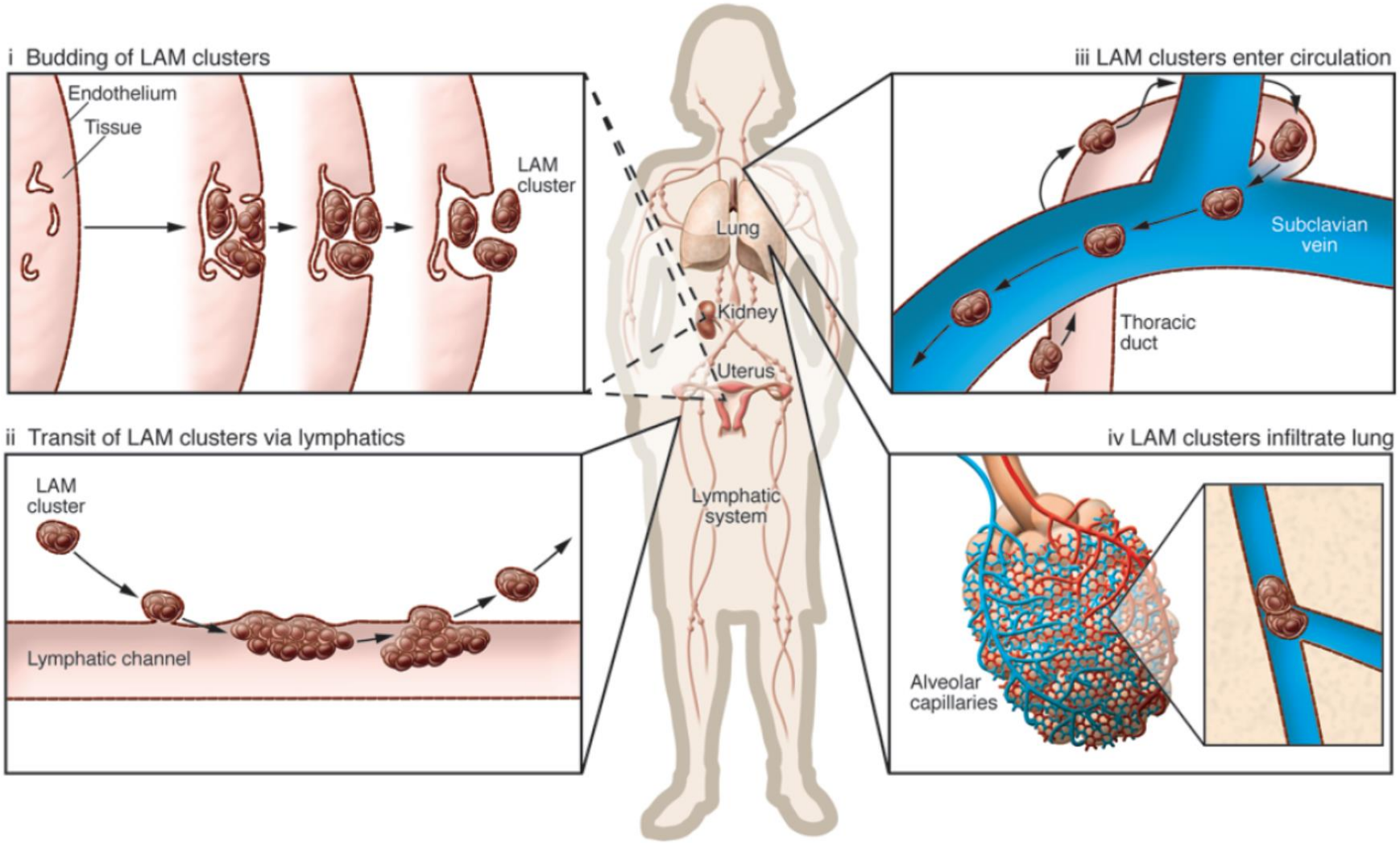


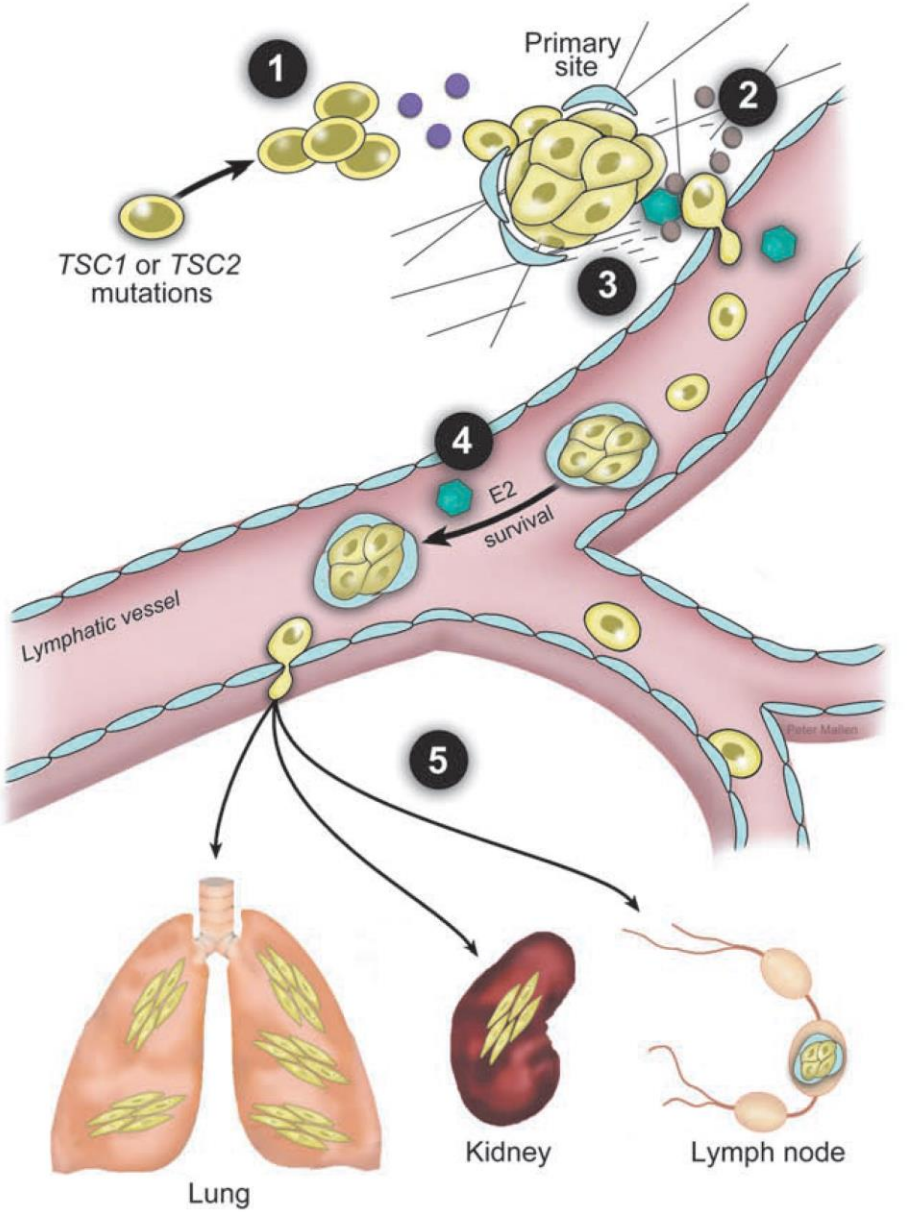
Fig. 1 | **The hamartin–tuberin complex regulates mTORC1 signalling by integrating extracellular and intracellular signals that promote metabolic homeostasis.**

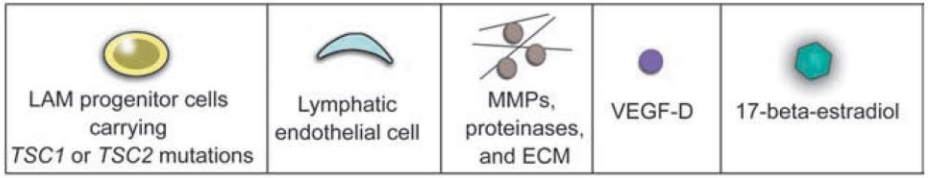
**mTORC= mammalian target of rapamycin complex*

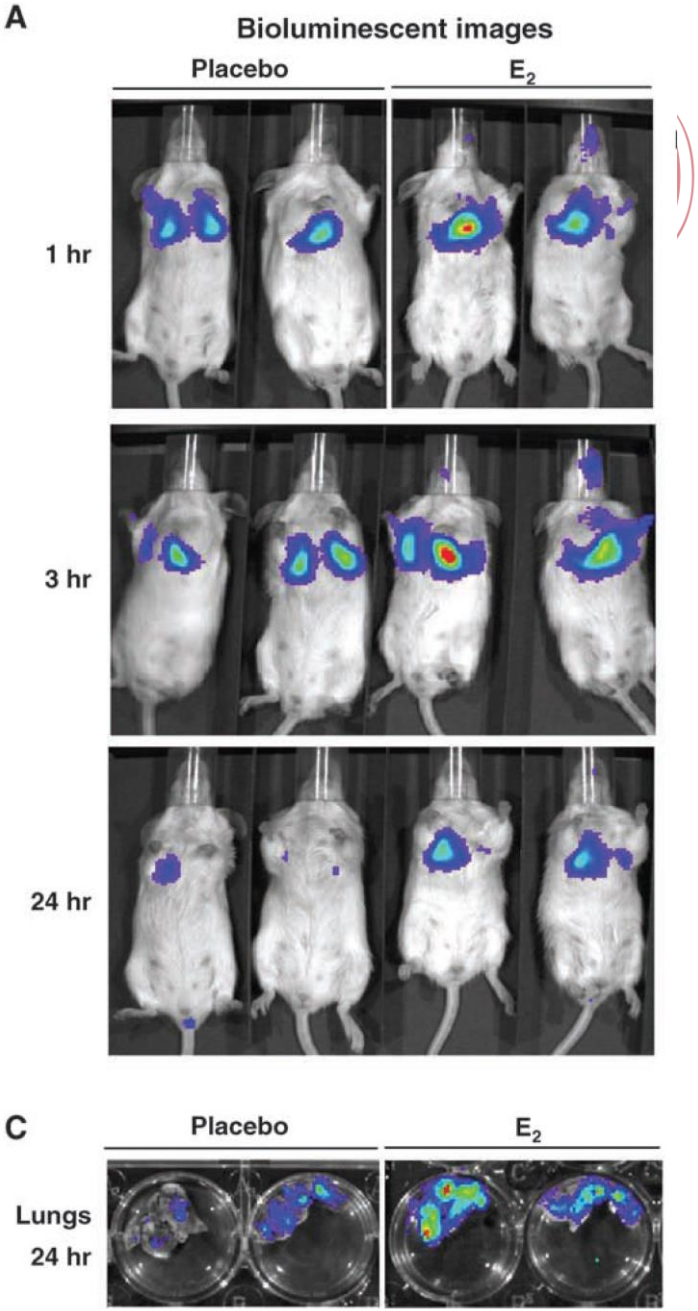
Nature Reviews Nephrology 2018;14:704–16



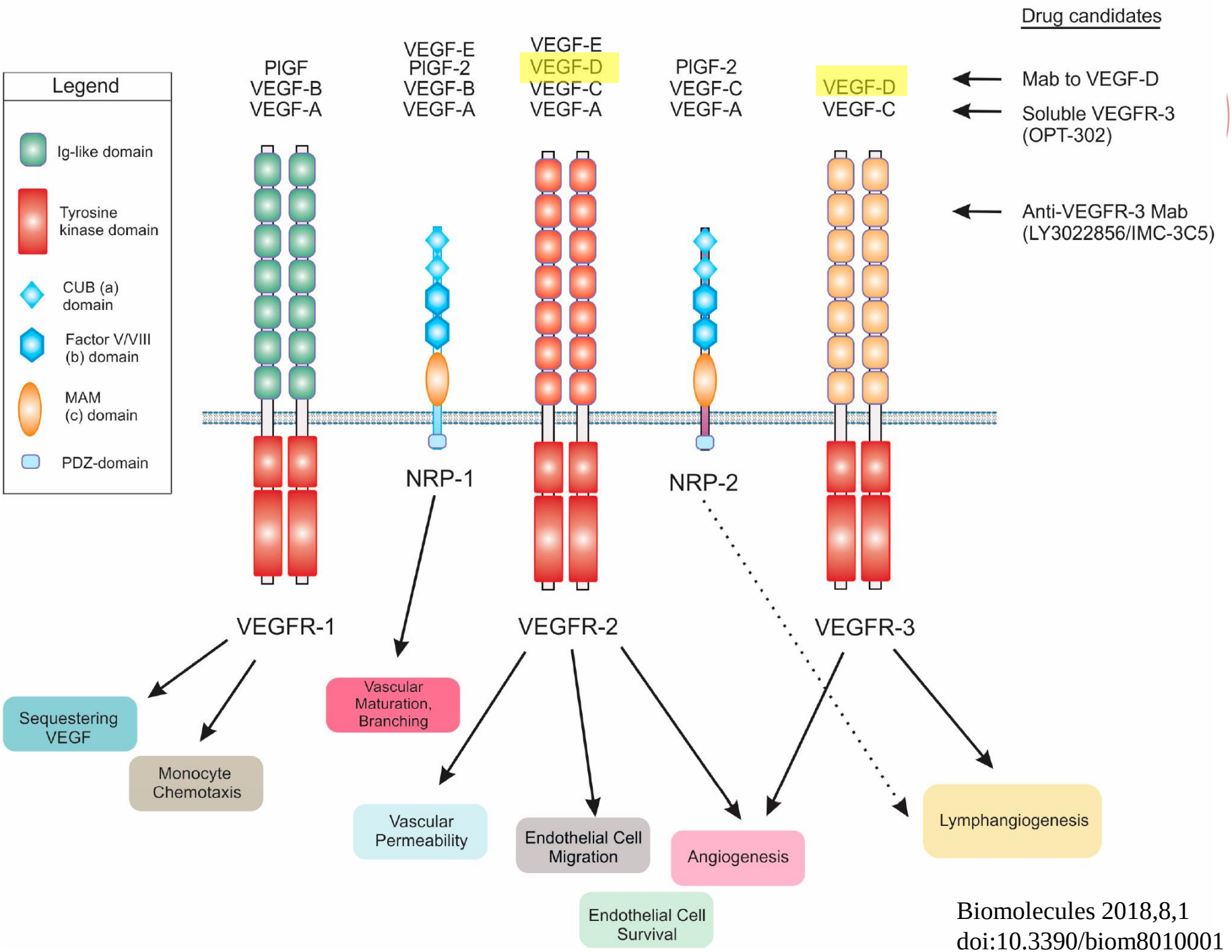
J Clin Invest. 2012;122:3807–16



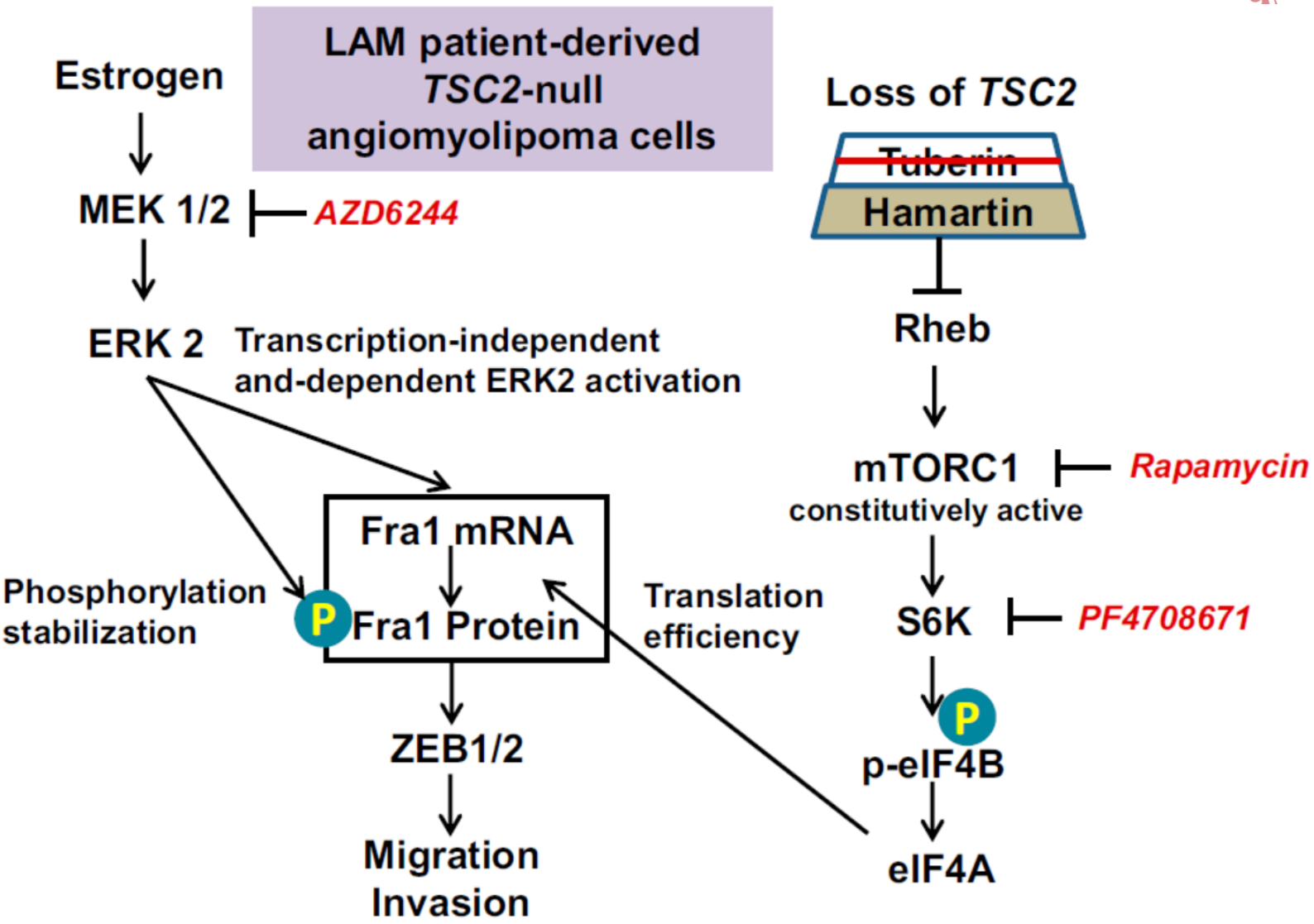




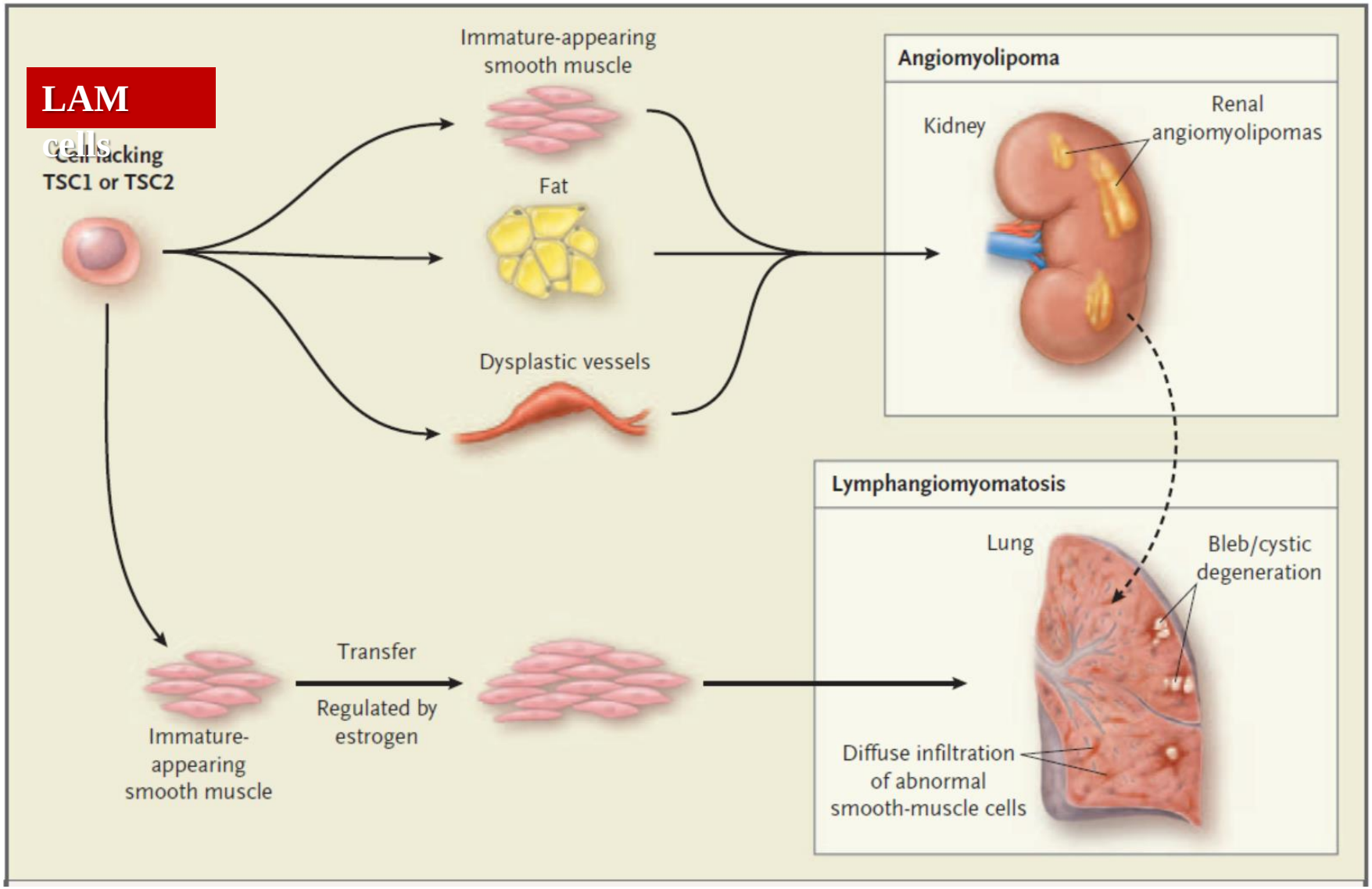
Lymphat Res Biol. 2010;8:43-9



Biomolecules 2018,8,1
doi:10.3390/biom8010001



Proc Natl Acad Sci USA. 2013;110:14960-5



N Engl J Med 2006;355:1345-56

What is LAM?

- A slowly progressive **neoplasm** that targets the lung
  - the accumulation of **LAM cells** within the lungs and axial lymphatics
  - cystic destruction
  - generally progresses to respiratory failure

Eur Respir J 2006; 27: 1056–65

J Clin Invest. 2012;122:3807–16

- median transplant-free survival of approximately 29 years from the onset of symptoms
- 10-year transplant-free survival of 86%

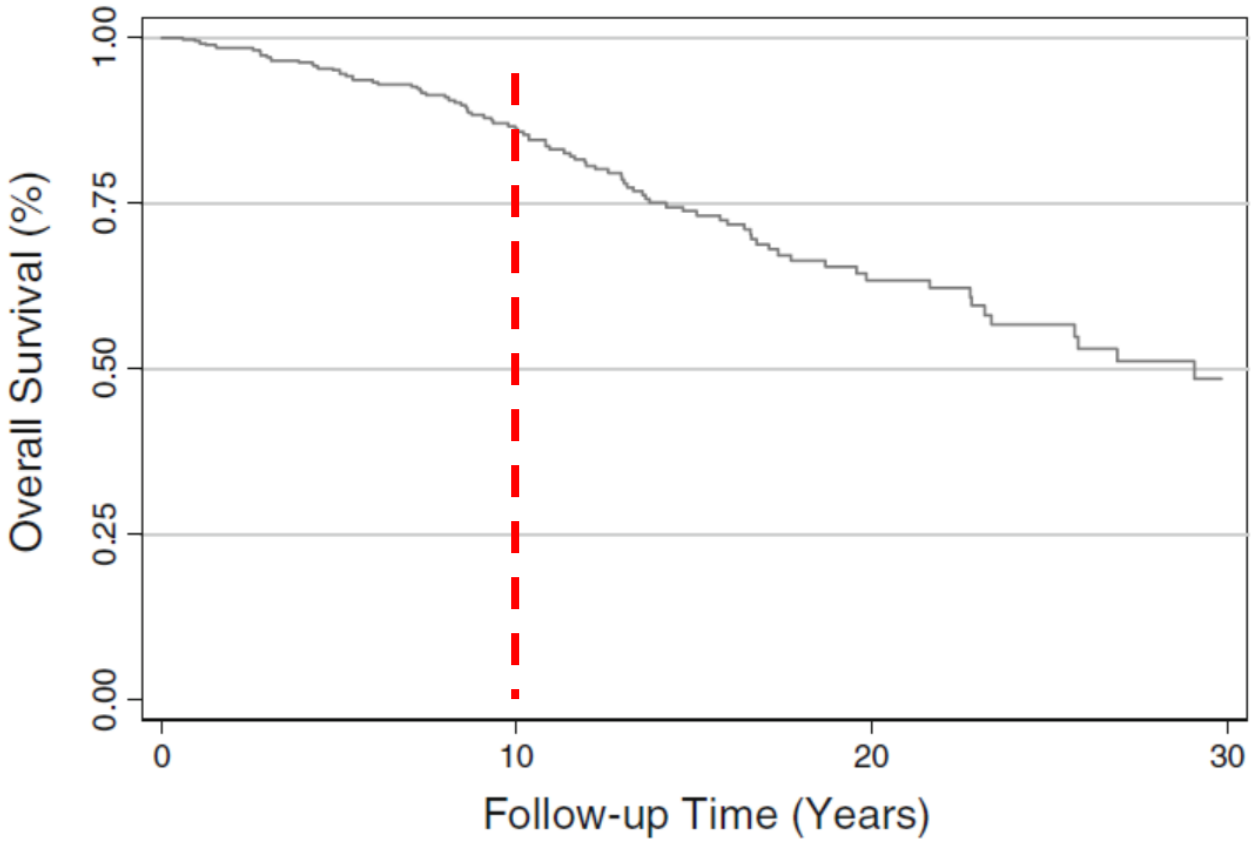


Fig. 1 Kaplan–Meier survival curve of estimated transplant-free survival among patients with LAM in the United States

J Clin Invest. 2012;122:3807–16
Lung 2013;191:35–42

The NHLBI LAM Registry

- N=230(S-LAM 196/TSC-LAM 34) → N=217
- From 1969 to 2001

TABLE 2] Baseline Pulmonary Function Test Values of the NHLBI LAM Registry Cohort

