CONTROVERSES ET ACTUALITÉS EN CHIRURGIE VASCULAIRE
CONTROVERSIES & UPDATES IN VASCULAR SURGERY
JANUARY 25-27 2018
MARRIOTT RIVE GAUCHE & CONFERENCE CENTER
PARIS, FRANCE WWW.CACVS.ORG

Indications and results of SIROLIMUS

In the treatment of Venous Malformations

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&
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Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

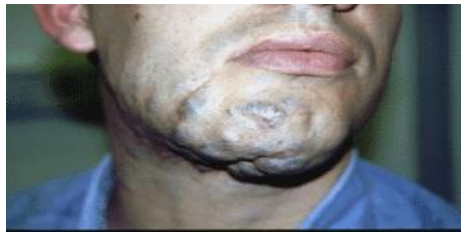
Emmanuel Seront, MD PhD

No disclosure

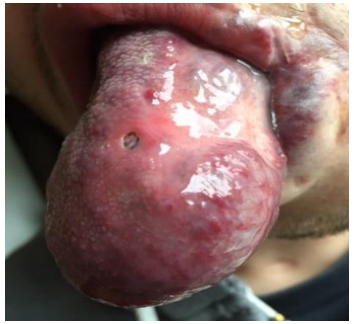
Anomalies occuring during morphological development of venous system

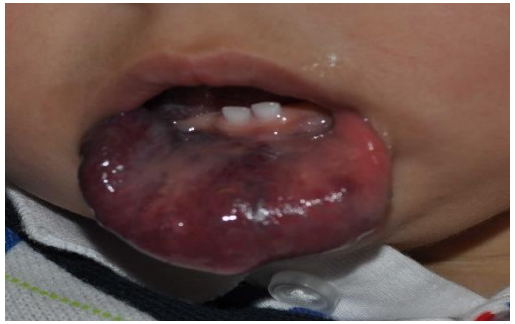
Present at birth and grow with child - Exacerbation (trauma, infection and hormonal changes)