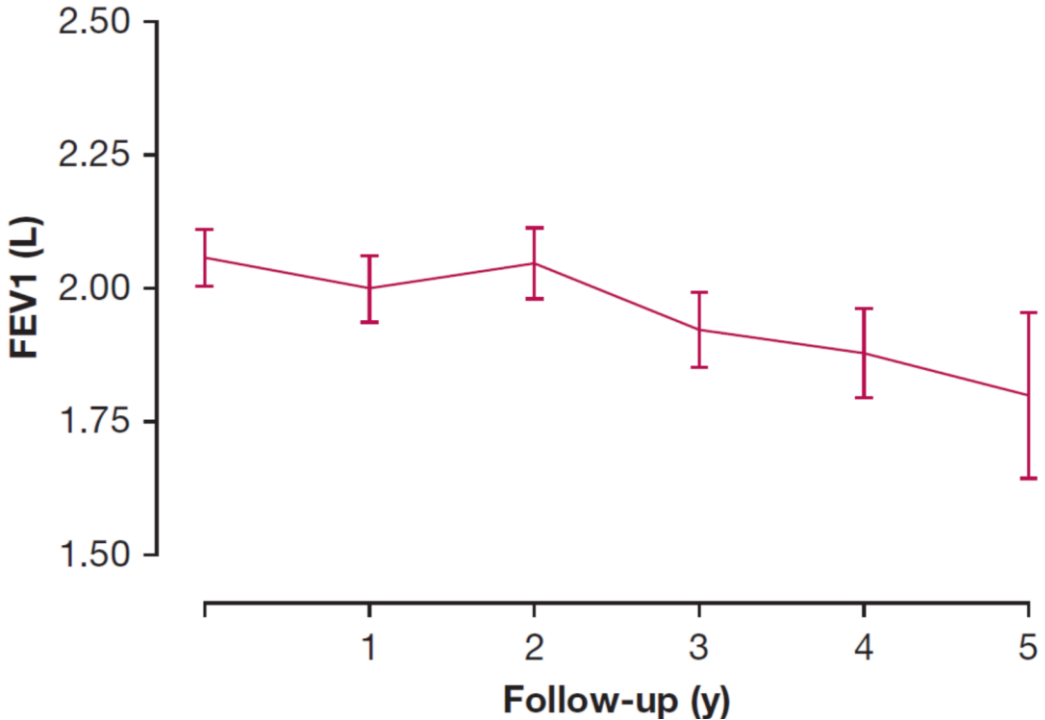
Characteristic	Mean Value	SD	% Predicted	SD
FEV_1	2.1 L	0.79	69	24
FVC	3.2 L	0.73	86	17
D_{LCO}	15.4 mL/ mmHg/ min	6.3	63	24

***pre-sirolimus era for LAM natural history and prognosis*

Am J Respir Crit Care Med 2006;173:105–111
CHEST 2019; 155:288-296

TABLE 3] Age-adjusted Rate of Decline in Pulmonary Function Measures During the 5-Year Follow-up

Variable	Mean Slope	SD	Mean Slope (% Predicted/ Year)	SD
FEV_1	−89.2 mL/y	53.4	−2.79	3.49
FVC	−71.3 mL/y	57.5	−1.88	3.21
D_{LCO}	−0.81 mL/ mmHg/ min/y	0.20	−3.05	0.15



CHEST 2019; 155:288-296

TABLE 4] Relationship Between Demographic, Clinical, Radiologic, and Serologic Characteristics and the Rate of Change of FEV1

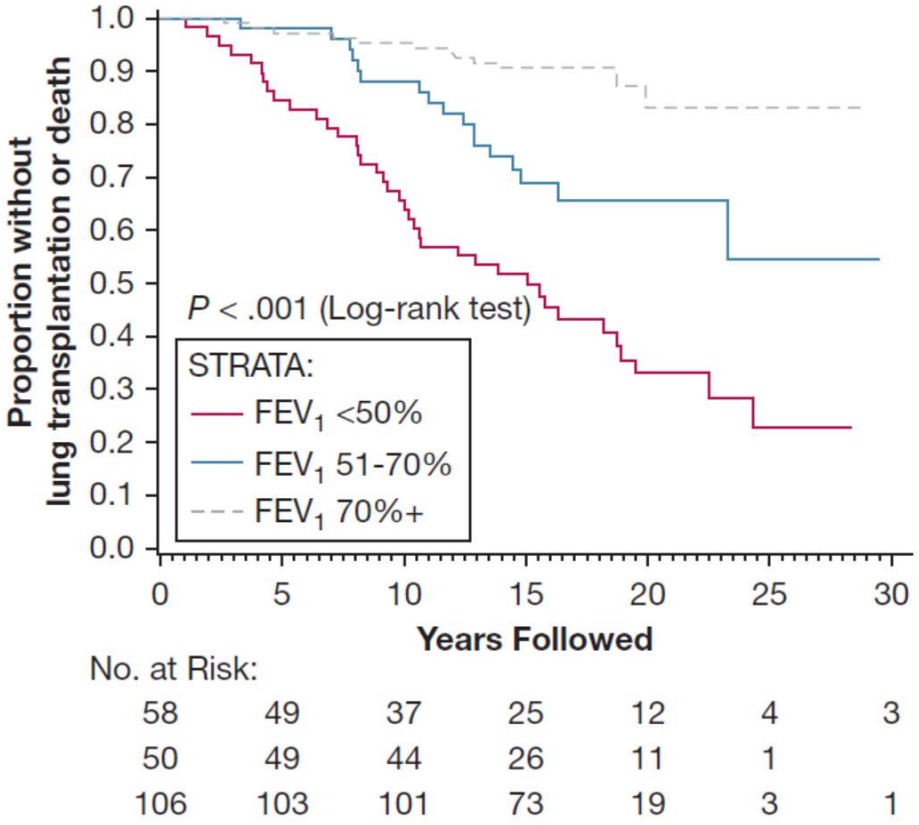
Characteristic	Parameter Estimate (SE)	*P* Value
Age at diagnosis[a]	1.39 (0.70)	.05
FEV_1 % predicted[a]	−0.31 (0.05)	< .0001
FVC % predicted[a]	−0.78 (0.29)	.007
D_{LCO} % predicted[a]	0.48 (0.29)	.10
CT score[a]	−3.53 (1.53)	.02
Log_2 (VEGF-D)[a]	−6.55 (5.01)	.19
Serum VEGF-D > 600 pg/mL		.32
No	−78.6 (11.6)	
Yes	−93.0 (8.3)	
Bronchodilator response		.09
No	−82.8 (7.5)	
Yes	−113.2 (16.4)	

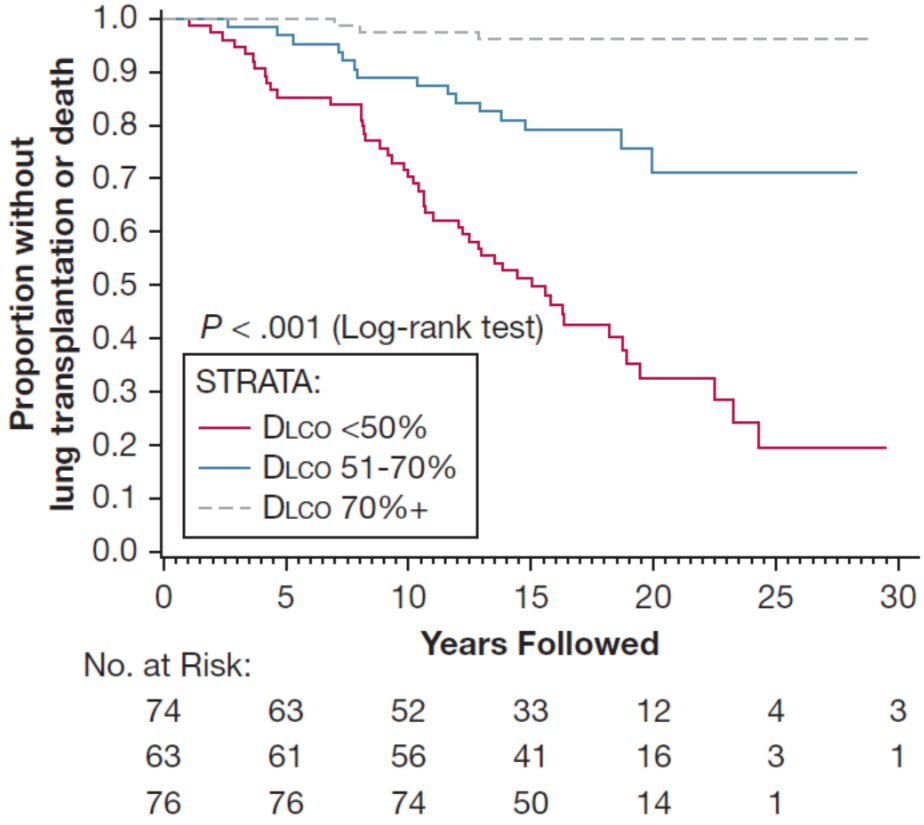
Characteristic	Parameter Estimate (SE)	*P* Value
AMLs		.13
No	−97.5 (8.9)	
Yes	−76.2 (10.5)	
Menopausal status		.003
No	−118 (12.4)	
Yes	−73.7 (8.1)	
History of pneumothorax		.98
No	−89.8 (10.2)	
Yes	−90.1 (9.2)	
Supplemental oxygen use		.61
No	−86.4 (8.2)	
Yes	−94.0 (12·5)	
No. of pneumothoraces[a]	2.2 (1.7)	.20
Sporadic LAM	−85.9 (7.1)	.68
TSC-LAM	−93.5 (16.8)	

*postmenopausal women declining 44 mL/year slower than the premenopausal

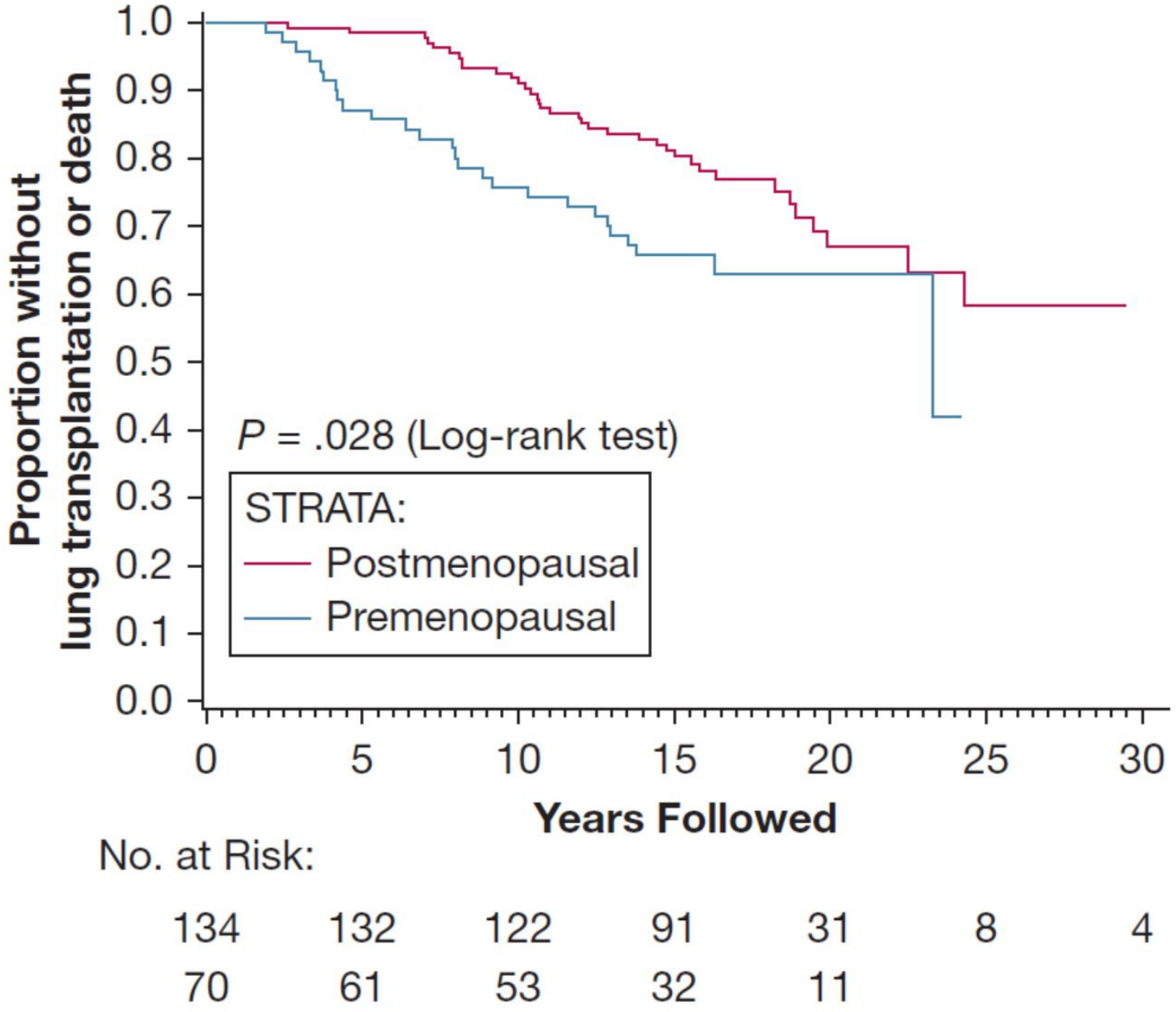
CHEST 2019; 155:288-296

Higher baseline lung function was associated with a decreased risk of progression to death or lung transplantation





CHEST 2019; 155:288-296



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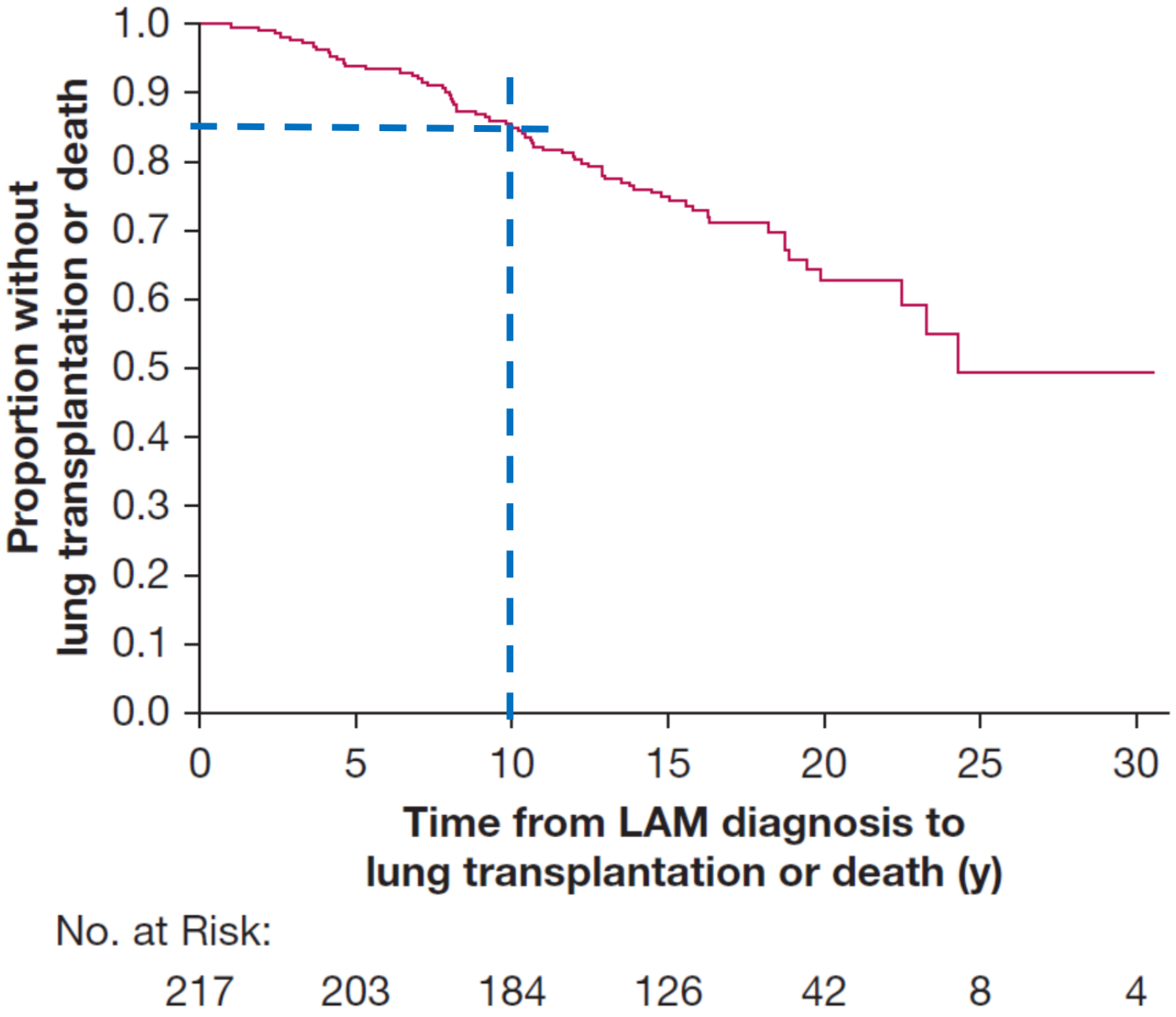
CHEST 2019; 155:288-296



CHEST 2019; 155:288-296

e-Table 2: Association between various disease-related parameters and the risk of death or lung transplantation. All disease-related parameters in this analysis were adjusted for age at diagnosis, except the one marked with asterisk.

Characteristics		N, Mean (standard deviation) or N (%)		Hazard ratio (95% confidence interval)	p-value
		Lung transplantation or death	Censored on December 31, 2014		
Age at diagnosis*		68, 40.0 (9.3)	148, 41.5 (10.2)	0.99 (0.96, 1.01)	0.26
FEV1 % predicted		69, 51.3 (20.1)	146, 78.0 (21.0)	0.96 (0.95, 0.97)	<0.0001
Supplemental oxygen use	No	27 (18)	120 (82)	Ref	<0.0001
	Yes	42 (60)	28 (40)	4.09 (2.48, 6.72)	
Number of pneumothoraces per patient		2.8 (4.5)	2.2 (5.3)	1.00 (0.96, 1.04)	0.96
Sporadic LAM		59 (33)	121 (67)	Ref	0.59
TSC LAM		9 (25)	27 (75)	0.83 (0.41, 1.67)	

CHEST 2019; 155:288-296

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Clinical Presentation

	At presentation	During course of disease
Dyspnea	42%	87%
Cough	20%	51%
Chest pain	14%	34%
Hemoptysis	14%	22%
Pneumothorax	43%	65%
Chylothorax	12%	28%

Eur Respir J 2006; 27: 1056–65

HRCT for LAM

- Lung cysts are the hallmark lesion in LAM and are present in all patients
- typically ranging from 2–5 mm in diameter
- Cyst wall thickness : 2 mm

Eur Respir J 2010; 35: 14–26

HRCT for LAM

- Characteristic-
  - multiple (>10) thin-walled round well-defined air-filled cysts
  - no other significant interstitial lung disease
  - possible features of multifocal micronodular pneumocyte hyperplasia(MMPH) in patients with TSC
- Compatible-
  - only few (2 ~10) cysts

Eur Respir J 2010; 35: 14–26

Diagnosis criteria for LAM

Definite LAM	1. Characteristic or compatible lung HRCT, and lung biopsy fitting the pathological criteria for LAM; or 2. Characteristic lung HRCT and any of the following: angiomyolipoma (kidney); thoracic or abdominal chylous effusion; lymphangioleiomyoma or lymph-node involved by LAM; Definite or probable TSC.
Probable LAM	1. Characteristic HRCT and compatible clinical history; or 2. Compatible HRCT and any of following: angiomyolipoma (kidney); and thoracic or abdominal chylous effusion.
Possible LAM	Characteristic or compatible HRCT.

Eur Respir J 2010; 35: 14–26
Ther Clin Risk Manag 2014;10:691–700

Differential diagnosis of diffuse thin-walled cystic lung diseases

- LAM
  - Sporadic LAM
  - Tuberous sclerosis complex-related LAM
- PLCH
- BHD
- LIP
  - Primary LIP
  - Secondary LIP*
- Amyloidosis*
- Light-chain deposition disease
- Follicular bronchiolitis*
- Metastatic malignancy
  - eg, sarcoma, meningioma, urothelial carcinoma
- Pulmonary adenocarcinoma
- Others

Abbreviations: LAM, lymphangioleiomyomatosis; PLCH, pulmonary Langerhans' cell histiocytosis; BHD, Birt-Hogg-Dubé syndrome; LIP, lymphoid interstitial pneumonia

Ther Clin Risk Manag 2014;10:691–700

LAM

Figure 1 Lymphangioleiomyomatosis. Frontal radiographs of chest in a 37-year-old woman reveal a large right pneumothorax related to underlying cystic lung disease.

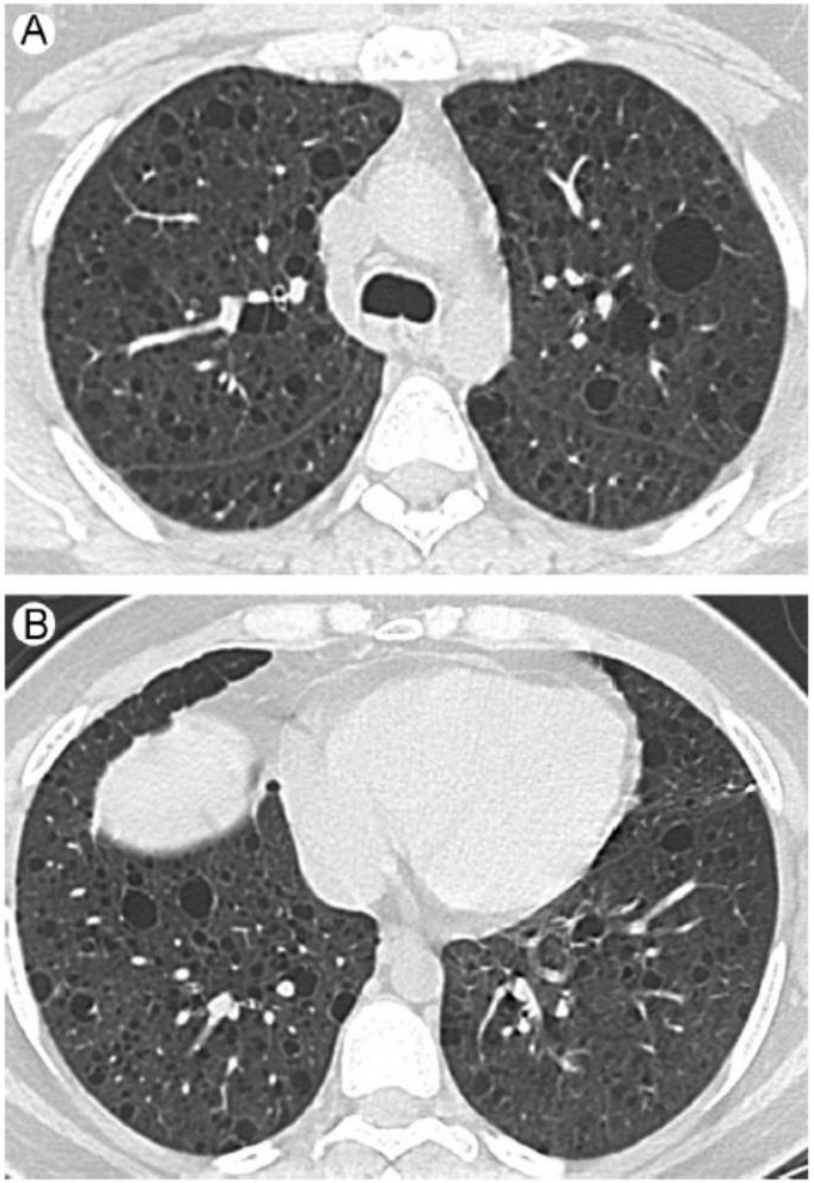


Figure 2 Lymphangioleiomyomatosis. Axial CT images at level of carina (A) and top of right diaphragm (B) in a 46-year-old woman reveal multiple well-circumscribed cysts distributed evenly throughout the lung parenchyma.

Semin Roentgenol. 2015;50:23-30.

TSC-LAM

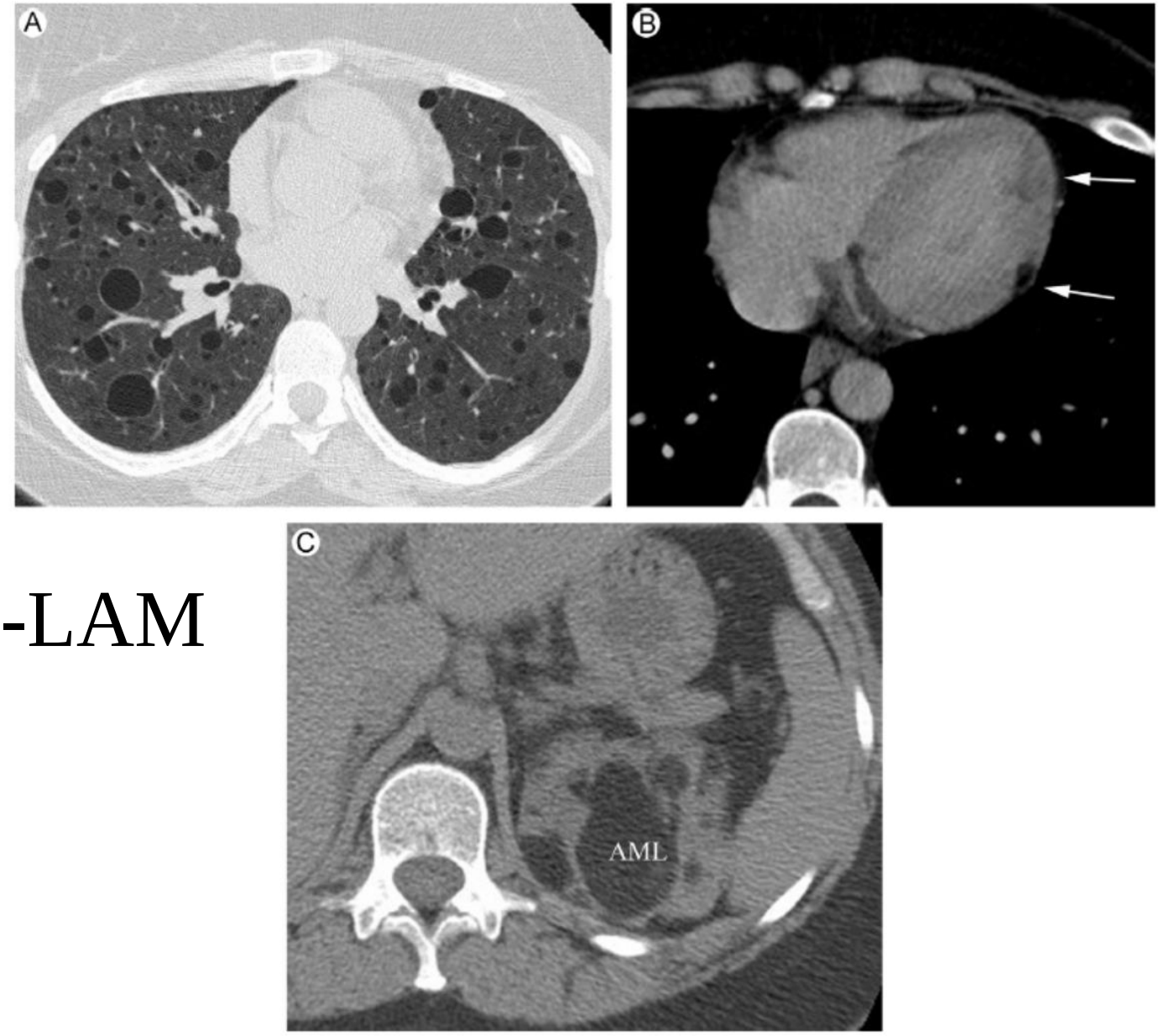


Figure 3 Tuberous sclerosis complex in a 42-year-old woman. (A) Axial image through lung bases reveals multiple well-circumscribed cysts. (B) Contrast-enhanced image through the heart reveals dysplastic nodules and fatty metaplasia indicative of cardiac rhabdomyomas (arrows). (C) Axial image through left kidney reveals a fat-predominant angiomyolipoma (AML).

Semin Roentgenol. 2015;50:23-30.

PLCH

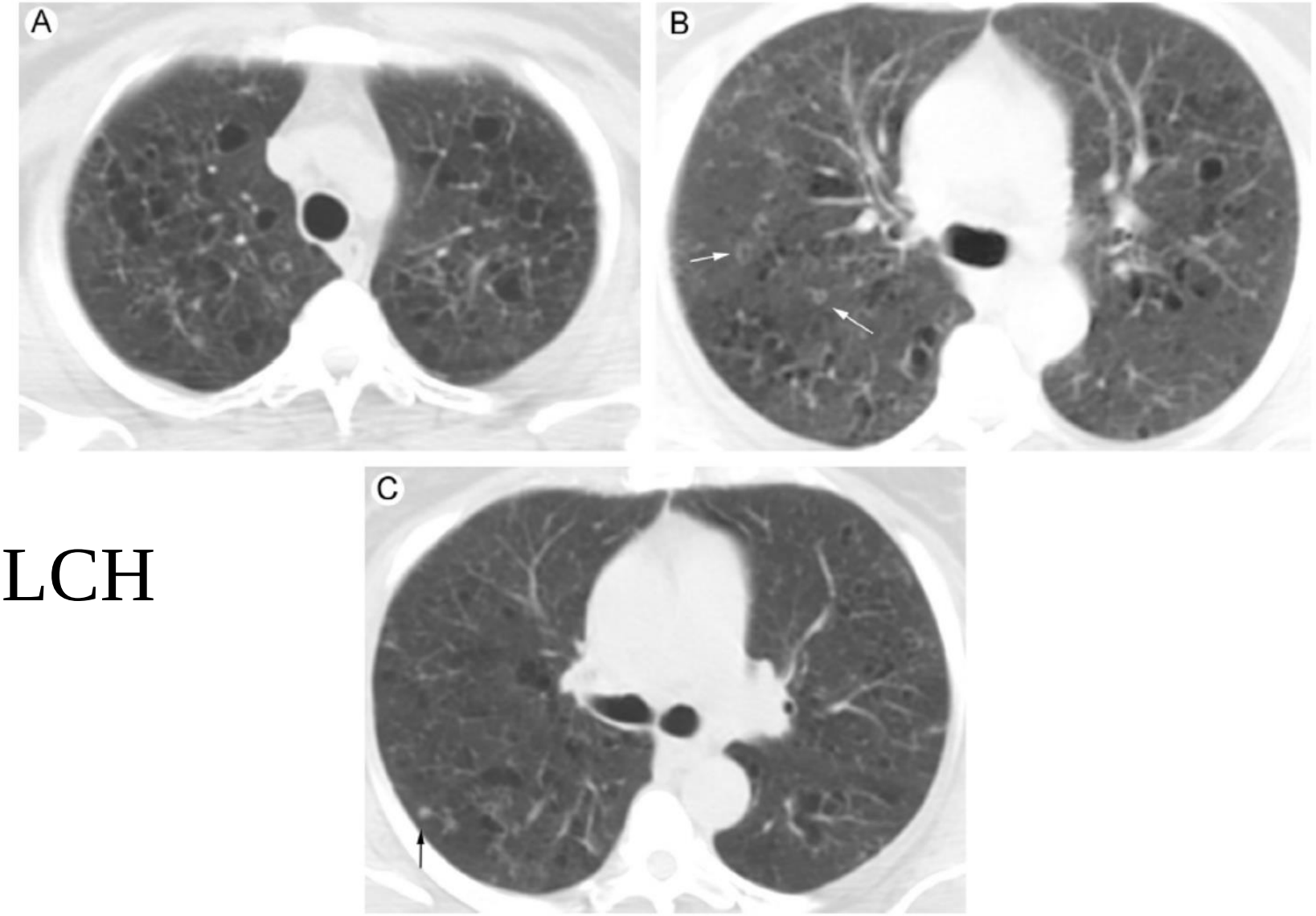


Figure 5 Langerhanscellhistiocytosis.AxialCTimagesina51-year- old female smoker with cough at the level of aortic arch(A),above carina(B),and below carina(C) reveal irregular-and polygonal shaped cysts in the lung apices with mixed small cysts with cheerio nodules(white arrows—B) and solid nodules(black arrow—C).

Semin Roentgenol. 2015;50:23-30.

LIP

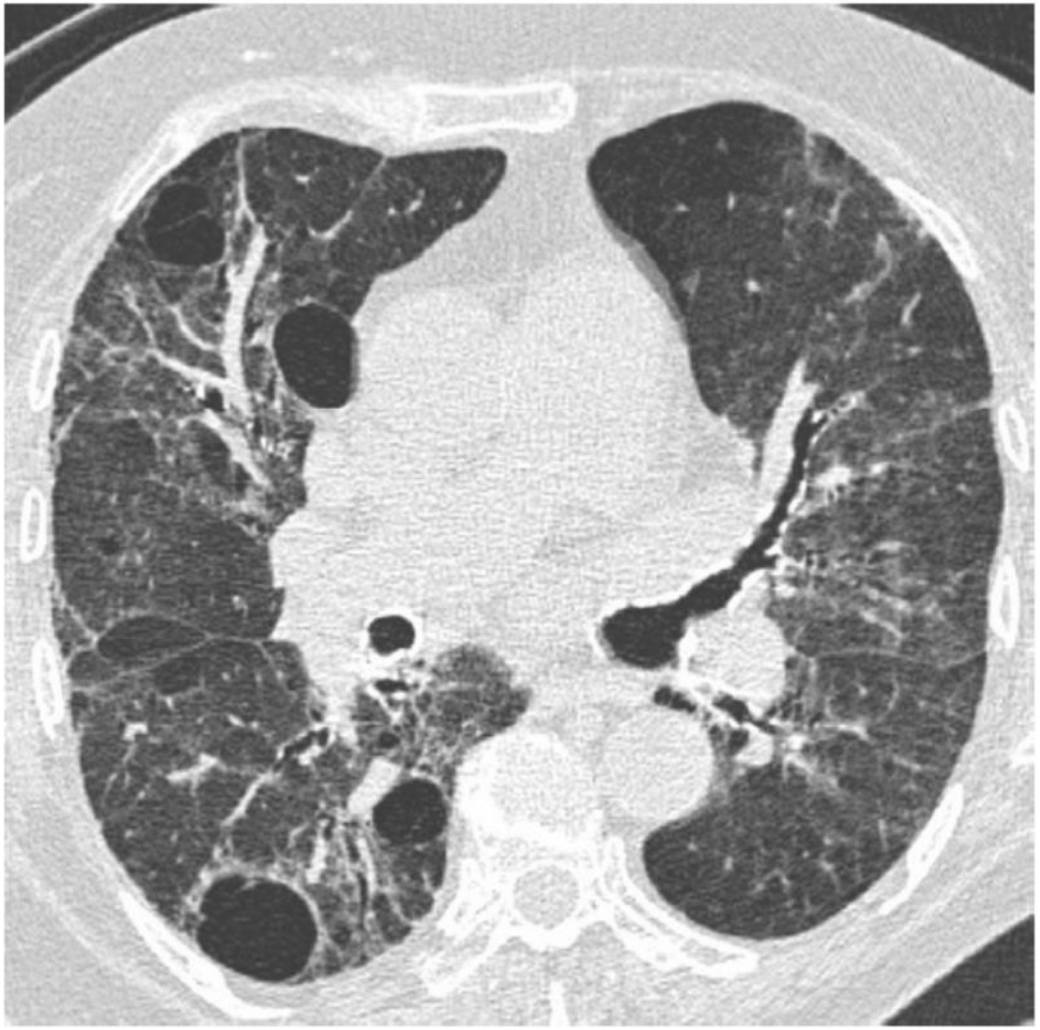
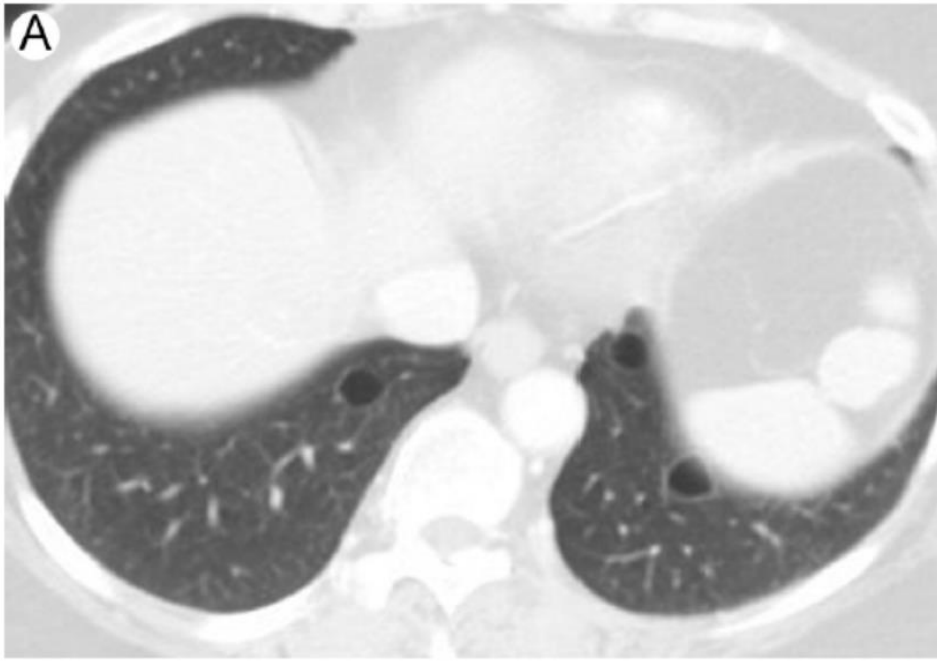


Figure 7 Lymphocytic interstitial pneumonitis in 69-year-old woman with systemic lupus erythematosus. Axial CT image reveals ground-glass opacity, interlobular septal thickening, and traction bronchiectasis associated with parenchymal cysts in the left lung.

Semin Roentgenol. 2015;50:23-30.



BHD

Figure 8 Birt-Hogg-Dube syndrome in a 47-year-old woman. (A) Axial CT through lung bases reveals scattered well-circumscribed cysts. (B) Contrast-enhanced image through left kidney reveals enhancing mass shown to be renal cell carcinoma at biopsy.

Semin Roentgenol. 2015;50:23-30.

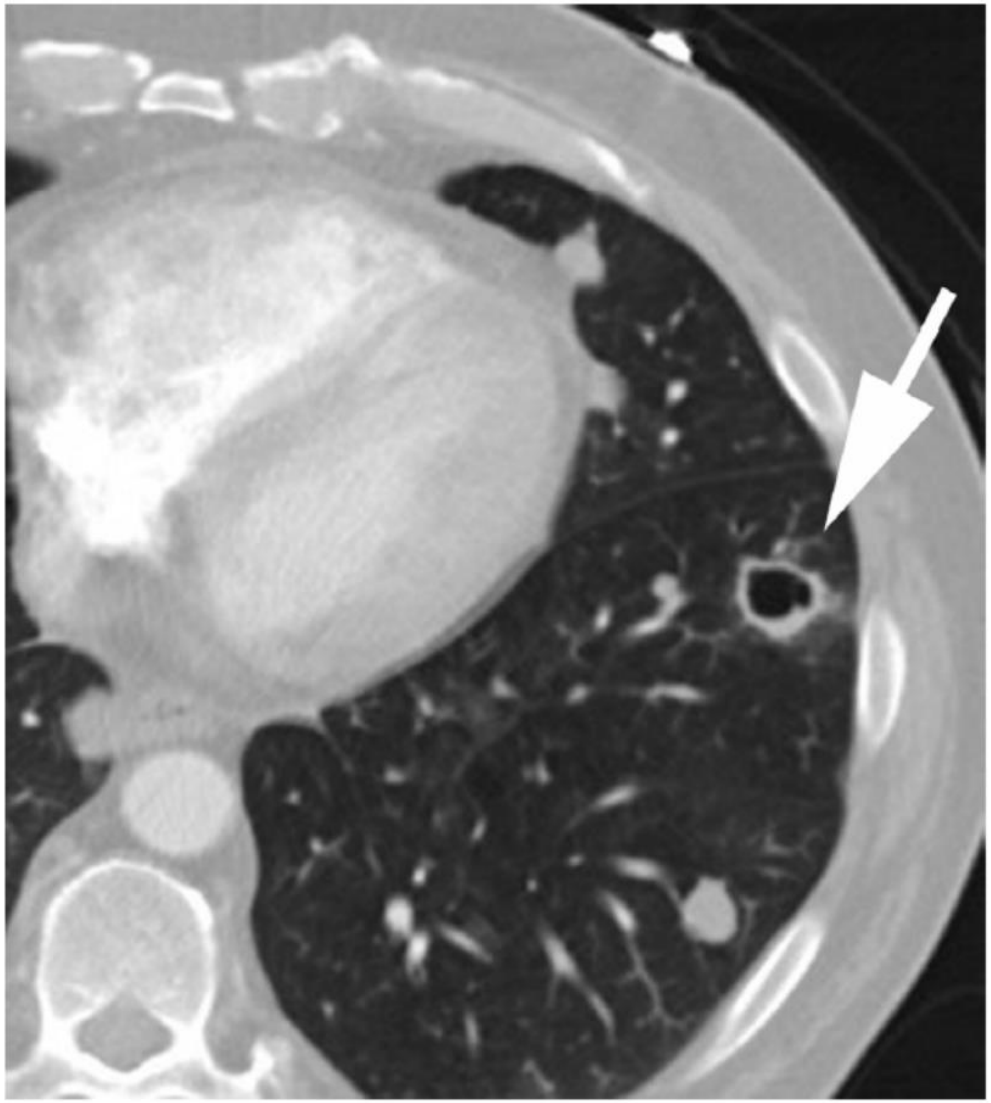


Figure 9 Cavitary metastasis. Axial CT image in 67-year-old man with metastatic squamous cell carcinoma. Note the thicker and more irregular wall of the cavitary metastasis compared with cystic lung disease (arrow).

Cancer

Semin Roentgenol. 2015;50:23-30.

Bronchiectasis

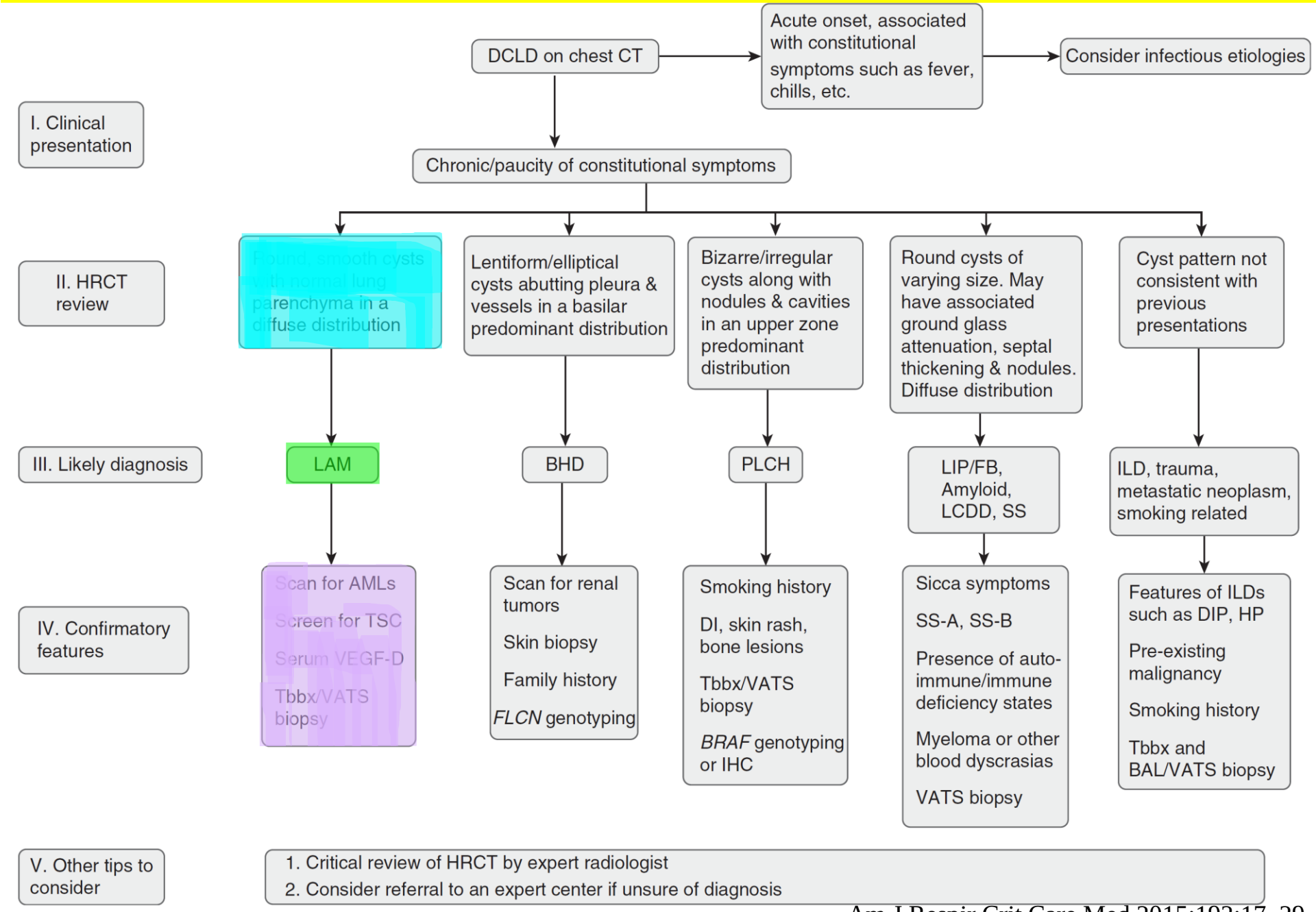
Figure 11 Cystic bronchiectasis in a 20-year-old man with hypogammaglobulinemia mimicking cystic lung disease.

UIP

Figure 12 Usual interstitial pneumonitis. Axial CT through the lung bases in a 74-year-old male shows extensive honeycombing in UIP. UIP, usual interstitial pneumonia.

Semin Roentgenol. 2015;50:23-30.

Algorithm to guide approach to the diagnosis of diffuse cystic lung diseases



Am J Respir Crit Care Med 2015;192:17–29

Multisystem Disorder

	TSC-LAM	S-LAM
Lung cysts	Often mild	Often profuse
Elevated serum VEGF-D	100%	70%
Chylous pleural effusion	10%	30%
Pneumocyte hyperplasia	12%	0%–1%
Abdominal lymphangioleiomyoma	9%	29%
Renal angiomyolipoma	93%	32%
Single	0%	46%
Bilateral	92%	19%
Uterine PEComas	100%	70%