- Esthetical problems

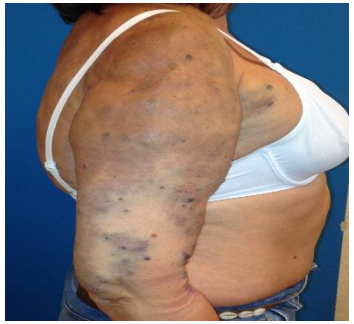


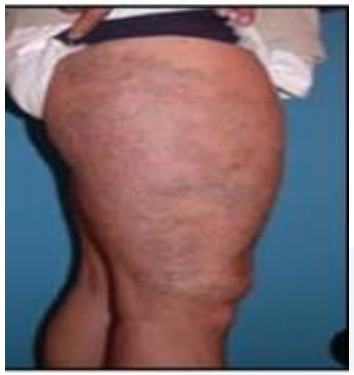
- Functional problems





- Chronic symptoms with exacerbations
  - Pain
  - Edema, oozing, bleeding

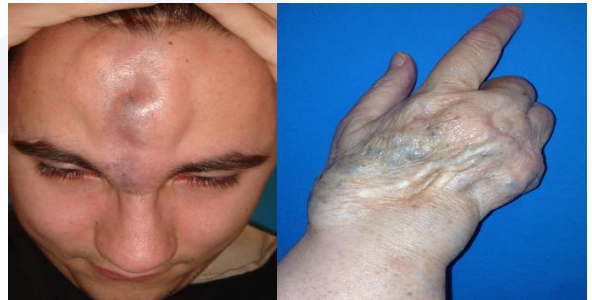


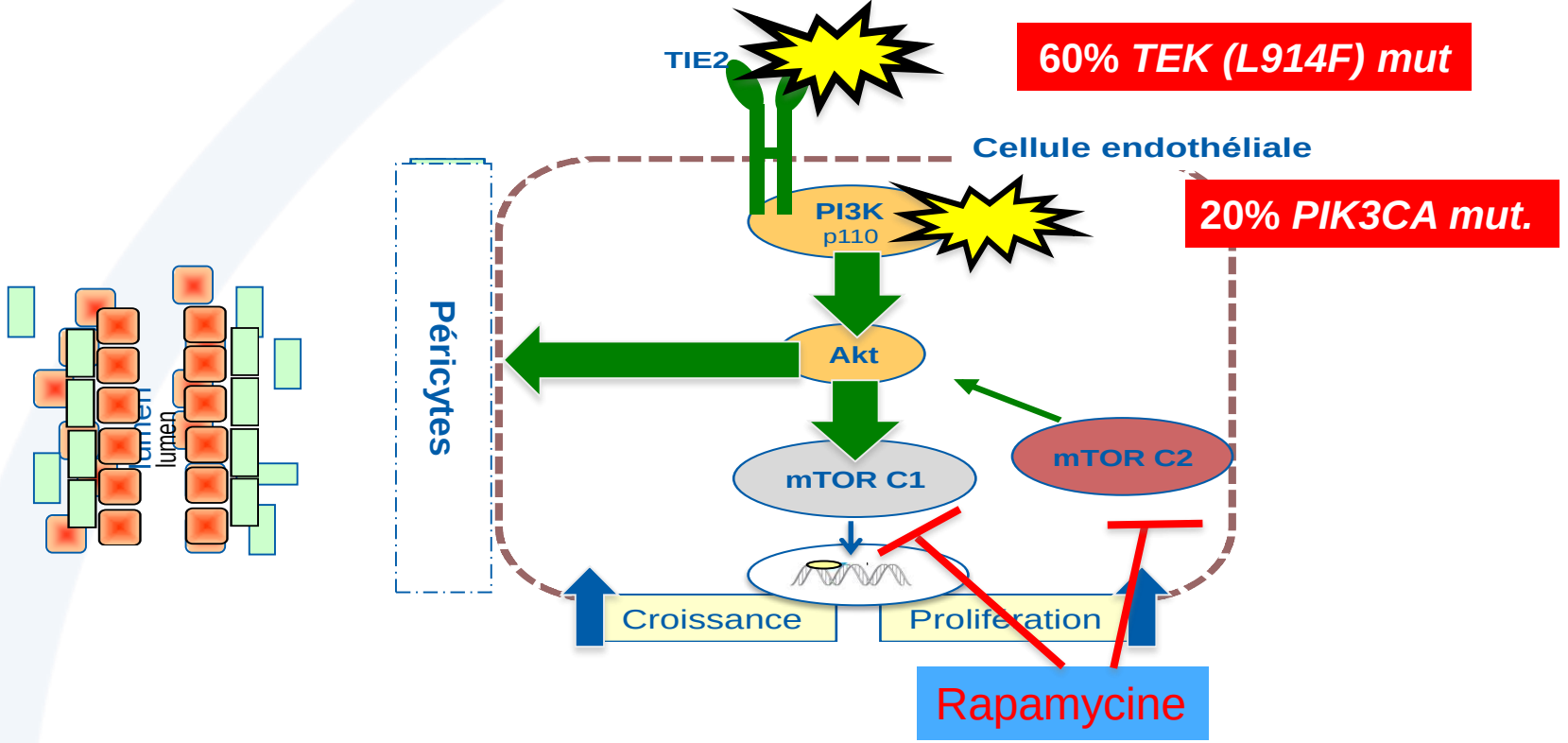


- Venous stasis
  - Thrombophlebitis
  - Coagulation disorder

<u>Standard treatment = Sclerotherapy +/- surgery</u>

- Often impossible
- Non curative, frequent recurrences
- Treatment toxicity



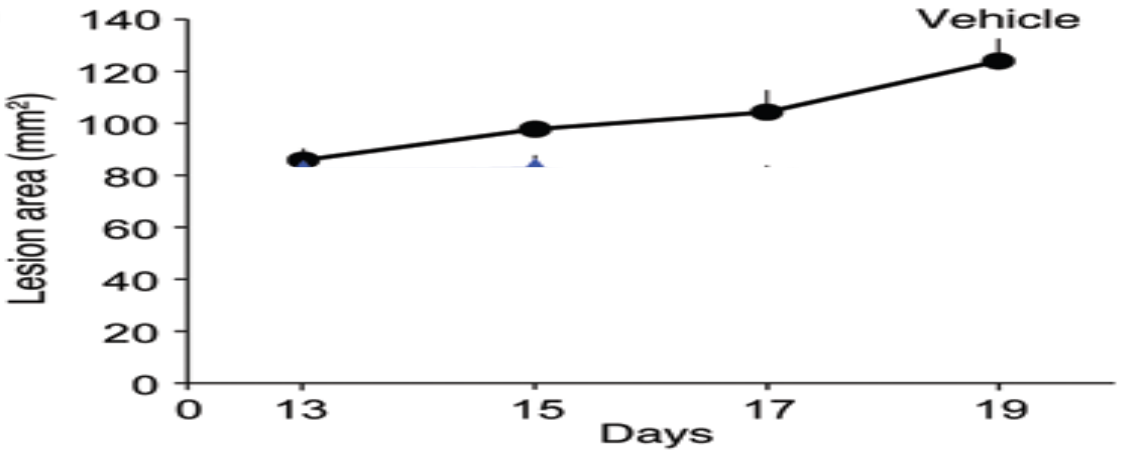


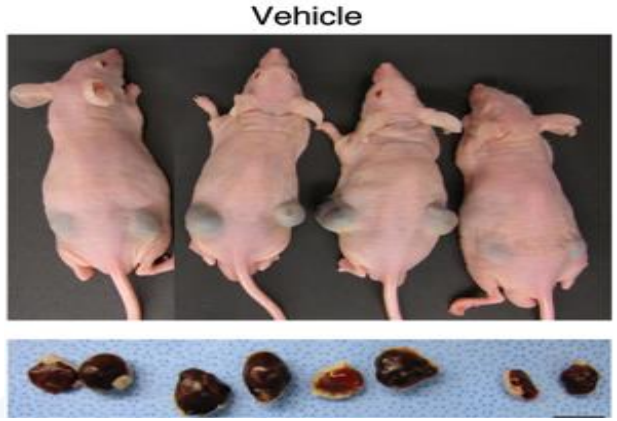
The Journal of Clinical Investigation

RESEARCH ARTICLE

Rapamycin improves *TIE2*-mutated venous malformation in murine model