J Clin Invest. 2012;122:3807–16

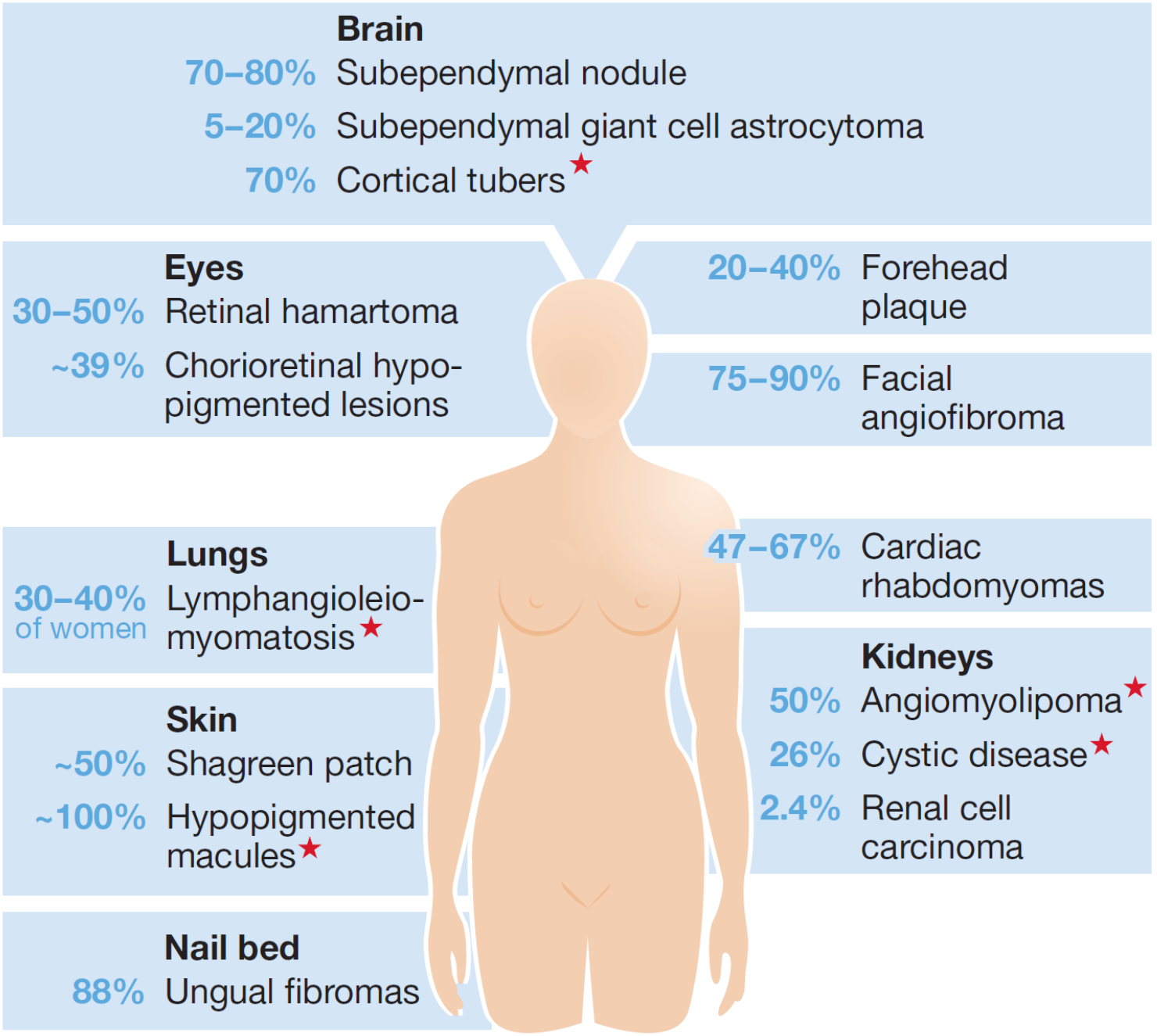


Figure 1. Clinical manifestations of TSC

EMBO Mol Med 2011;3:189–200

Periungual fibromas

Subependymal giant-cell astrocytoma

Hypomelanotic macule

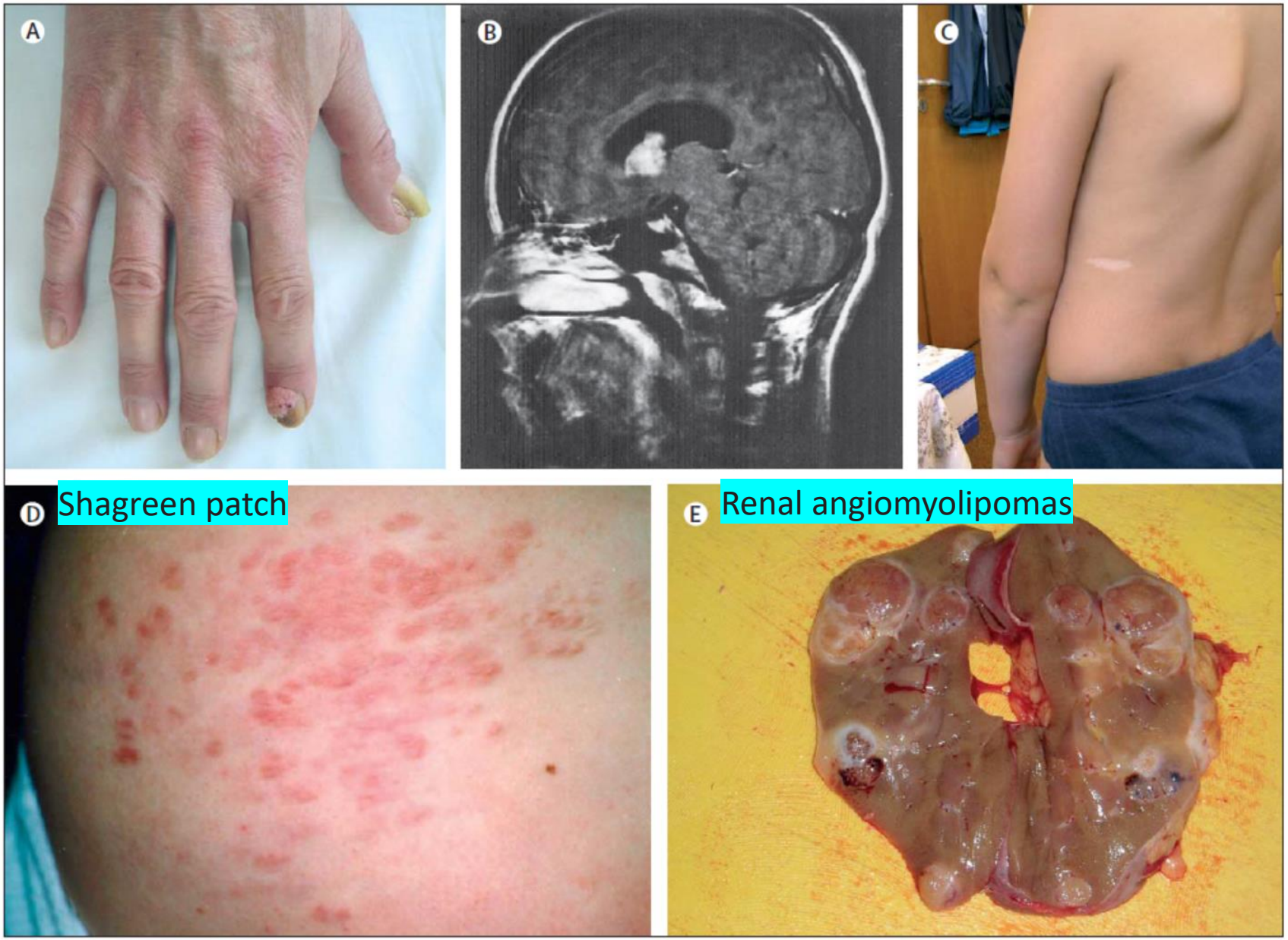
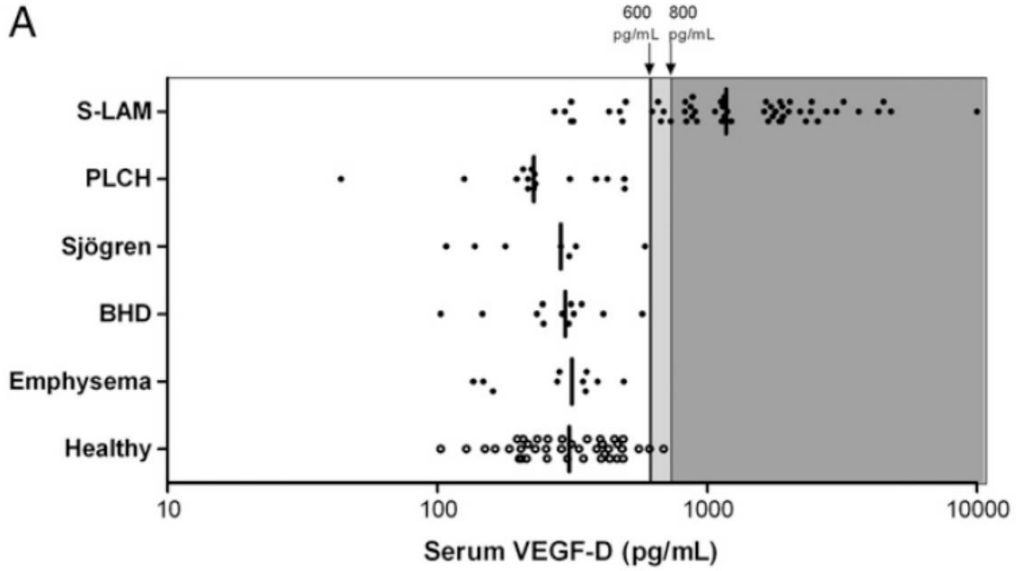
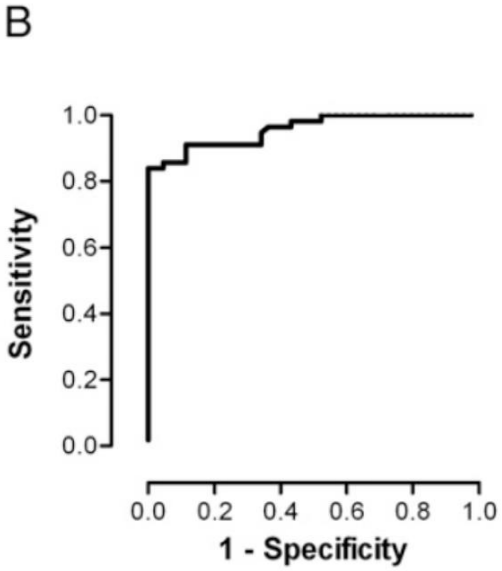
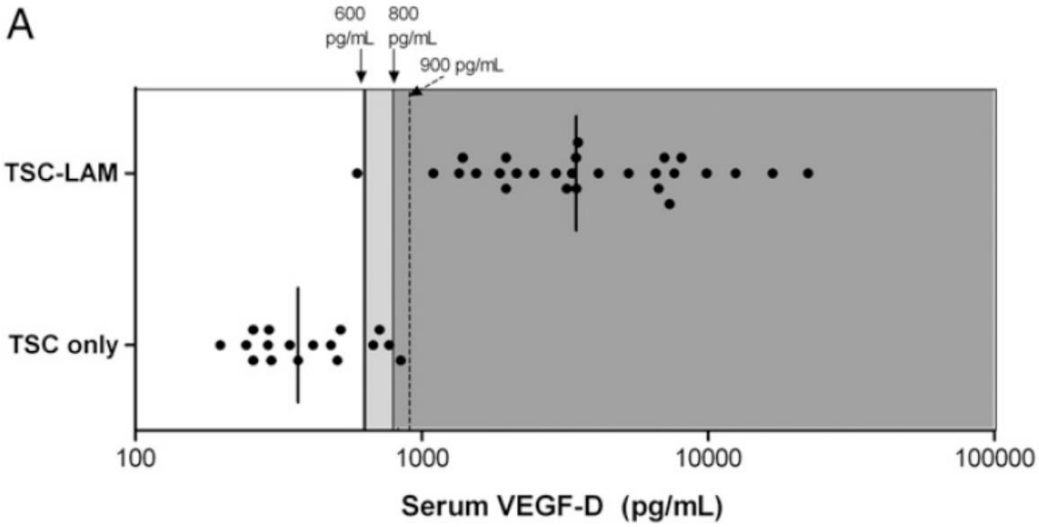


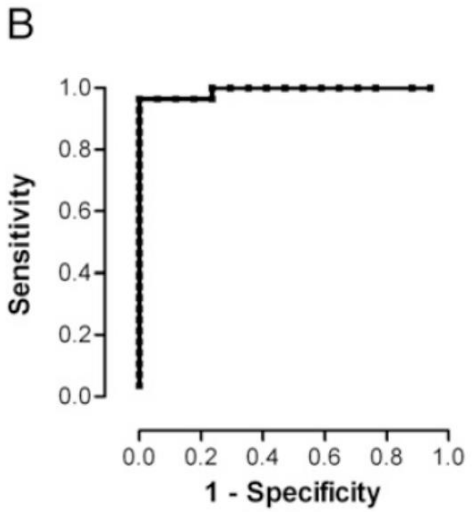
Figure 2: **More symptoms of tuberous sclerosis**

Lancet Oncol 2008;9:73–9

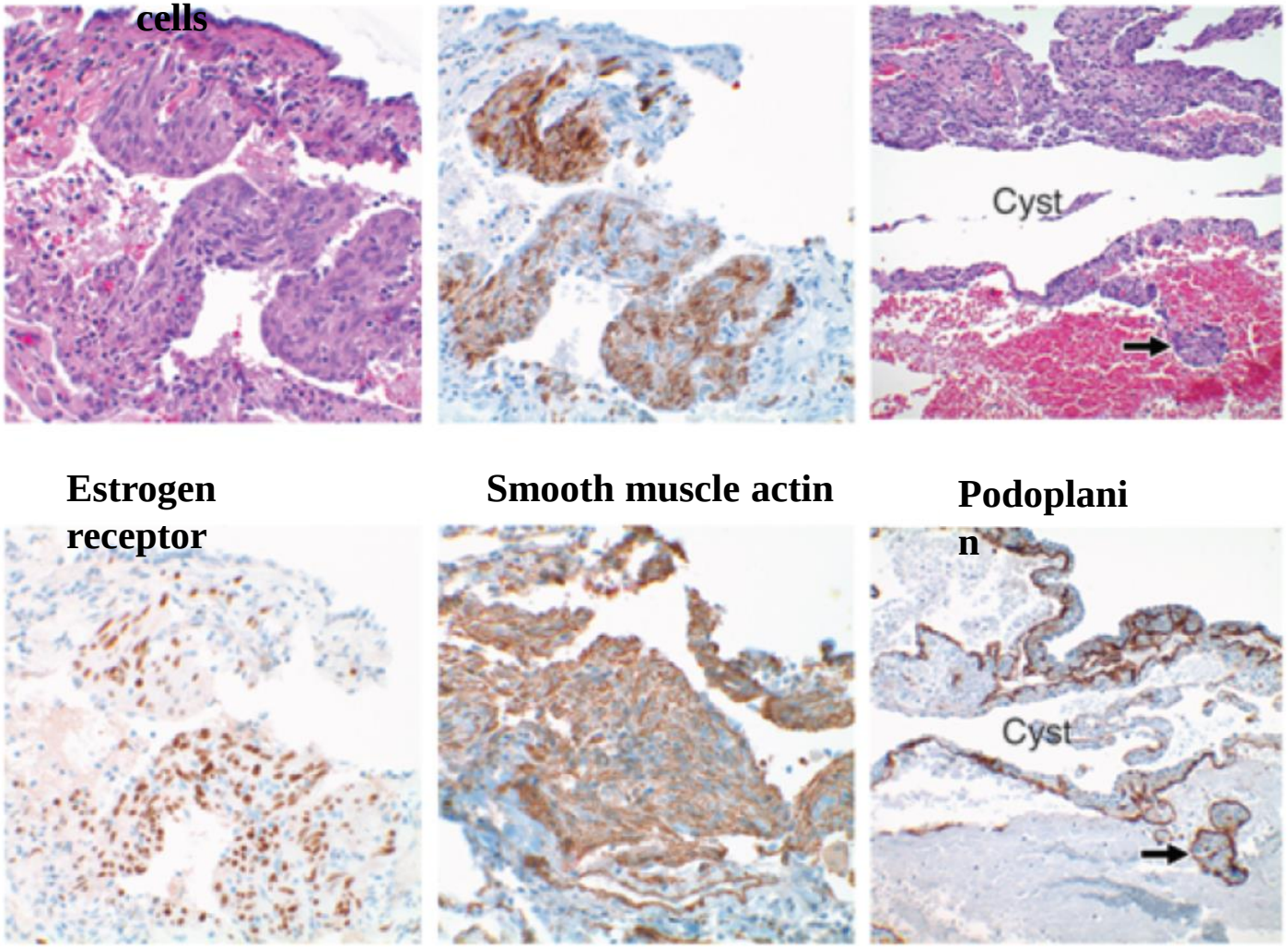








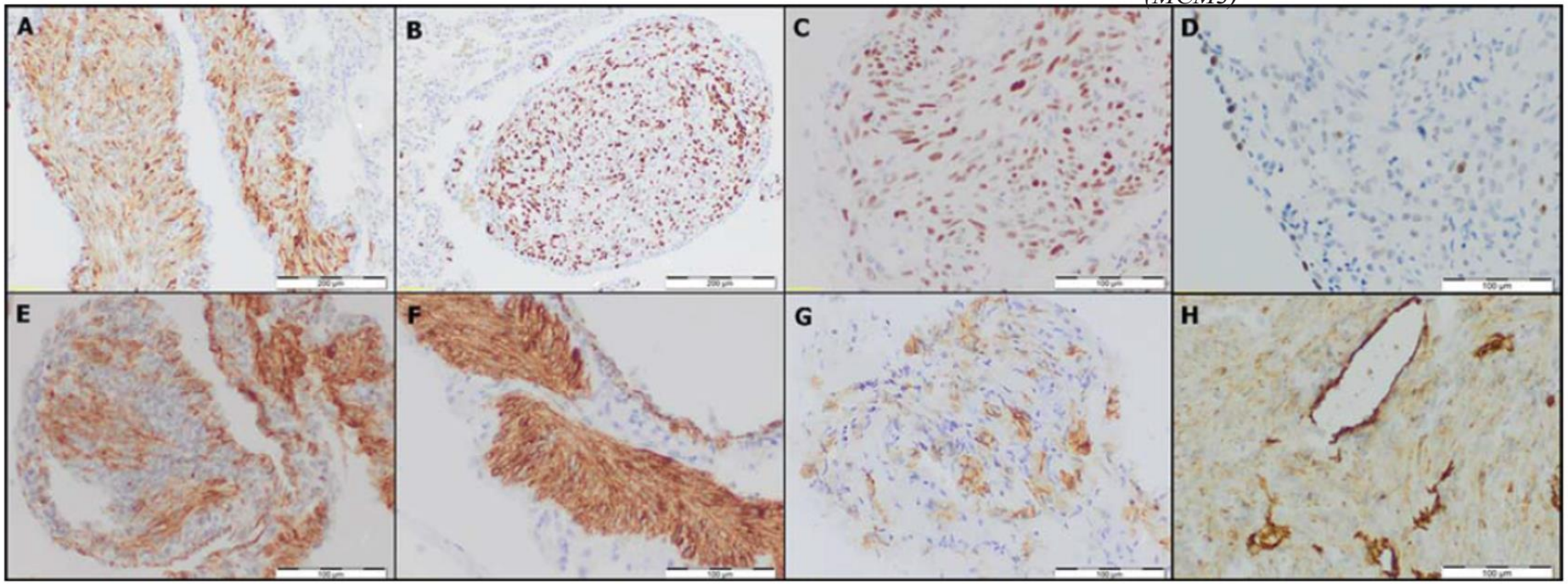
CHEST 2010;138:674–681



- High-power view of cystic change with surrounding LAM in the lung.
- LAM cells express the melanocystic antigen, HMB-45, as well as estrogen receptor and the smooth muscle cell antigen, smooth muscle actin.
- An immunohistochemical stain for podoplanin highlights lymphatic channels within cystic lesions and LAM cells clusters within the lymphatic lumen

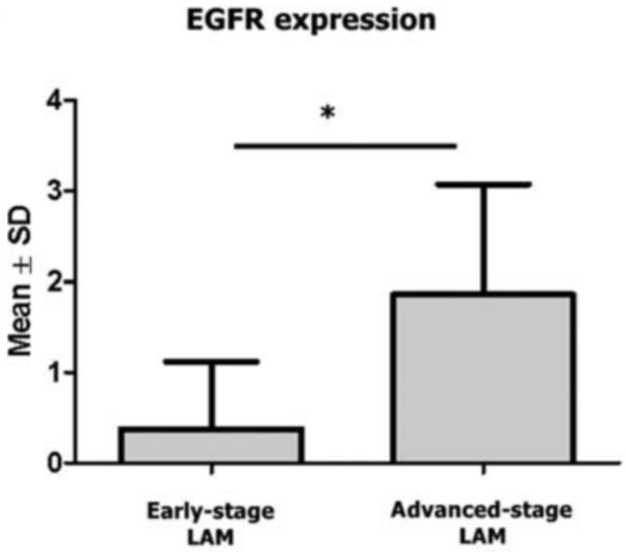
J Clin Invest. 2012;122:3807–16

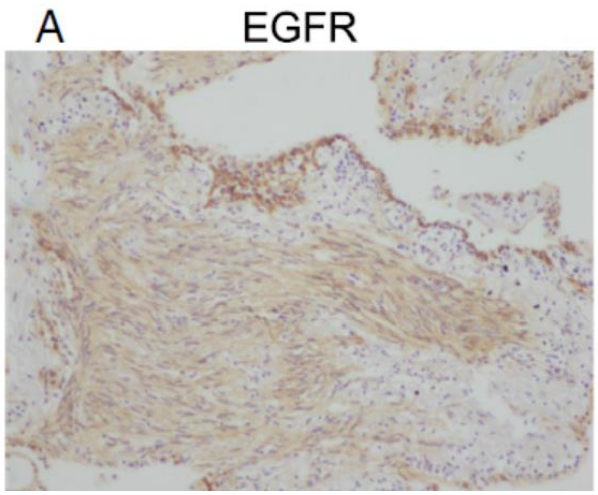
HMB-45 *progesterone receptor (PR)* *estrogen receptor(ER)* *mini-chromosome maintenance protein 3 (MCM3)*

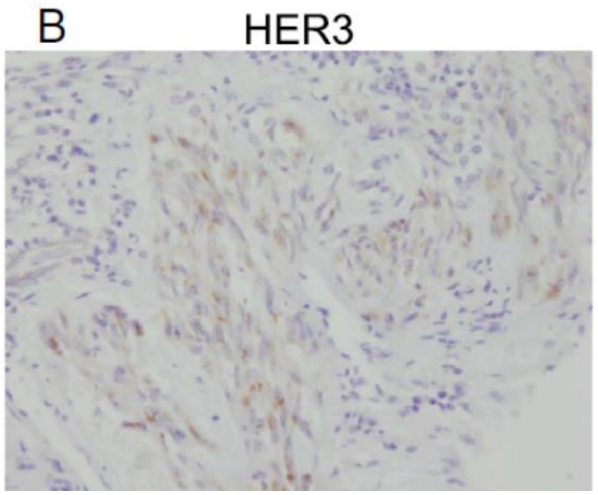


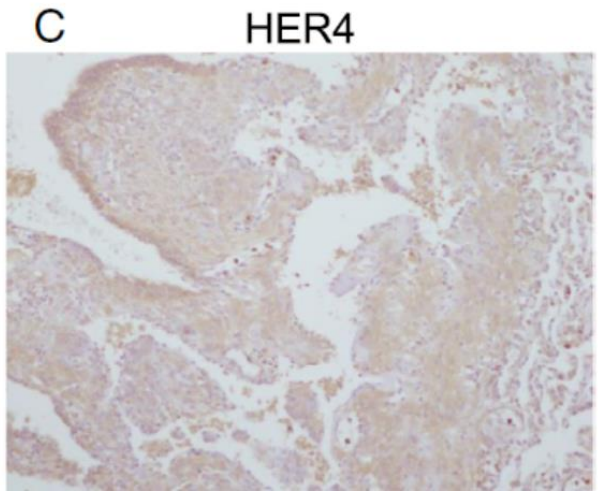
β-catenin *E-cadherin* *EGFR* *podoplanin*

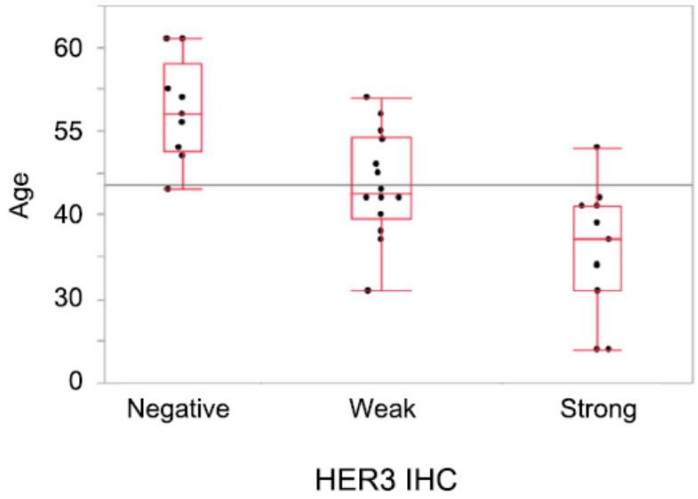
ranked using the modified semi-quantitative Immunoreactive Remmele Score (IRS)

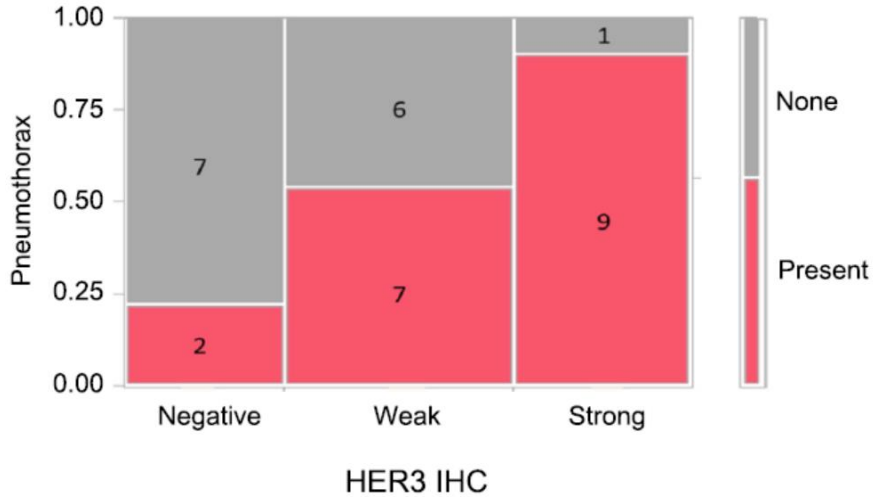




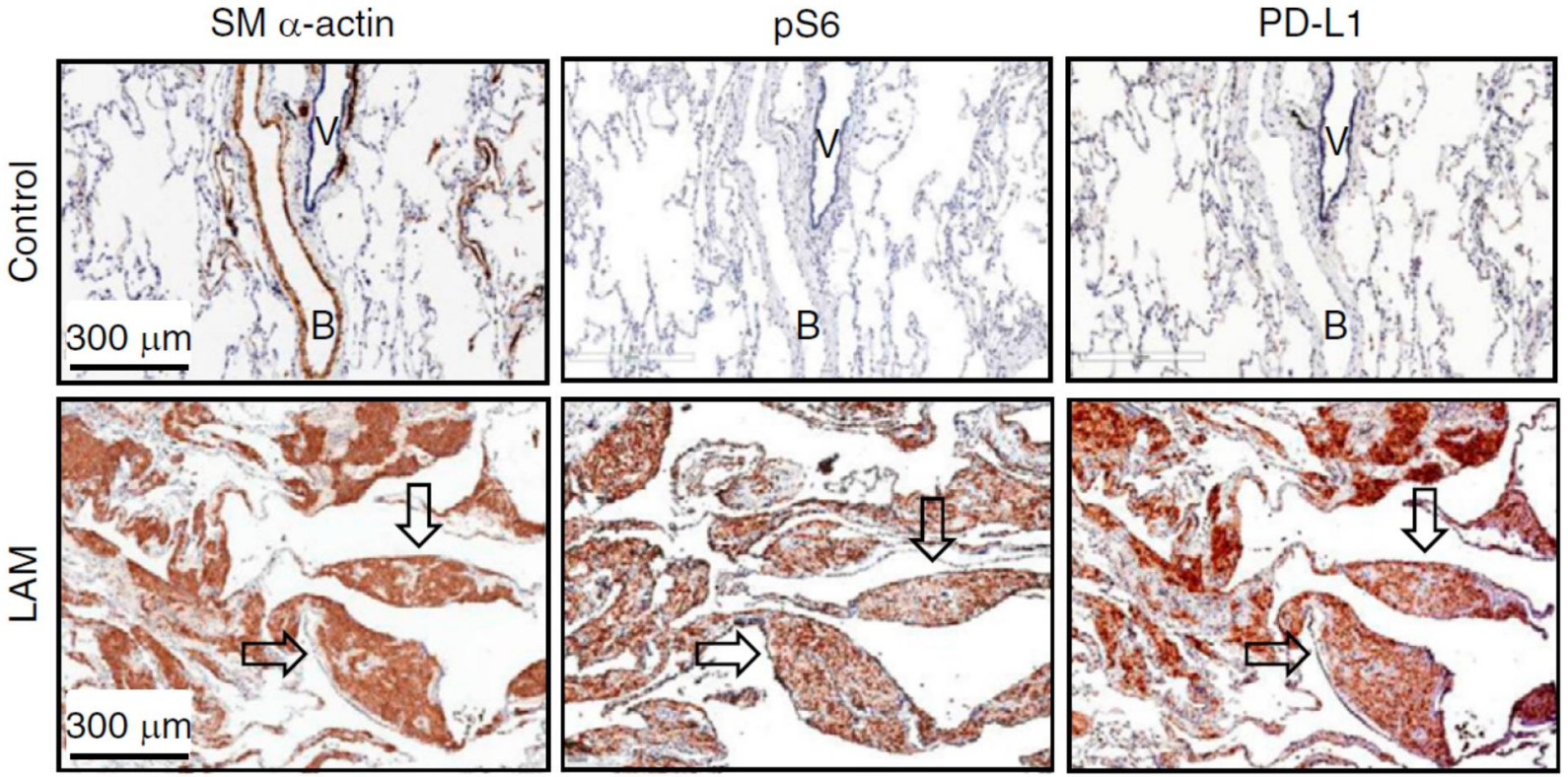


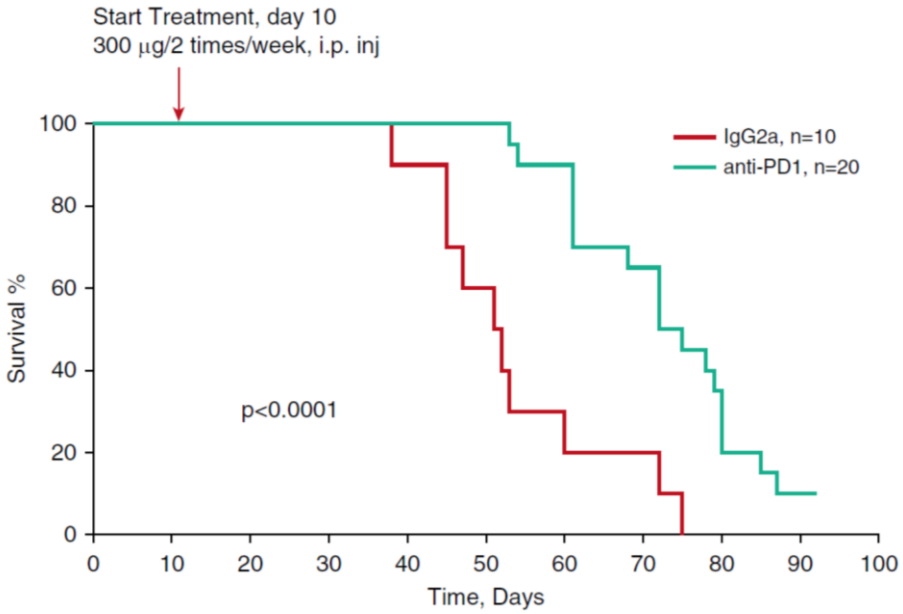






Human Pathology 2018;81:121–130





Am J Respir Cell Mol Biol 2018;59:723–732

Content

- What is LAM?
- Diagnosis
- Management

Management of LAM

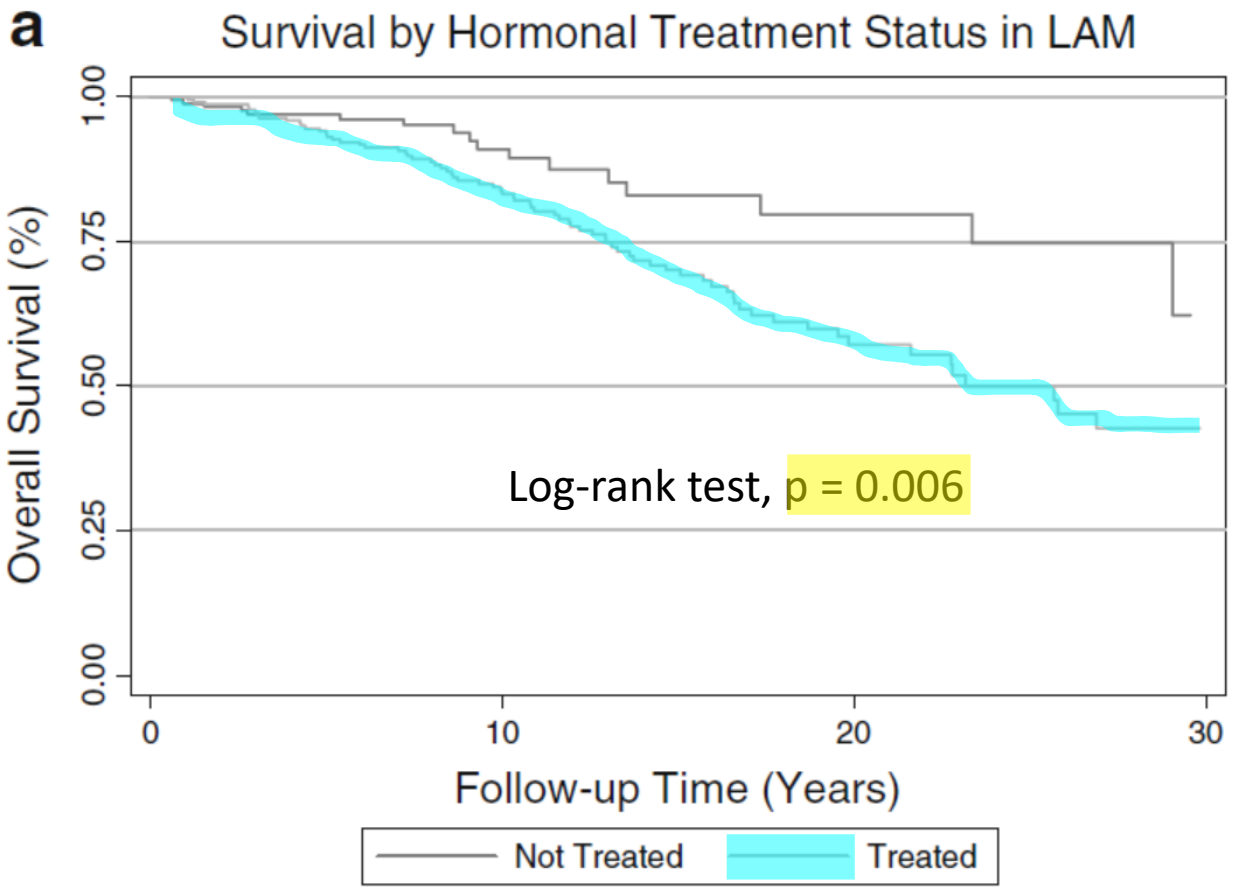
- Unproven Therapies
  - **Anti-estrogen therapies**

    **No randomized controlled trials of progesterone

  - **Corticosteroids, immunomodulatory cytotoxic agents or ovarian irradiation**

  - **Oophorectomy** (removal of the ovaries)

Eur Respir J 2010; 35: 14–26
The LAM Foundation



- Hormonal treatment included progesterone, GnRh agonists, and chemical or surgical oophorectomy at any point in the disease course.