Elisa Boscolo,[1] Nisha Limaye,[2] Lan Huang,[1] Kyu-Tae Kang,[1] Julie Soblet,[2] M
Emmanuel Seront,[4] Sophie Dupont,[4] Jennifer Hammer,[5] Catherine Legranc
Joyce Bischoff,[1] and Laurence M. Boon[2,5]





The Journal of Clinical Investigation RESEARCH ARTICLE

Rapamycin improves *TIE2*-mutated venous malformation in murine model and human subjects

Elisa Boscolo,[1] Nisha Limaye,[2] Lan Huang,[1] Kyu-Tae Kang,[1] Julie Soblet,[2] Melanie Uebelhoer,[2] Antonella Mendola,[2] Marjut Natynki,[3] Emmanuel Seront,[4] Sophie Dupont,[4] Jennifer Hammer,[5] Catherine Legrand,[6] Carlo Brugnara,[7] Lauri Eklund,[3] Miikka Vikkula,[2,5] Joyce Bischoff,[1] and Laurence M. Boon[2,5]

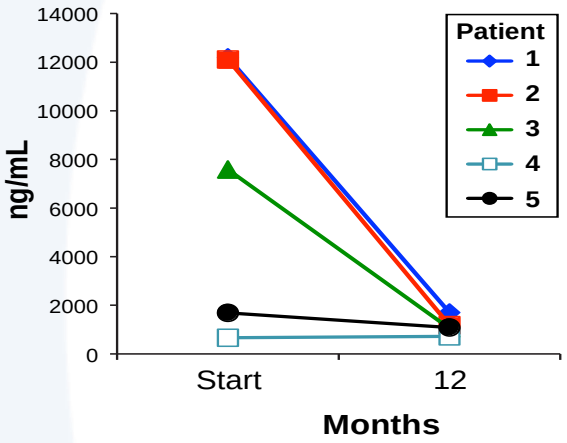
6 patients (14y-64y)