Lung 2013;191:35–42

Management of LAM

- Supportive Measures
  - Oxygen therapy
  - Bronchodilators
- **mTOR Inhibitor Therapy**
  - RAPAMUNE® (sirolimus)
  - Afinitor (everolimus)
- Pulmonary rehabilitation
- **Lung Transplantation**

Eur Respir J 2010; 35: 14–26
The LAM Foundation

Table 1 Summary of rapamycin (sirolimus) trials for LAM

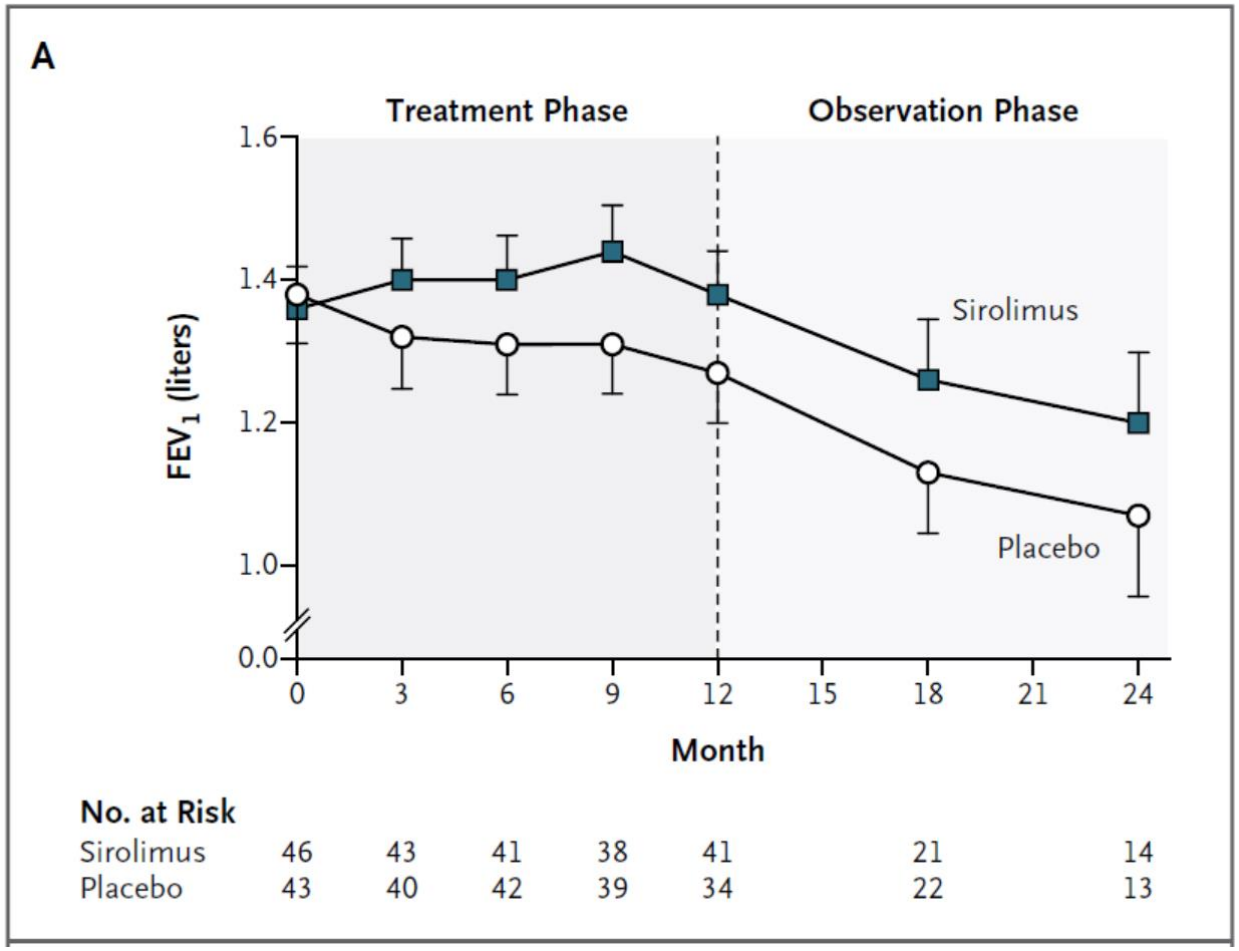
Year	Type of study	Sample size	Intervention	Drug levels	Duration	Effects
2008[3]	Open label	11 (LAM) 20 (AML)	Sirolimus	10–15 ng/mL except one case	12 m treatment 12 m observation	↑ FEV_1, FVC ↓ AML size
2011[4 7]	Randomised, double blind	89	Sirolimus versus placebo	5–15 ng/mL	12 m treatment 12 m observation	↑ FEV_1, FVC, QoL, functional performance ↓ VEGF-D, FRC, air trapping ↔ 6MWD, DLCO
2011[9]	Observation	19	Sirolimus	5–15 ng/mL	2.6±1.2 years	↑ FEV_1, FVC, DLCO ↓ Chylothorax volume
2011[13]	Observation	10	Sirolimus	5–10 ng/mL	12.1±2.8 m	↑ FEV_1, FVC, 6MWD, DLCO ↔ TLC, PaO_2
2011[18]	Open label	16	Sirolimus	3–10 ng/mL	24 m	↓ AML size ↔ FEV_1, FVC, DLCO
2013[12]	Retrospective	15	Sirolimus	2.16 (0.8–4.3) ng/mL	17.5±5.9 m without chylothorax 12.0±5.5 m with chylothorax	↑ FEV_1, FVC ↓ VEGF-D, chylothorax
2014[19]	Observation	38	Sirolimus	5–15 ng/mL	3.4±2.4 years; 5 years in 12 patients	↑ FEV_1, DLCO ↔ Cysts, 6MWD
2015[20]	Retrospective	78	Sirolimus, simvastatin or combined		Mean 2.7–2.8 years	↑ FEV_1, DLCO ↔ No effects from adding simvastatin
2016[11]	Open label	63	Sirolimus	5–15 ng/mL	24 m	↑ FEV_1, FVC in a chylothorax subgroup ↔ QoL, FEV_1, FVC
2016[10]	Observation	25	Sirolimus	5–15 ng/mL	4.5±1.6 years	↓ Chylothorax, VEGF-D, AML size ↔ FEV_1, DLCO

6MWD, 6 min walk distance; AML, angiomyolipoma; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; LAM, lymphangioleiomyomatosis; m, months; QoL, quality of life; RV, residual volume; TLC, total lung capacity; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor-D; ↑, improved or increased in size or value; ↓, worsened or decreased in size or value; ↔, similar or unchanged.

Thorax 2018;73:308–310.

Multicenter International Lymphangioleiomyomatosis (LAM) Efficacy of Sirolimus (**MILES**) trial

NCT00414648.



N Engl J Med 2011;364:1595-606

Multicenter International Lymphangioleiomyomatosis (LAM) Efficacy of Sirolimus (**MILES**) trial

NCT00414648.

- stabilized lung function

(**in patients with post-bronchodilator %FEV1 ⩽70% predicted)

- reduced serum VEGF-D levels
- reduction in symptoms
- improvement in quality of life.

N Engl J Med 2011;364:1595-606

Further Analysis of the **MILES** cohort

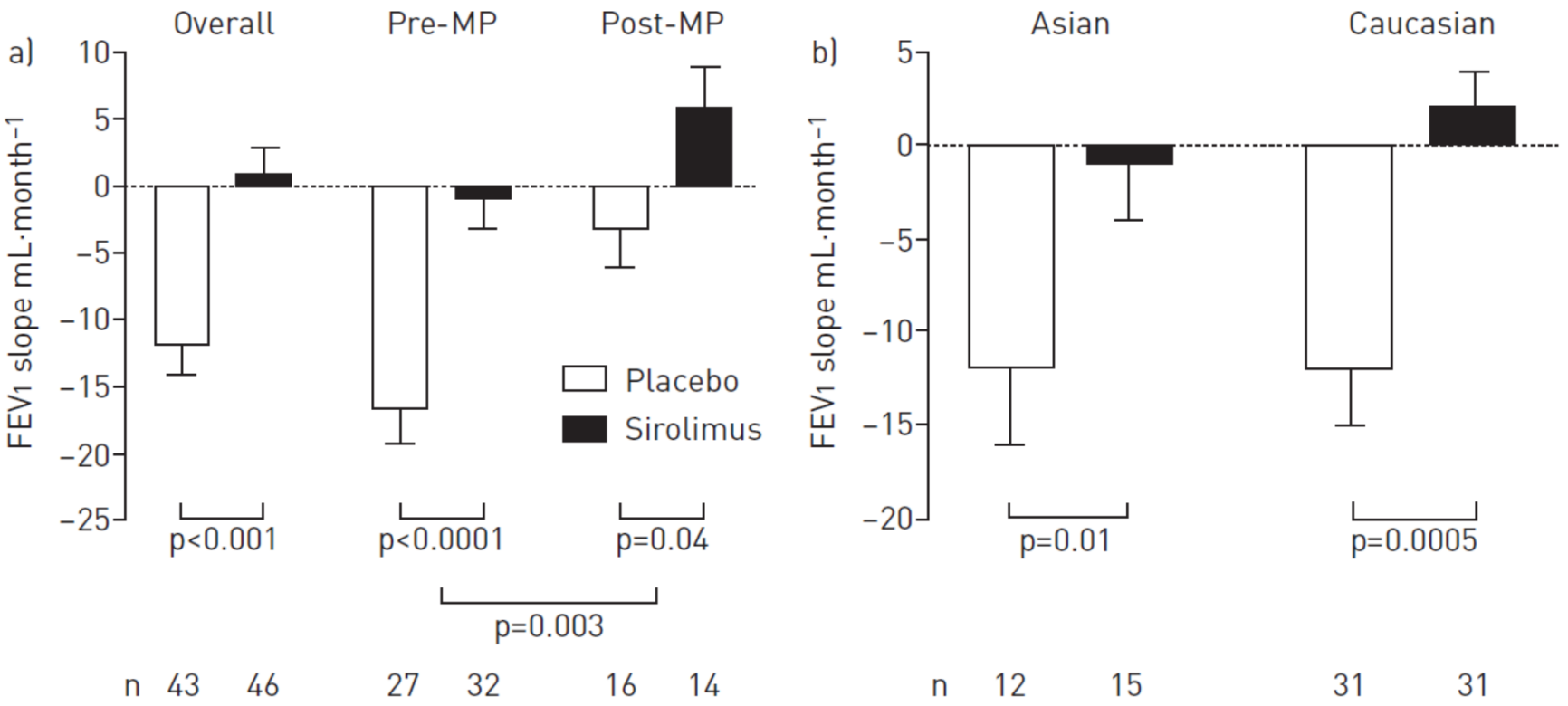


FIGURE 1. Effect of a) menopause and b) race on forced expiratory volume in 1 s (FEV_1) response

Eur Respir J 2019; 53: 1802066

Further Analysis of the **MILES** cohort

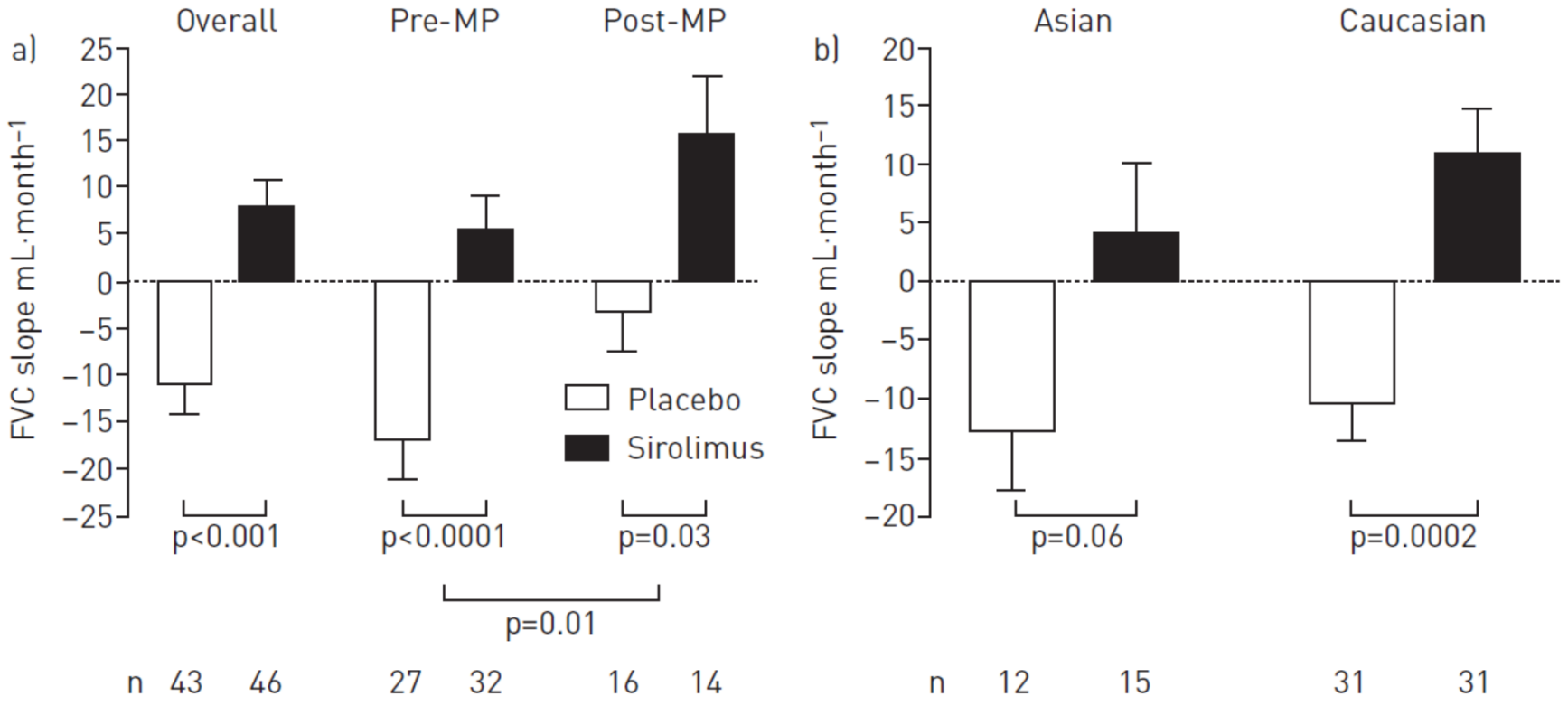


FIGURE 2. Effect of a) menopause and b) race on forced vital capacity (FVC) response

Eur Respir J 2019; 53: 1802066

Further Analysis of the **MILES** cohort

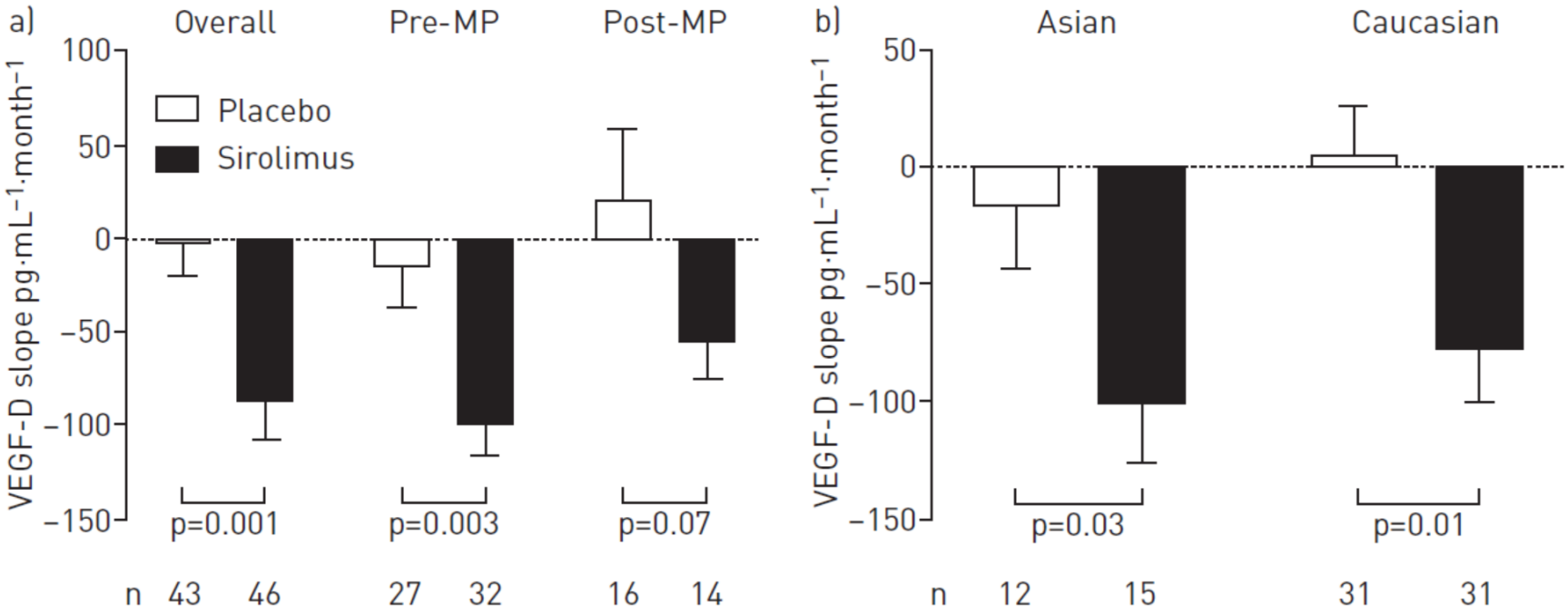


FIGURE 3. Effect of a) menopause and b) race on serum vascular endothelial growth factor (VEGF)-D response

Eur Respir J 2019; 53: 1802066

Further Analysis of the **MILES** cohort

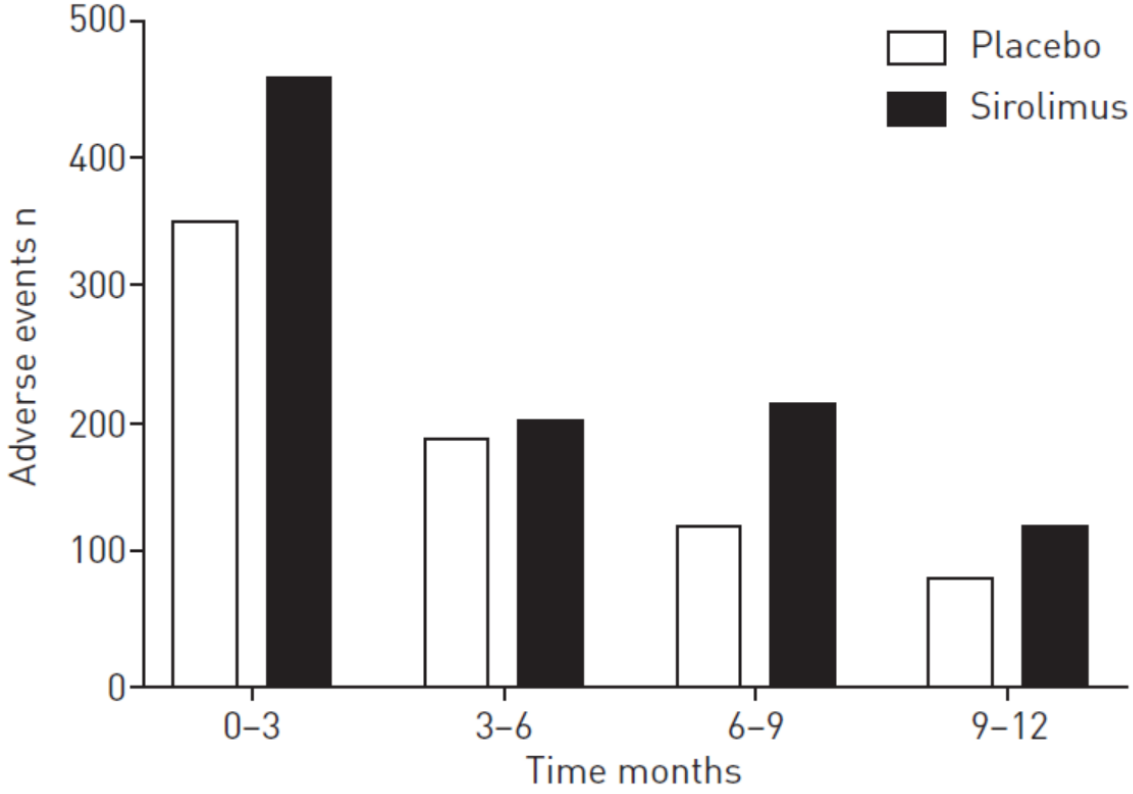
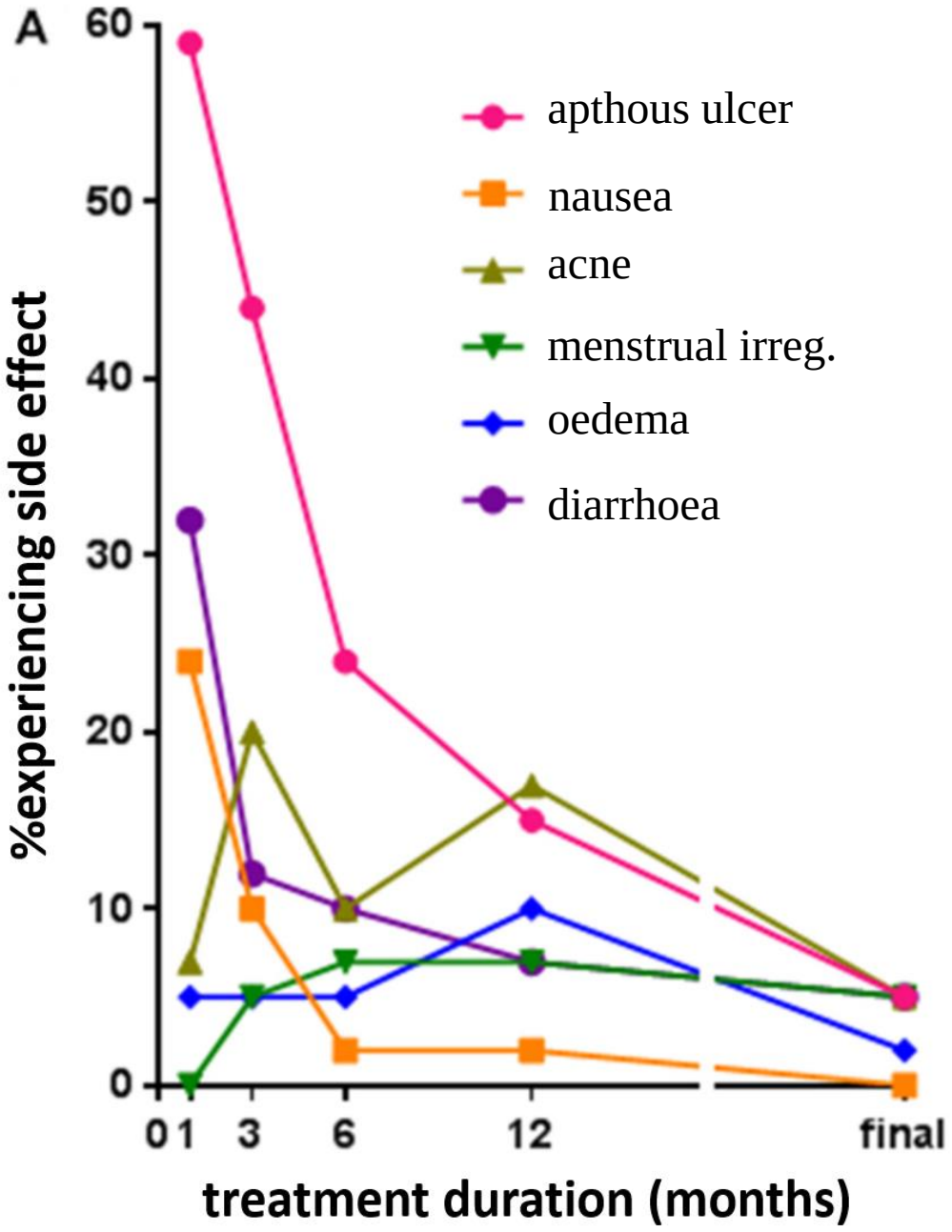


FIGURE 6. Time course of adverse events during the first 12 months of the MILES trial

Eur Respir J 2019; 53: 1802066



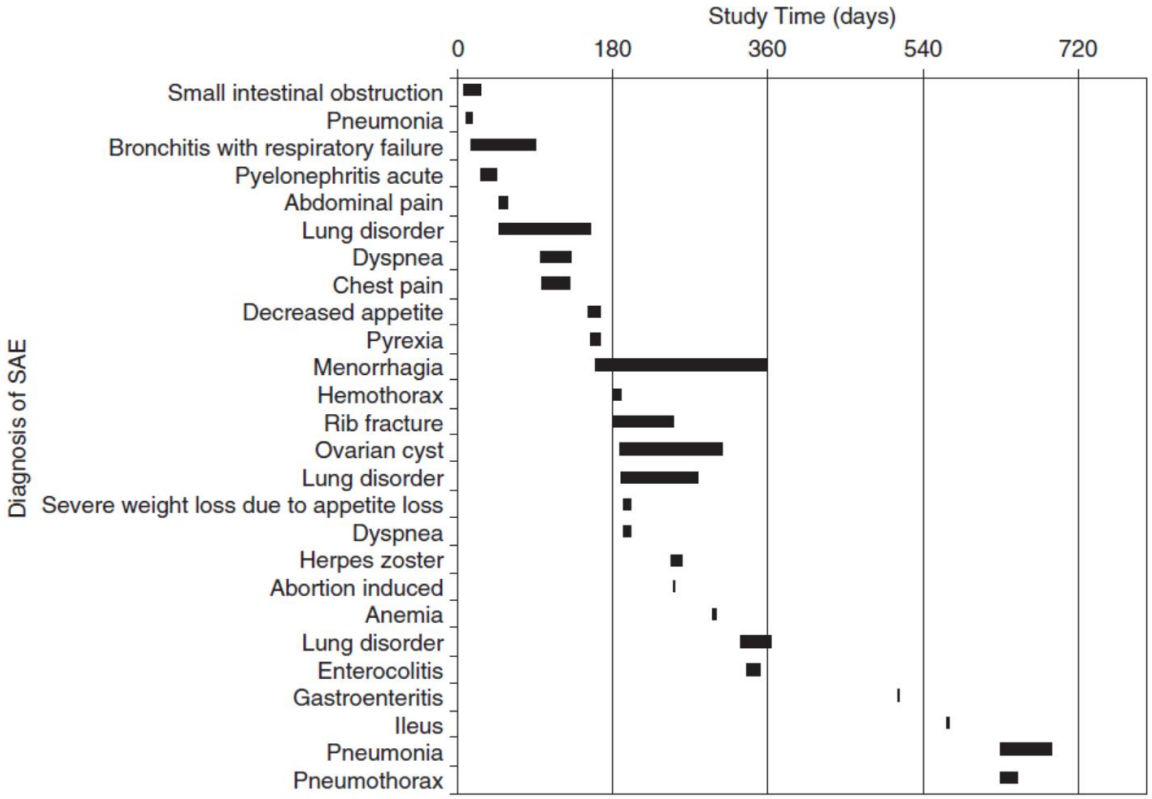
1969 - 2019

Thorax 2018;73:369–375

Multicenter Lymphangioleiomyomatosis Sirolimus Trial for Safety (**MLSTS**)

JMA-IIA00096

**patients with normal lung function (FEV_1 >70% predicted) and physiologically impactful chylous effusions were not excluded



Ann Am Thorac Soc 2016;13:1912–1922

Multicenter Lymphangioleiomyomatosis Sirolimus Trial for Safety (**MLSTS**)

JMA-IIA00096

Table 4. Cases of sirolimus-induced pneumonitis

Case	Age (*yr*)	FEV_1 % predicted at baseline	Sirolimus			CT Image	Treatment	Outcome
			Period (*mo*)	Dose (*mg/d*)	Trough* (*ng/ml*)			
1	38	NA	11	2	4.8	Diffuse GGO	Sirolimus cessation (6 wk)	Recovered and resumed sirolimus (1 mg/d)
2	39	96.2	6	2	7.6	GGO in bilateral lower lobes	Sirolimus cessation (14 wk)	Recovered and resumed sirolimus (1 mg/d)
3	40	63.1	1.5	2	13.7	Diffuse GGO, fine nodules	Sirolimus cessation; corticosteroid (pulse)	Recovered

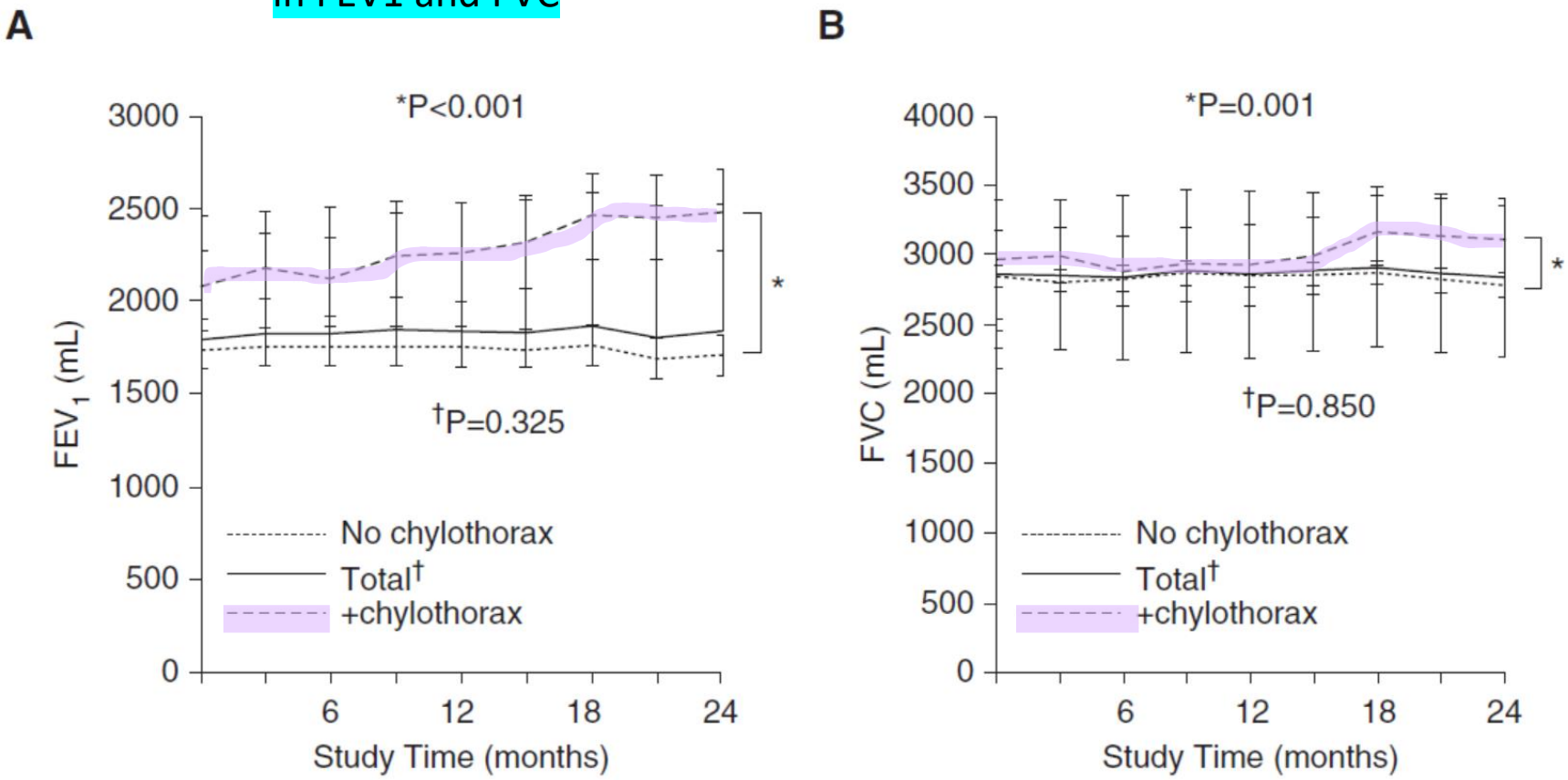
Definition of abbreviations: CT = computed tomographic; GGO = ground-glass opacities; NA = not available.
*Trough sirolimus value immediately prior to the development of pneumonitis.

Ann Am Thorac Soc 2016;13:1912–1922

MLST

S

Those with a **history of chylothorax** had a significant increase in FEV1 and FVC



No. of cases									
total	56	50	49	50	48	47	47	45	44
+chylothorax	9	9	9	9	8	8	7	7	7
No chylothorax	47	41	40	41	40	39	40	38	37

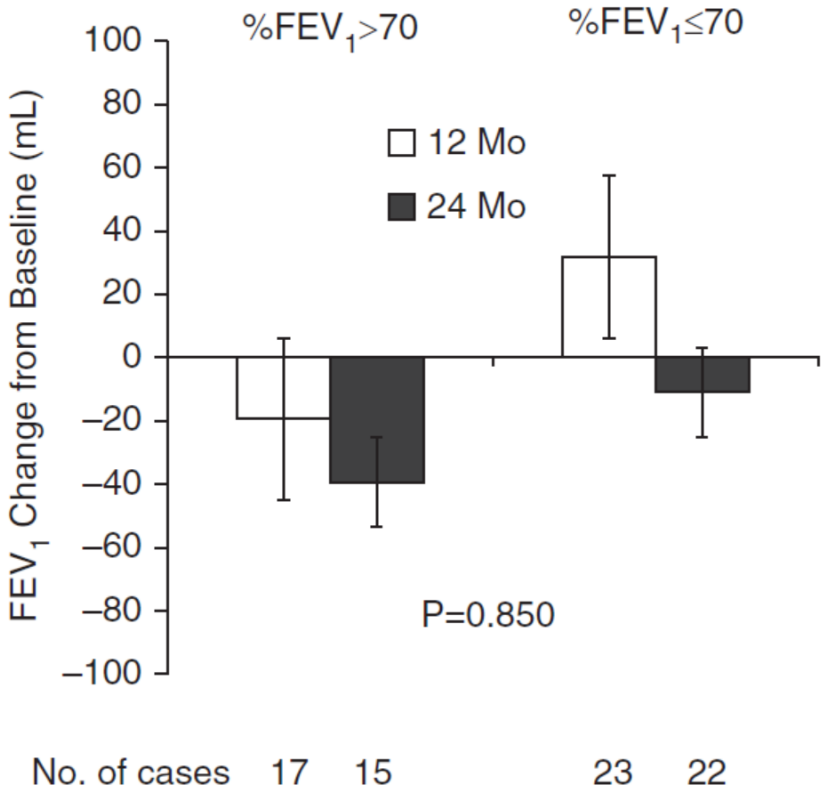
No. of cases									
total	56	50	49	50	48	47	47	45	44
+chylothorax	9	9	9	9	8	8	7	7	7
No chylothorax	47	41	40	41	40	39	40	38	37

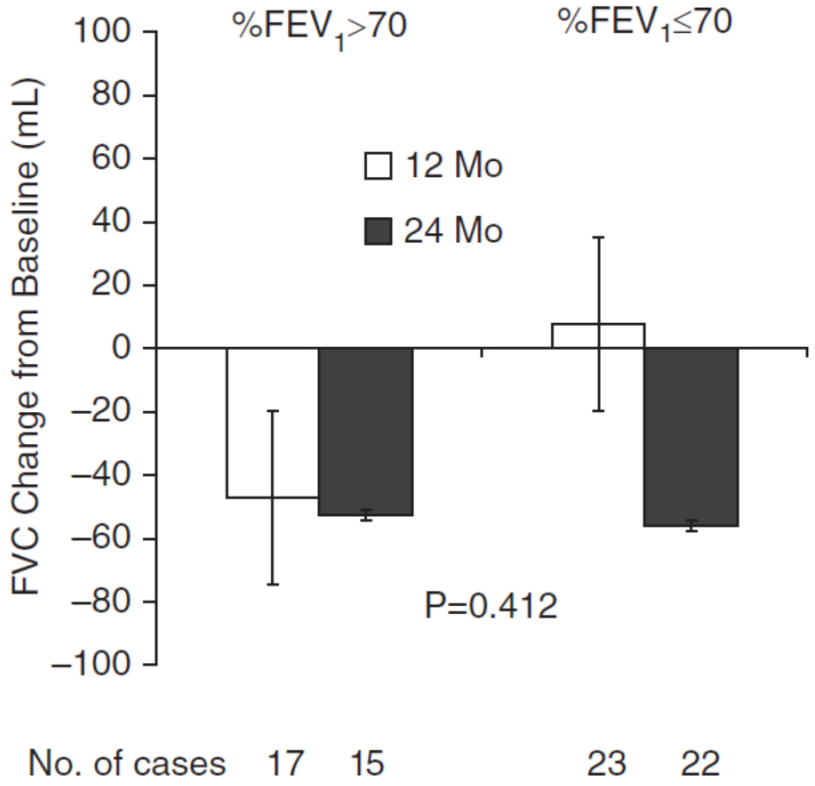
Ann Am Thorac Soc 2016;13:1912–1922

MLST

S

Mean changes from baseline to 12 and 24 months in FEV1 and FVC for the patients **without a history of chylothorax**

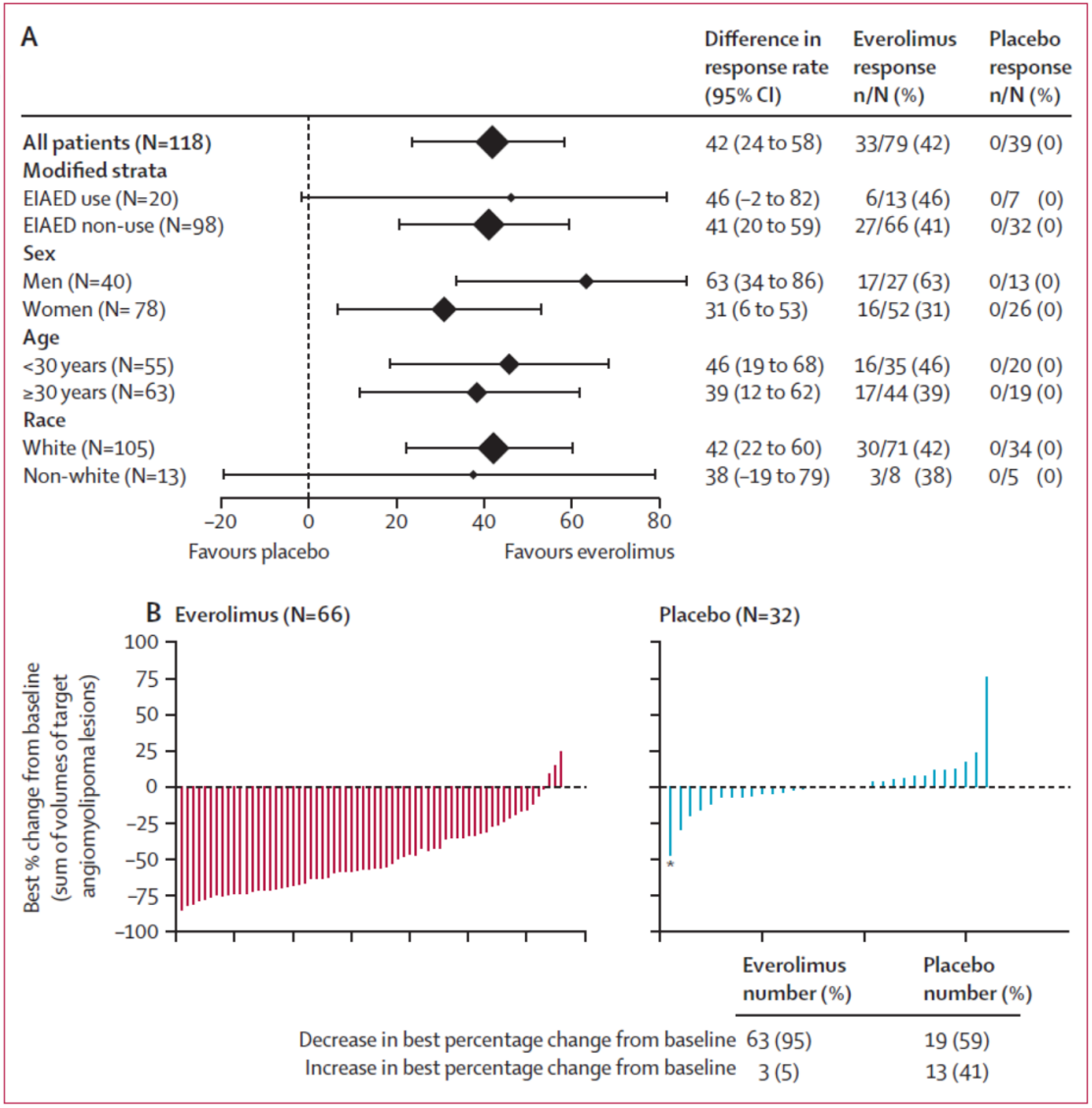




Ann Am Thorac Soc 2016;13:1912–1922


50
TSPCCM
1969 - 2019

EXIST-2



◆ **Everolimus reduced angiomyolipoma volume with an acceptable safety profile**

Lancet 2013;381: 817–824

EXIST-2

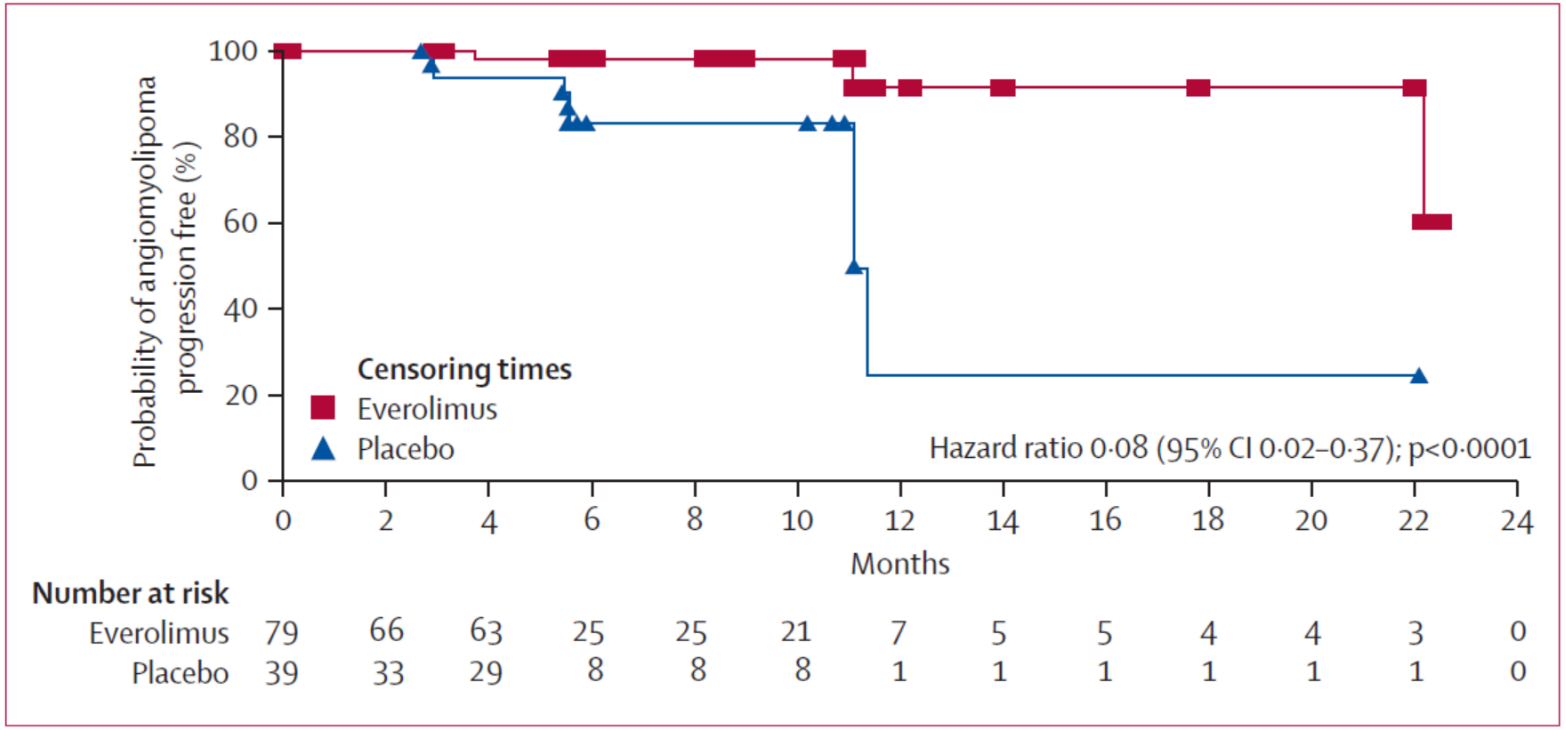


Figure 3: Kaplan-Meier plot showing time to angiomyolipoma progression, as assessed by central review

Lancet 2013;381: 817–824

EXIST-2

Four-year update

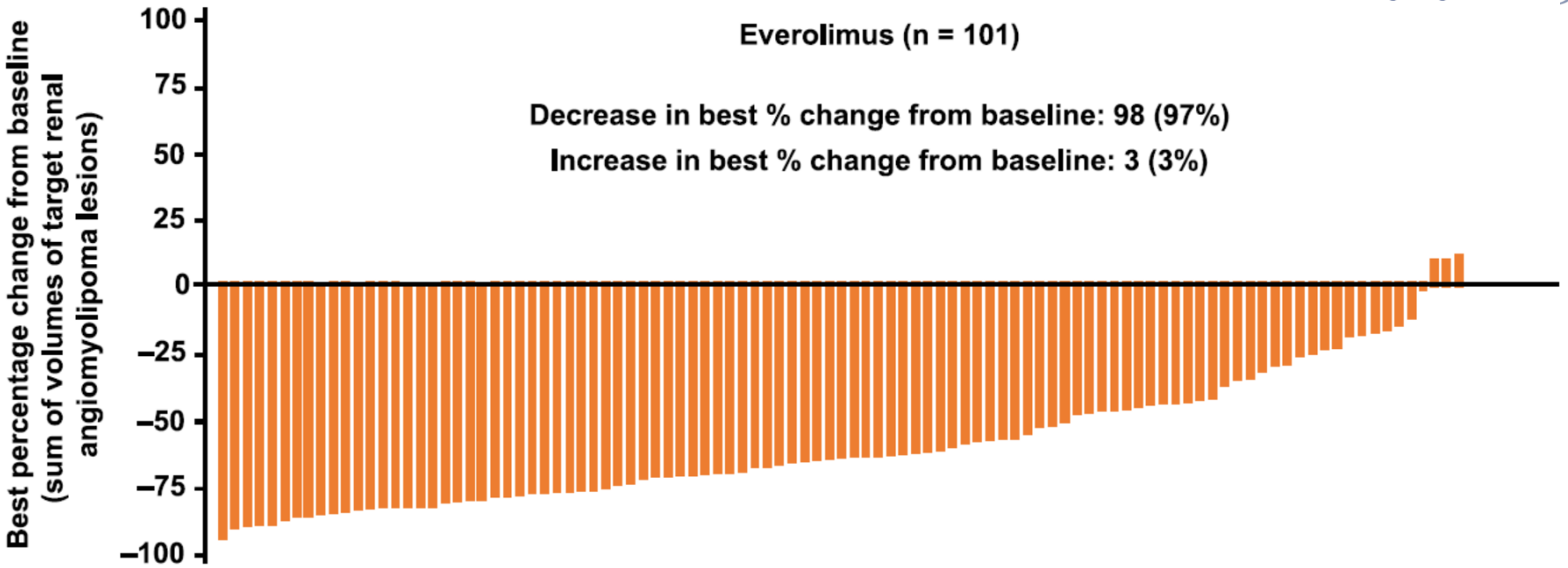


Fig 2. Best percentage reduction in the sum volume of target renal angiomyolipomas each individual patient reported at any time point in the study in 101 evaluable patients.[a] [a]11 patients were considered "non-evaluable" due to missing overall angiomyolipoma response status at each radiological assessment. Among the 12 patients with a best overall response with the status "not evaluable", only one patient reported at least one radiological assessment with a non-missing overall angiomyolipoma response status.

PLoS ONE 2017;12: e0180939.

EXIST-2

Four-year update

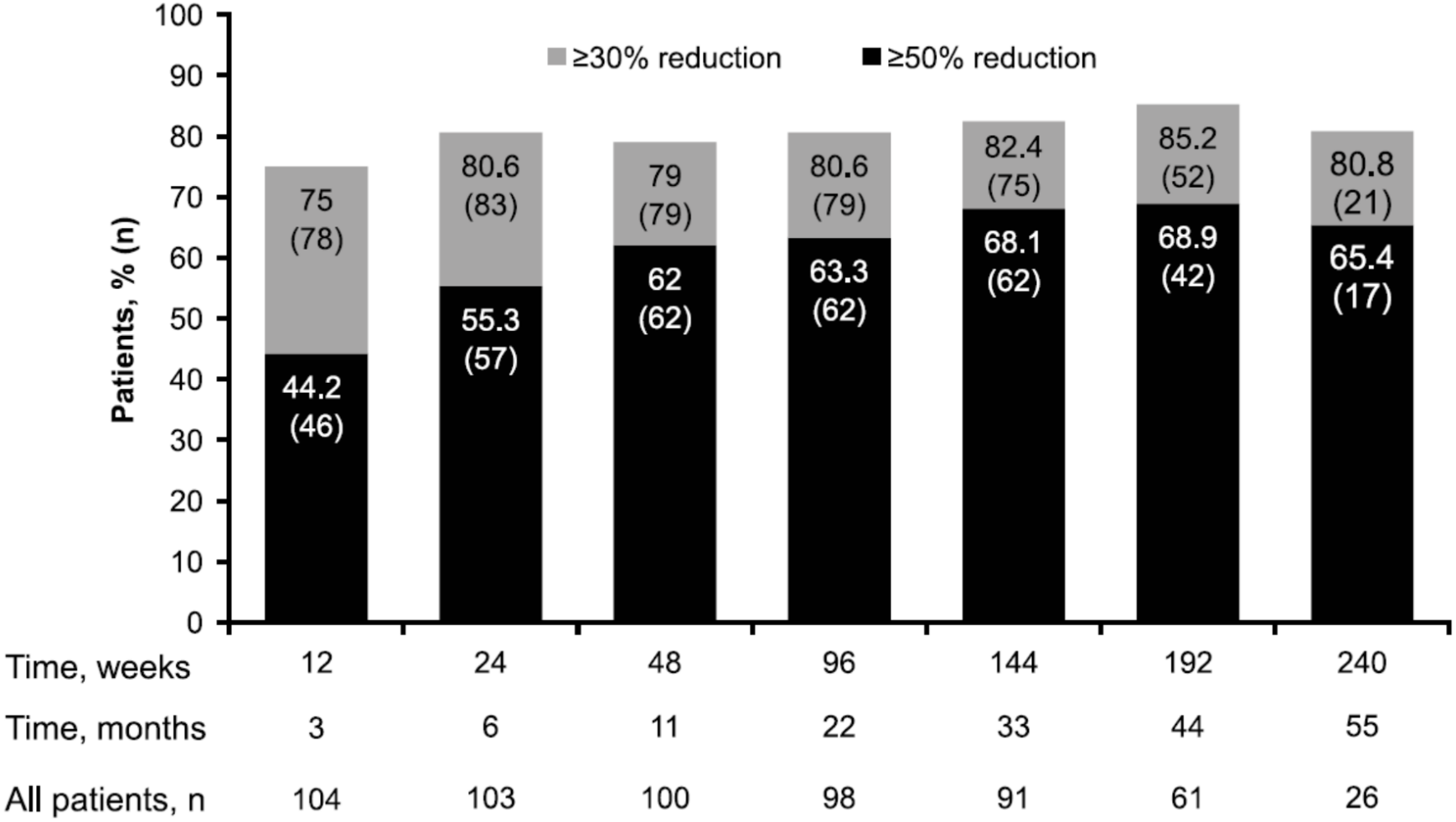


Fig 3. Renal angiomyolipoma response rate with everolimus over time.

PLoS ONE 2017;12: e0180939.

Lung Transplantation

- New York Heart Association (NYHA) functional class III or IV with severe impairment in lung function and exercise capacity (V'O2max < 50% pred, hypoxaemia at rest)

- One, five, and ten-year survival rates after lung transplantation are 89%, 67%, and 47%, respectively.

Eur Respir J 2010; 35: 14–26
The LAM Foundation

NYHA 四種等級	心臟病人的日常功能活動力
第一級	身體活動不受限制，一般日常活動不會引起疲倦、心悸、呼吸困難或心絞痛。例如：爬四層以上的樓梯不會喘，運動員就屬此類。
第二級	身體活動輕度受限制，正常的活動感覺呼吸急促，可以從事日常活動，如：爬樓梯或掃地；若作劇烈運動則會感覺呼吸困難、疲倦、心悸或心絞痛。例如：正常走路都很好，爬三層樓梯會稍微喘一下。
第三級	身體活動明顯受限制，輕度活動就呼吸急促，休息時會緩解，但從事日常的輕微活動（如：洗澡、穿衣服、爬樓梯或掃地）就會引起疲倦、心悸、呼吸困難或心絞痛。例如：爬二樓就喘，住三樓爬樓梯需花 3 ～ 5 分鐘。
第四級	執行任何身體活動都會不舒服，走去開個門，上洗手間就喘；休息時也會覺得呼吸急促，甚至躺在床上或站著不動時，也會感覺呼吸困難、疲倦、心悸或心絞痛，而需藉由坐起來或墊高枕頭才得以緩解。

Table 4. Summaries of studies on lung transplantation for LAM

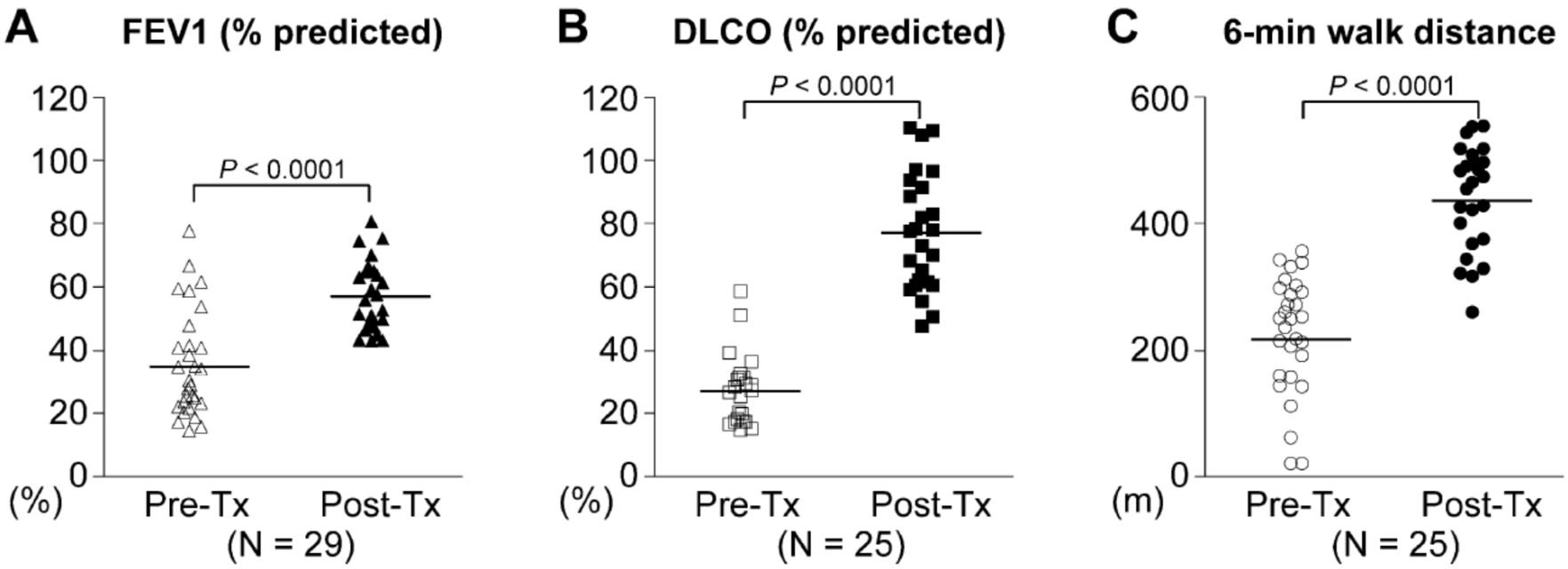
Study	Multi-center studies					Single-center studies	
	Boehler A, et al.[6]	Kpodonu J, et al. [15]	Reynaud-Gaubert M, et al. [16]	Benden C, et al. [17]	Ando K, et al. (This study)	Pechet TT, et al. [18]	Machuca TN, et al. [19]
Country	Switzerland	U.S.	France	Europe	Japan	U.S.	Brazil
Period	1992 to 1995	1987 to 2002	1988 to 2006	1997 to 2007	2000 to 2014	1989 to 2001	1989 to 2009
No. of patients	34	79	44	61	57	14	10
No. of centers	16	31	9	21	6	1	1
Age at onset (mean)	29	-	33	-	31.9	-	-
Age at diagnosis (mean)	34	-	36	34.4	34.0	35.7	-
Age at transplan-tation (mean)	40	41.1	41	41.3	41.8	41.8	43.8
FEV_1%pred (mean)	24	-	22.8	27	32.7	20	32.9
DL_{co} %pred (mean)	26	-	27.2[a]	26	24.7	23	38
PaO_2 (mean), mmHg	56	-	52.8	(59.3)[b]	54.2	53.7	-
6MWD (mean), m	-	-	214	220	248	(251)[c]	-
Mean waiting time (SD)	-	448 days (322)	-	-	1,060 days (649)	1.9 year (1.0)	-
Survival rate	69% (1y) 58% (2y)	85.8% (1y) 76.4% (3y) 64.9% (5y)	79.6% (1y) 74.4% (2 y) 64.7% (5y) 52.4% (10y)	79% (1y) 73% (3y)	86.7% (1y) 82.5% (3y) 73.7% (5y) 73.7% (10y)	100% (1y) 90% (2y) 69% (5y)	90% (1y) 80% (3y)
Recurrence of LAM (No. of patients)	1	-	2	4	4	1	-

**alter with the use of sirolimus

PLoS One. 2016;11:e0146749.

Single lung transplantation

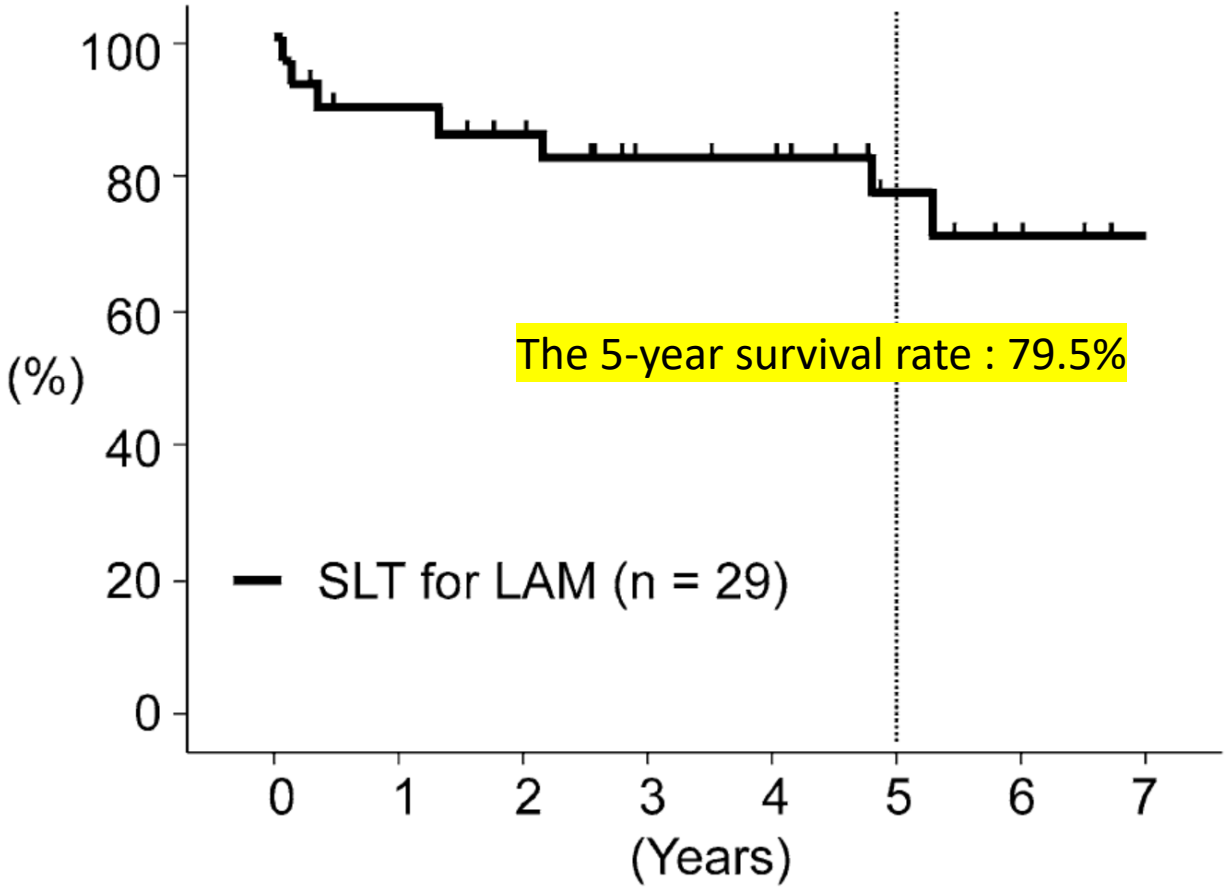
*Tohoku University Hospital



Surgery Today 2018;48:944–950

Single lung transplantation

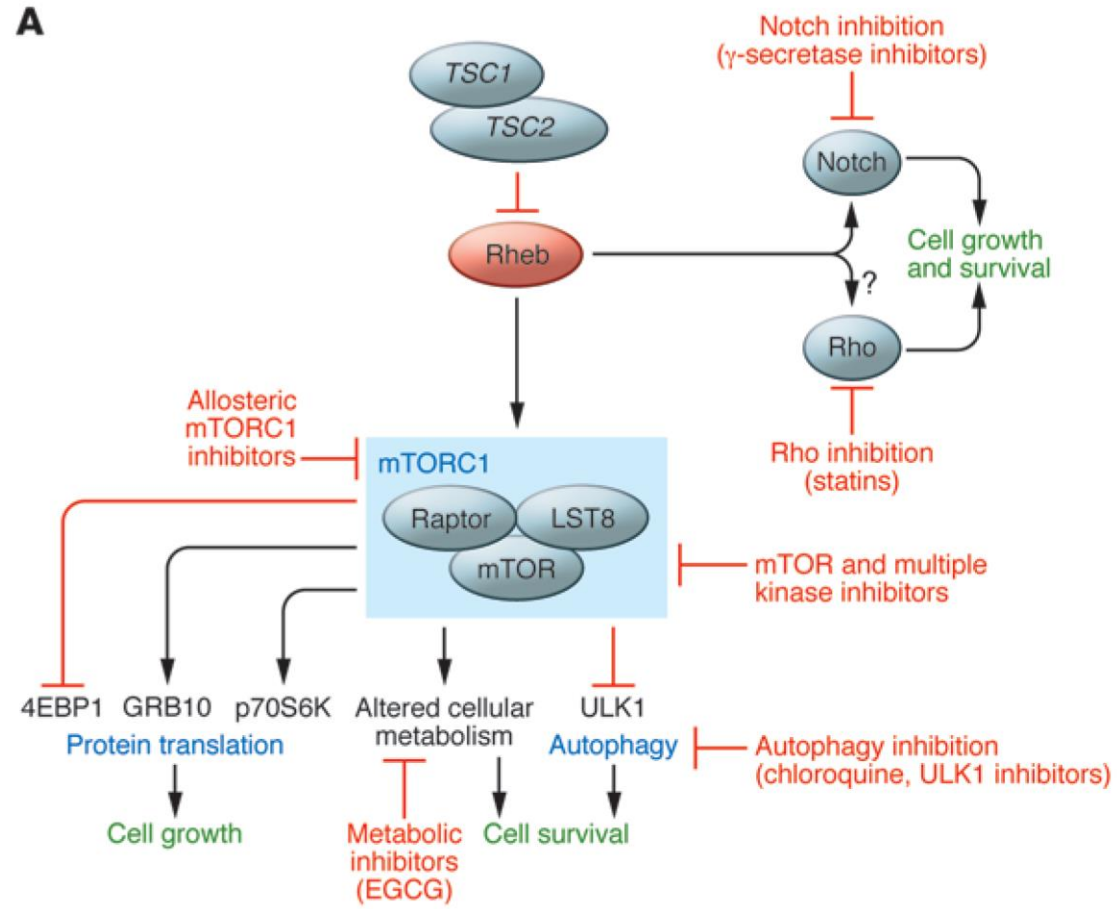
*Tohoku University Hospital

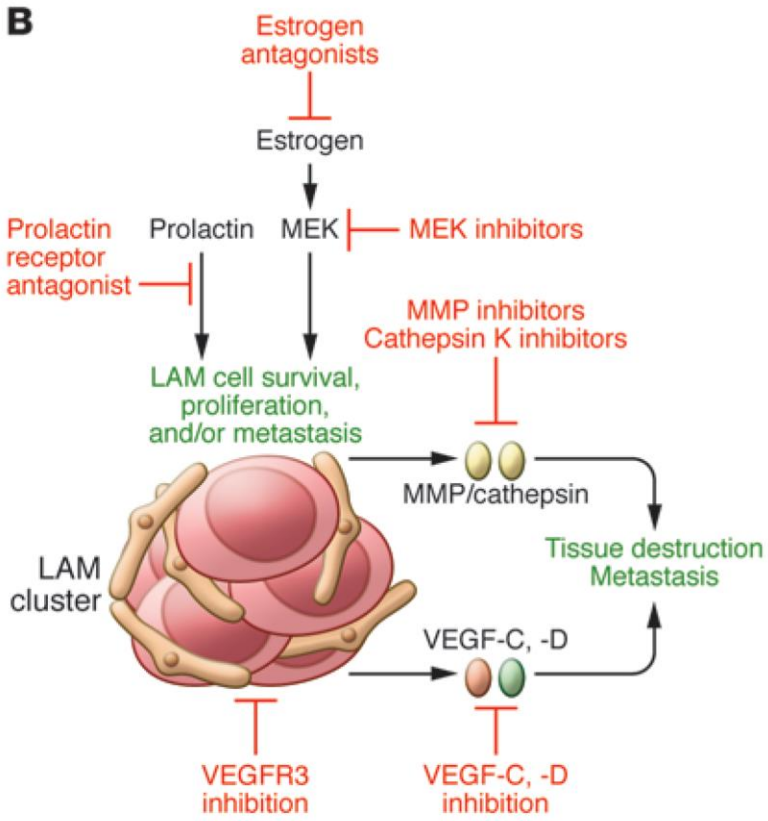


The 5-year survival rate : 79.5%

Surgery Today 2018;48:944–950

Future directions in therapy for LAM





J Clin Invest. 2012;122:3807–16

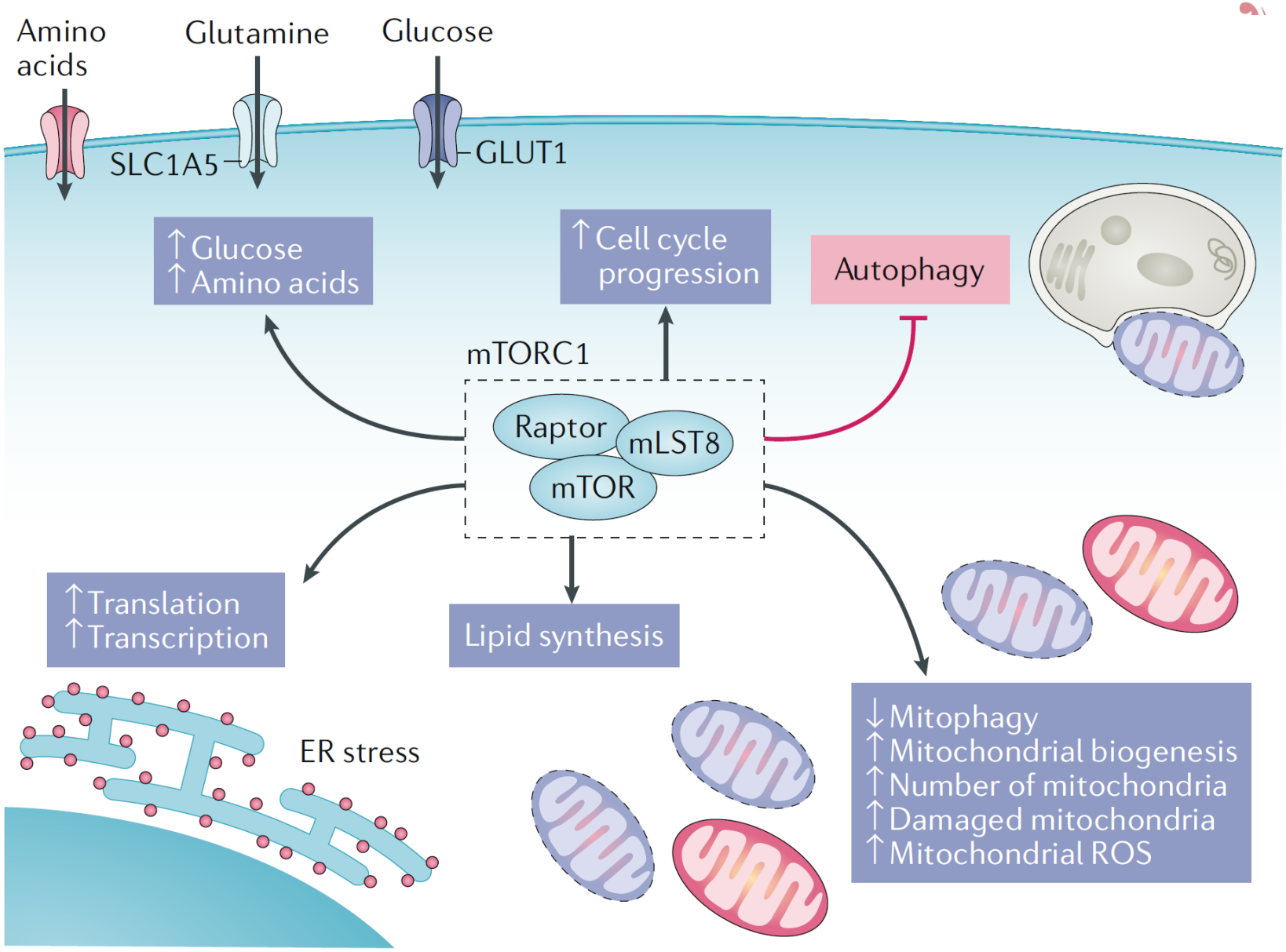
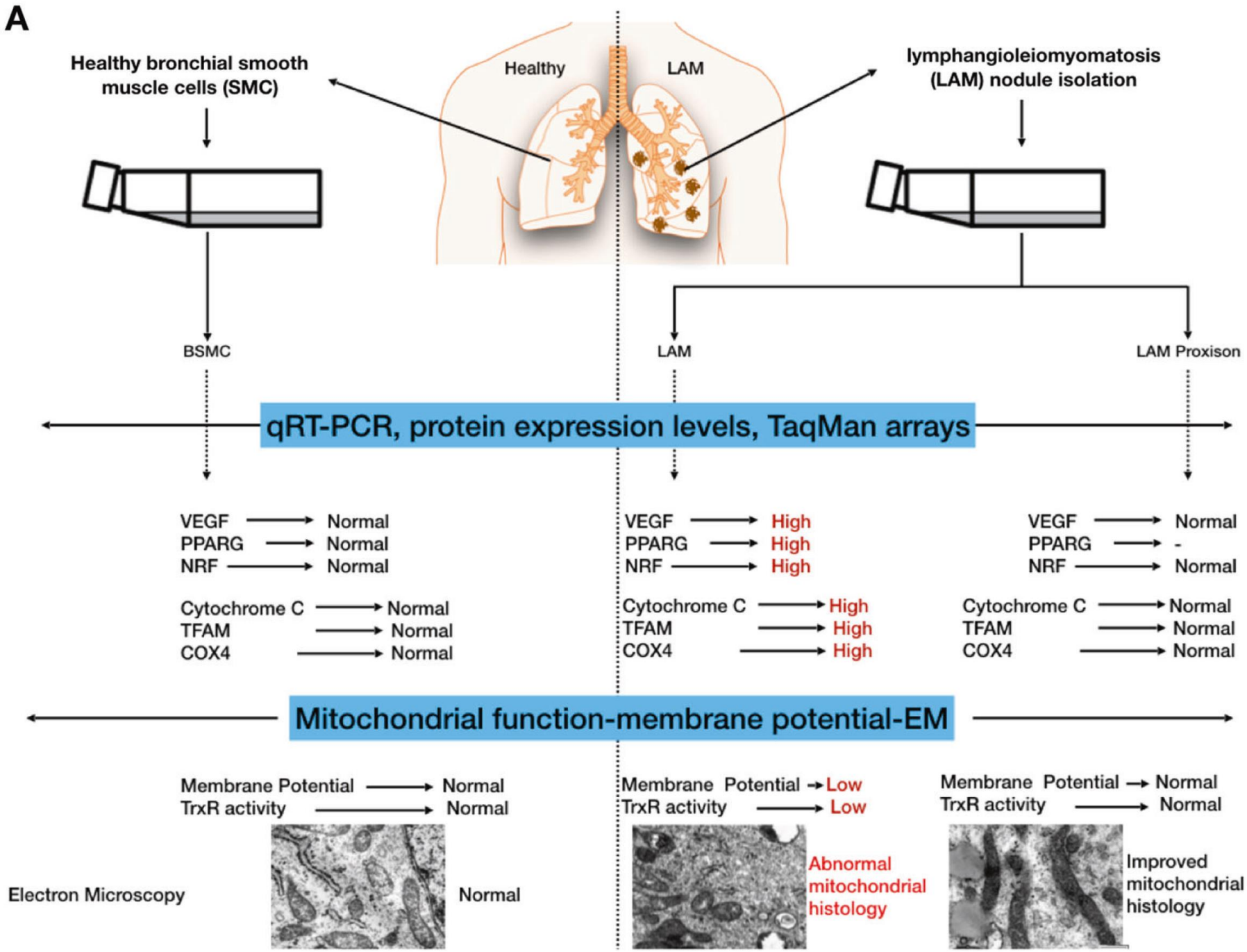


Fig. 3 | **Metabolic and molecular changes associated with mTORC1 hyperactivation in TSC.**

Nature Reviews Nephrology 2018;14:704–16



Oncogene 2019;38:3093–3101

Table 2. Overview of ongoing clinical trials of lymphangioleiomyomatosis

Therapeutic intervention	Primary outcome	Phase	Recruitment status	Clinical trial identifier
Resveratrol in combination with sirolimus vs. sirolimus (RESULT)	Change in serum VEGF-D level after 24 weeks of treatment	II (open label)	Recruiting	NCT03253913
Nintedanib as a single agent	Changes in FEV1 at week 52	II (open label)	Recruiting	NCT03062943
Saracatinib as a single agent	Changes in FEV1 over a 9-month period	II (open label)	Recruiting	NCT02737202
Albuterol	Greater improvement in FEV1 with nebulized vs. inhaled albuterol	II (open label)	Recruiting	NCT01799538
Sirolimus or everolimus	Safety and durability of mTOR inhibitors over at least 2 years	Longitudinal observational study	Recruiting	NCT02432560
Sirolimus	Identification of potential blood and urine markers to evaluate the correct dose of sirolimus	Observational study	Recruiting	NCT03304678
Imatinib mesylate ± co-administration of an mTOR inhibitor	1-month change in serum VEGF-D level	I/II	Recruiting	NCT03131999
Simvastatin co-administered to patients on mTOR inhibitor	Safety over 3 months	I/II (open label)	Recruiting	NCT02061397
Celecoxib (COX-2 inhibitor) as a single agent (COLA)	Safety and tolerability at 6 months	II (open label)	Recruiting	NCT02484664
Long-term, low dose (1 mg daily) sirolimus	Change in FEV1 at 2 years	III	Recruiting	NCT03150914
Long-term, low dose (1 mg daily) sirolimus	Change in FEV1 at 2 years	III	Recruiting	NCT03150914

COX-2, cyclo-oxygenase-2; FEV1, forced expiratory volume in 1 s; mTOR, mammalian target of rapamycin; VEGF-D, vascular endothelial growth factor-D.

Curr Opin Pulm Med 2018, 24:469–476

NIH U.S. National Library of Medicine

ClinicalTrials.gov

LAM Registry

1969 - 2019

- **National Lymphangioleiomyomatosis Registry, France (RE-LAM-CE)**

  NCT01484236

  - N=200
  - Jan.2012~Dec.2020
- **A National Registry on Chinese Patients With Lymphangioleiomyomatosis**

  NCT03193892

  - N=800
  - Jan.2017~Dec.2020

Take Home Massage

- LAM: rare lung disease
- TSC-LAM: more renal involvement
- HRCT, Lung function test, VEGF-D, Biopsy
- mTOR Inhibitor Therapy

Case 1

- Miss Cheng
- 25 y/o → 37 y/o
- First visit on 2007-08

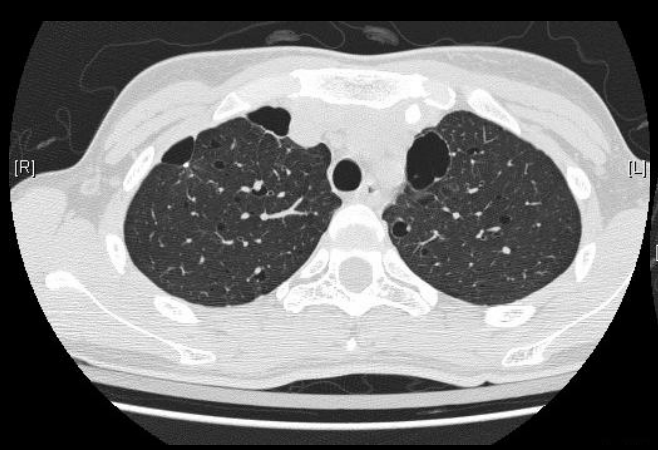
Case 1

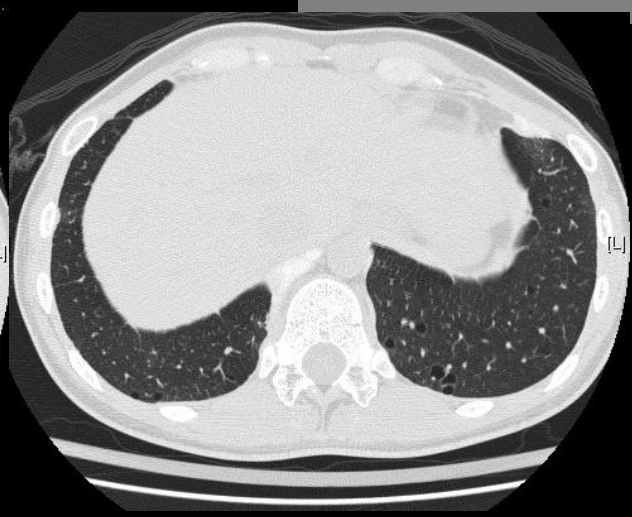
- **Chylothorax**: Right → Left pleural effusion on 2005-08

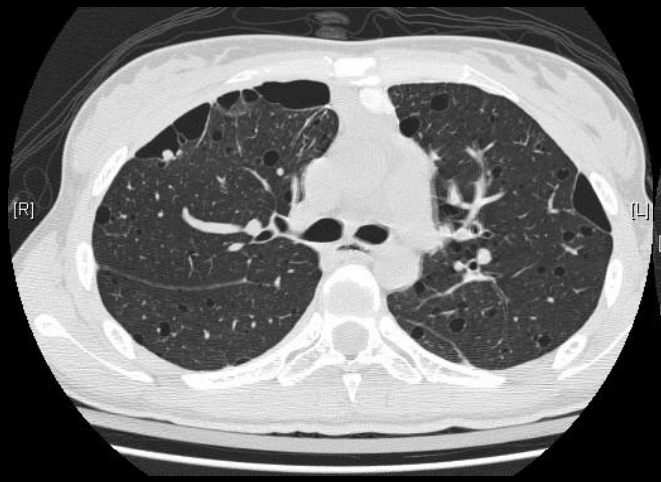
- **LAM** was Dx at ***Massachusetts General Hospital***

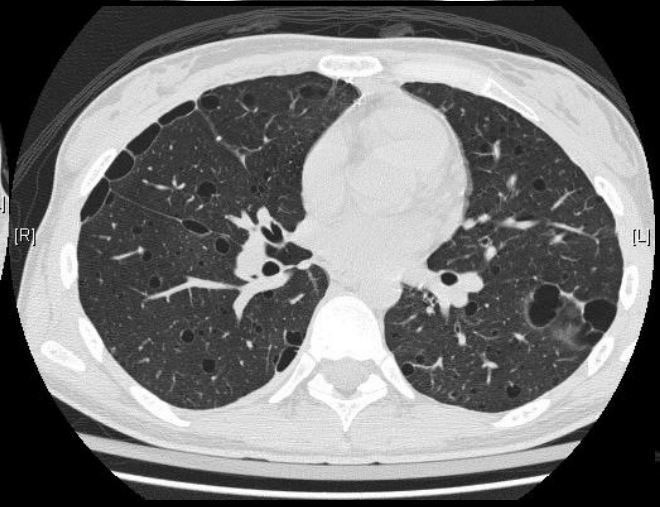
2007-09-17

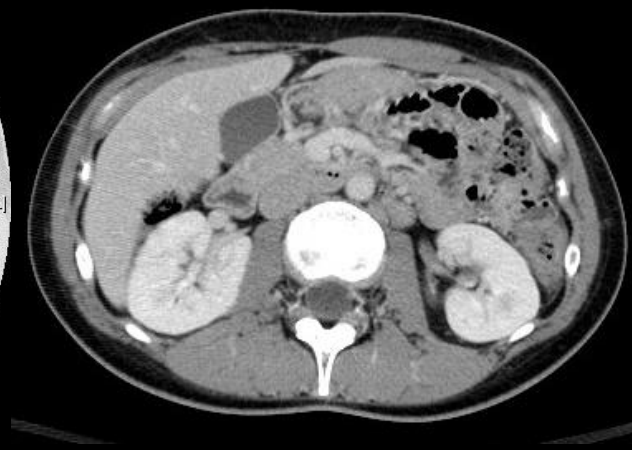
Characteristic CT





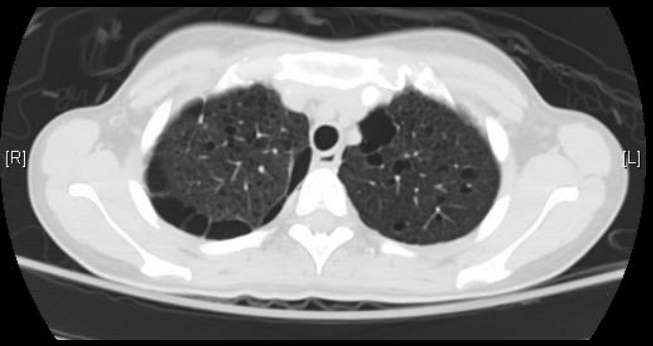


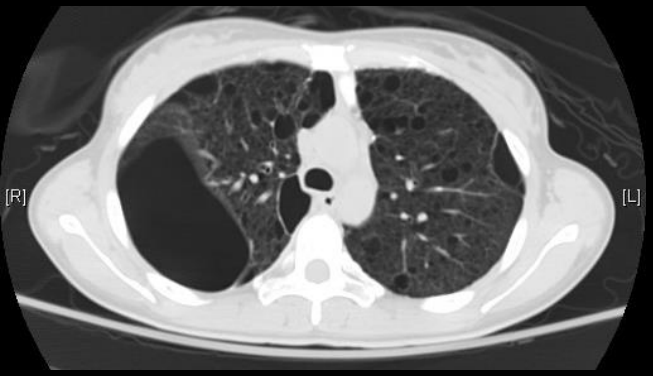


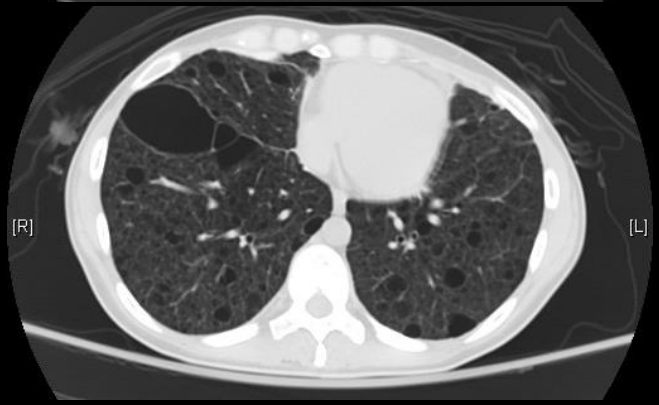


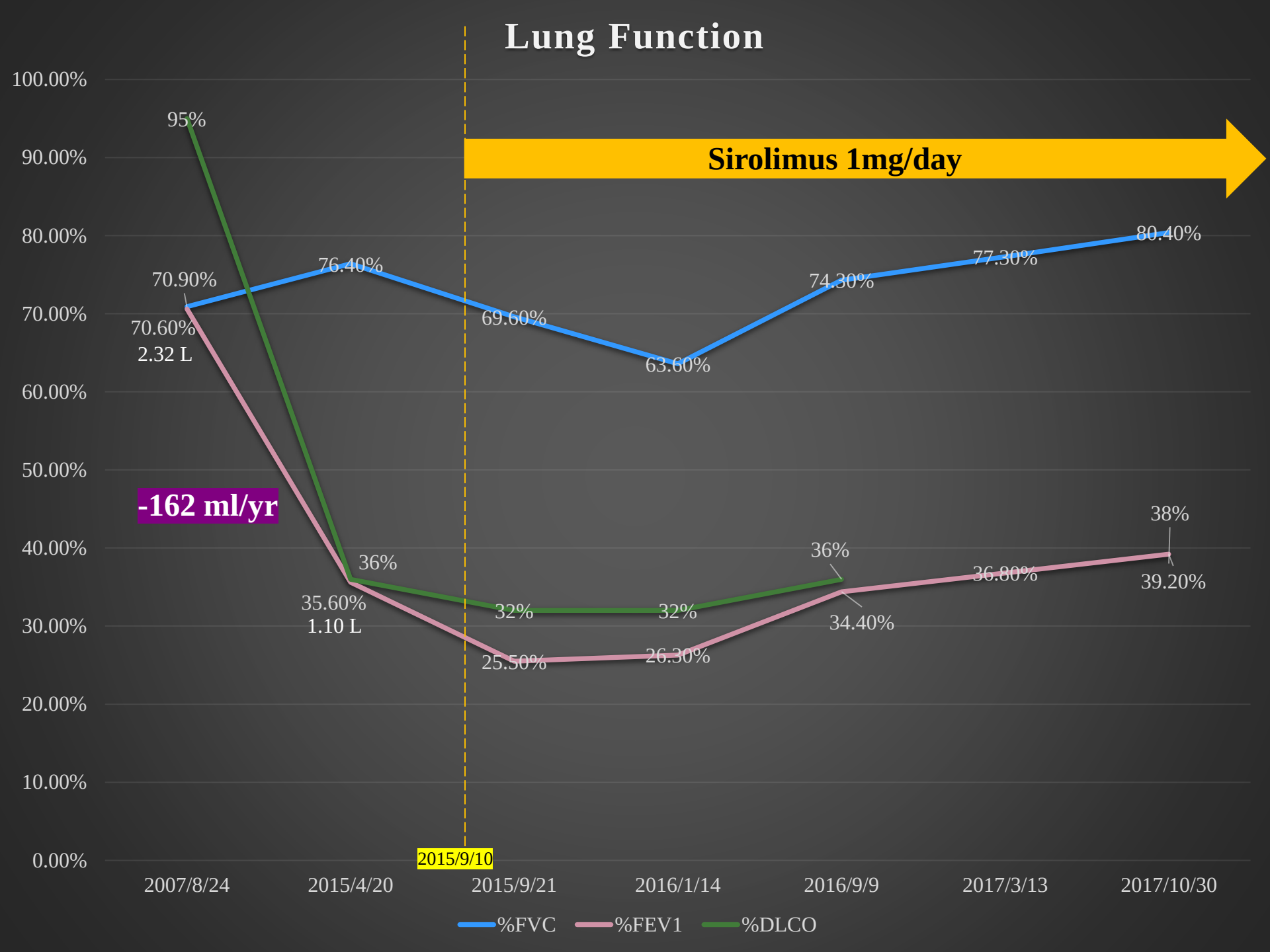
2014-05-10

Progressive Disease







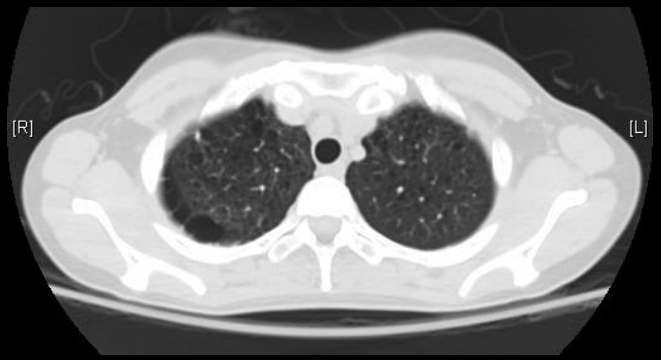

Lung Function
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Sirolimus 1mg/day
95%
70.90%
76.40%
69.60%
63.60%
74.30%
77.30%
80.40%
70.60%
2.32 L
-162 ml/yr
36%
35.60%
1.10 L
32%
32%
36%
38%
36.80%
39.20%
34.40%
25.50%
26.30%
2015/9/10
2007/8/24
2015/4/20
2015/9/21
2016/1/14
2016/9/9
2017/3/13
2017/10/30
%FVC
%FEV1
%DLCO

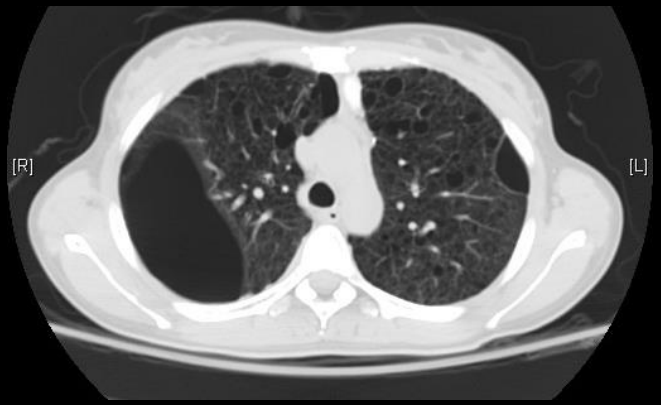
6 mins walking test

	Rest	1 min	2 min	3 min	4 min	5 min	6 min	End	%Distance
2010/07/26	98%	93%	97%	98%	97%	95%	95%	98%	86%
2015/06/15	93%	86%	79%	69%	64%	61%	74%	89%	70%
2015/09/21	96%	90%	86%	79%	79%	80%	83%	92%	64%
			O2 4L/min						
2017/03/13	97%	92%	84%	81%	77%	69%	73%	95%	85%

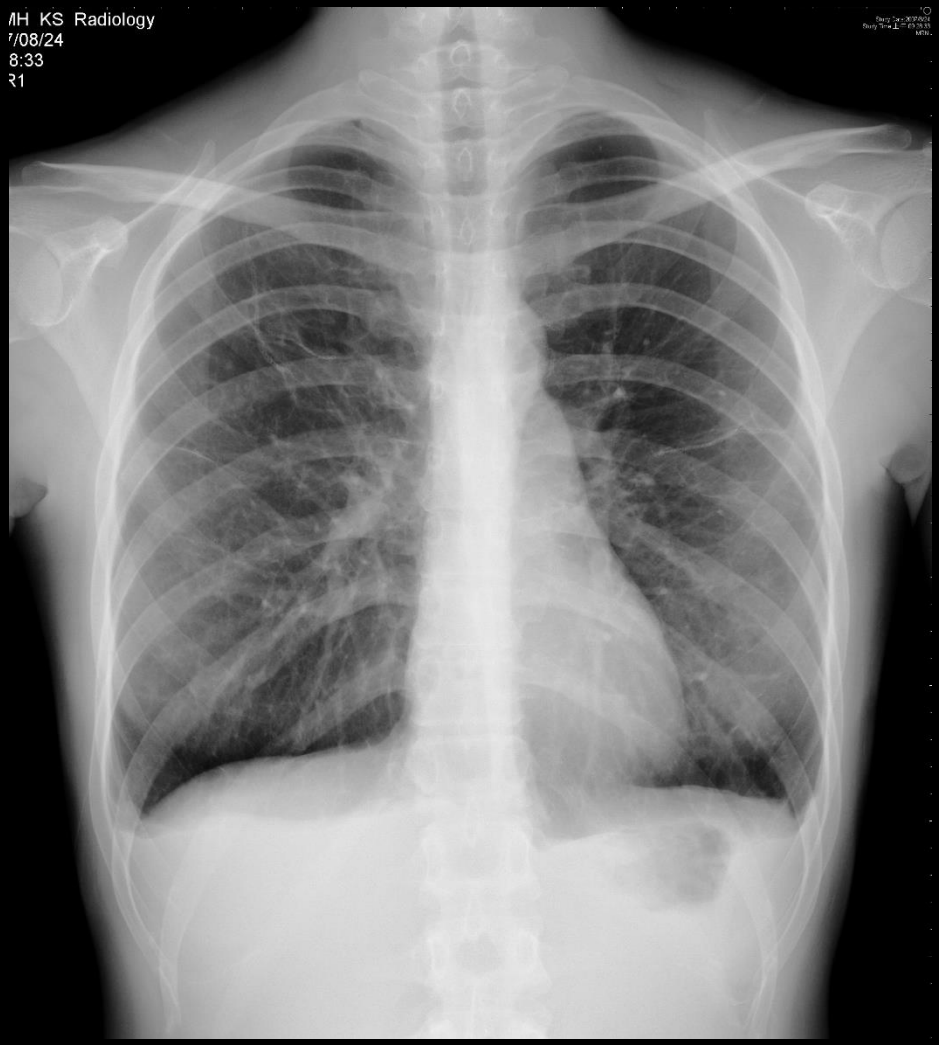
2016-05-12

Stable Disease

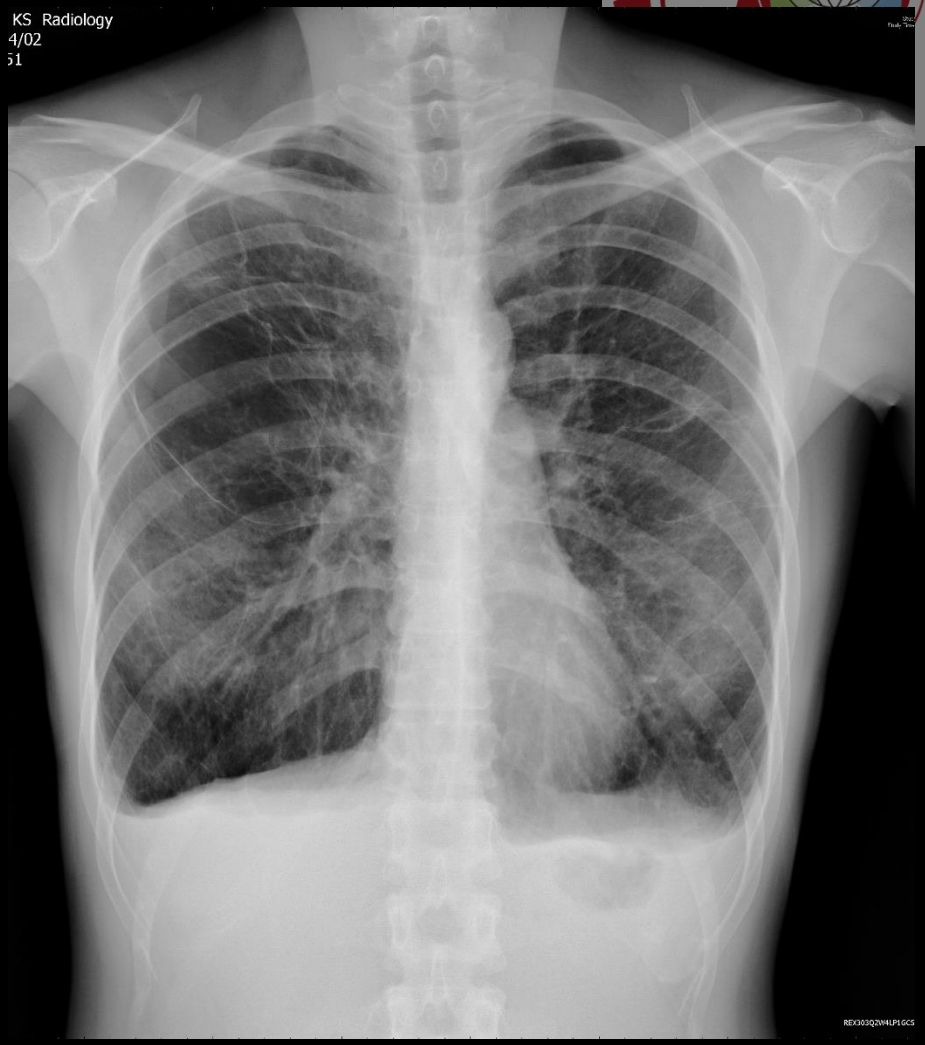




2007-08-24



2018-04-02



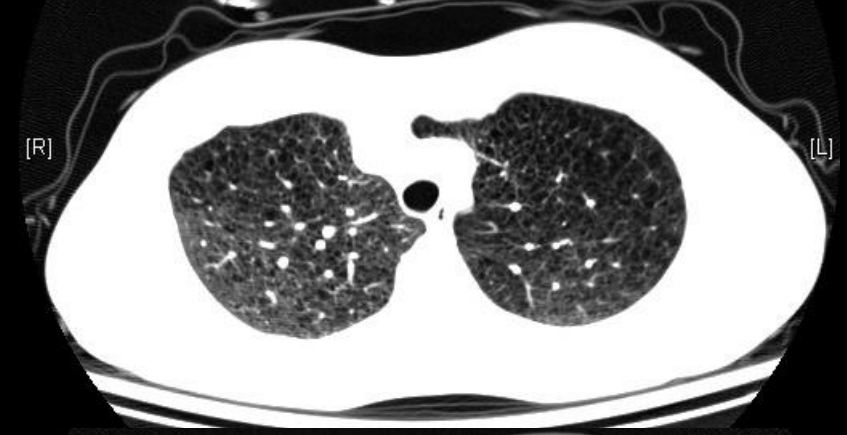
Case 2

- Miss 張
- 24 y/o → 39 y/o
- First visit on 2004/02

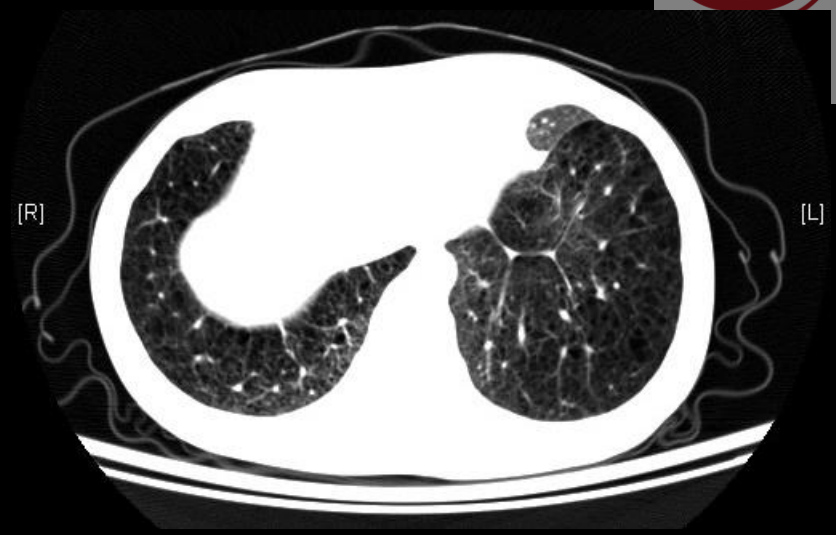
Case 2

- **LAM** was Dx at VGH on 2002

- Progressive dyspnea → Respiratory failure with Home-BiPAP support

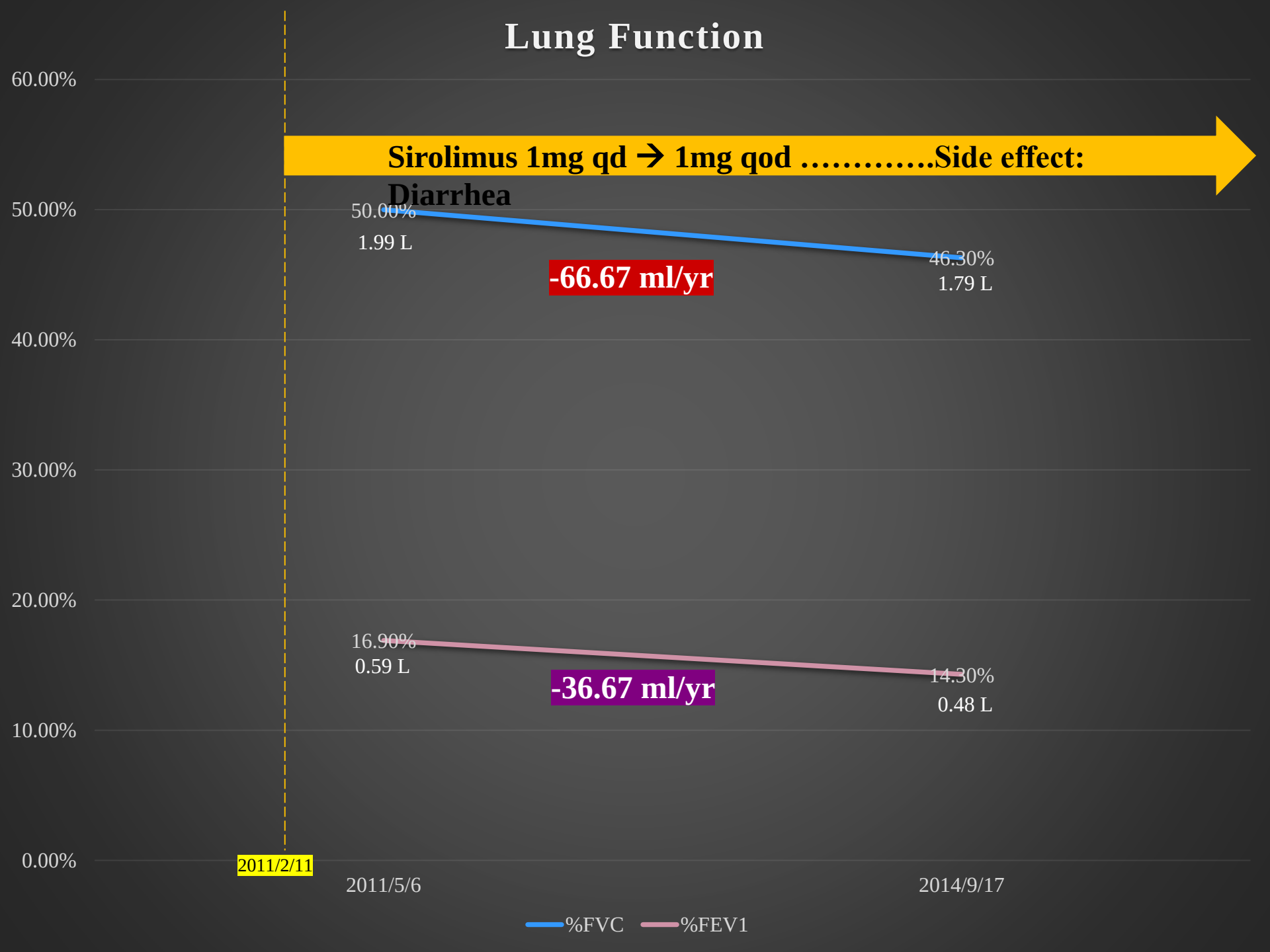


2007-09-17



2009-06-15

Chylous ascites


Lung Function
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Sirolimus 1mg qd → 1mg qod ……Side effect: Diarrhea
50.00%
1.99 L
46.30%
1.79 L
-66.67 ml/yr
16.90%
0.59 L
14.30%
0.48 L
-36.67 ml/yr
2011/2/11
2011/5/6
2014/9/17
%FVC
%FEV1

2009-06-15

2014-12-22

Improved Chylous ascites