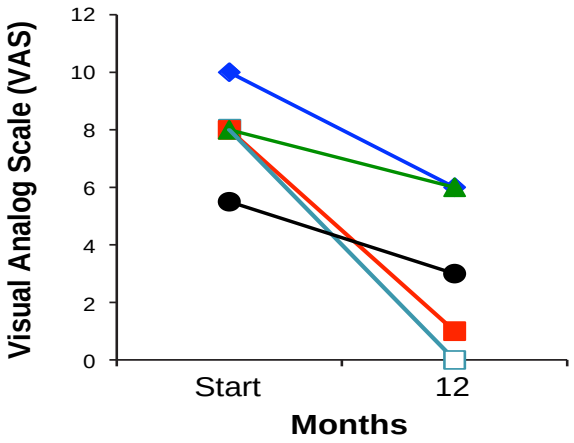
4 sporadic VMs, 1 KTS and 1 MSVM

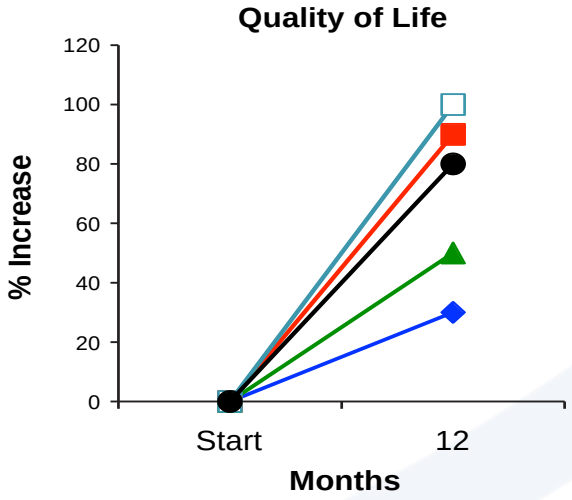
3 *PIK3CA* mut and 3 *TIE2* mut

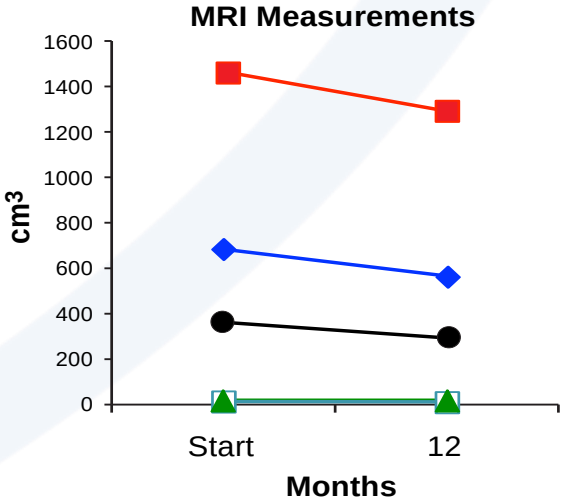
All previously treated (sclerotherapy of surgery)

Sirolimus 2mg daily









Well tolerated

Sirolimus treatment for extensive and complex slow-flow vascular malformations: a monocentric prospective phase II study
Hammer J et al (submitted)

19 patients with median age 15 years (3-64 years)

7 with venous malformation

Sirolimus 2 mg daily or 0.8mg/m^2 twice daily

<u>In patients with venous malformation</u>

Pain reduced
Functional improvement
Esthetical improvement
Quality of life increased
Coagulopathy decreased

In 100%

Decrease of tumor volume in 25%

Side effect related to sirolimus
- Mild to moderate
- Easily manageable

Side effects	*Grade 1-2 N (%)*	*Grade 3-4 N (%)*
Conjunctiva	1 (5.3%)	0
Pneumonitis/pulmonary infiltrates	1 (5.3%)	0
Neuropathy	1 (5.3%)	0
Skin tumor (basocellular)	0	1 (5.3%)
Lymphoma	0	1 (5.3%)
Anemia	0	0
Thrombopenia	1 (5.3%)	0
Leucopenia	0	0
Hypercholesterolemia/hyperglycemia	0	0
Headache	11 (57.9%)	0
HTA	1 (5.3%)	0
Diarrhea	7 (36.9%)	0
Nausea/vomiting	5 (26.4%)	0
Mucositis/stomatitis	7 (36.9%)	2 (10.6%)
Abnormal liver function tests	0	0
Rash	7 (36.9%)	0
Arthralgia	1 (5.3%)	0
Flu-like syndrome	6 (31.6%)	0
Fatigue	9 (47.4%)	0
Wound healing	2 (10.6%)	0
Weight loss	3 (15.8%)	0
Insomnia	4 (21.1%)	0

Phase III multicentric study evaluating the efficacy and safety of sirolimus in Vascular Anomalies that are refractory to standard care

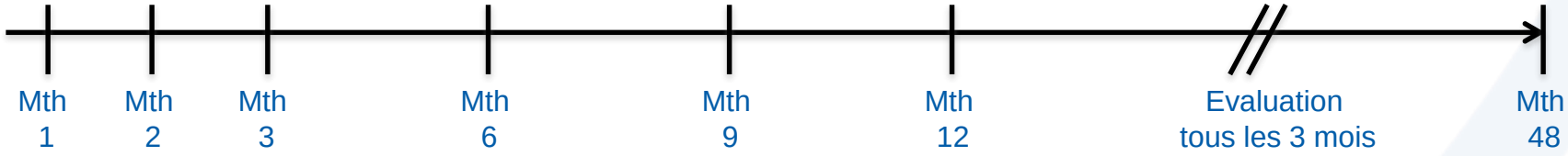
VASE Study, EudraCT number: 2015-001703-32

Patients with vascular anomalies

1mois – 70 years

Ineffective or unfeasible conventionnal R/

Sirolimus 2mg daily in adult
or 0.8mg/m2 twice daily in children



MRI

MRI

STOP Sirolimus

250 pts planned to be enrolled over 3 years

Primary endpoint

➔ Safety

➔ Efficacy

- Clinical and radiological size
- Symptoms: pain, functional limitation
- Quality of life questionnary

Currently enrolling (start January 2016)

44 patients (median age 44y; 2y-71y)

including 31 VMs

4 lymphatic malformations
5 capillary-venous malformations
1 KTS, 1 BRBN, 1 CLOVES, 1 PHTS

Combining Pilot Study, Phase II and Phase III studies

69 patients; median age 45 years (2-71 years)

Including **42 patients with venous malformations**

50 patients treated ≥ 12 months

Complete response = 0

Disappearance of lesion (clinical and/or radiological), of symptoms and normalisation QoL

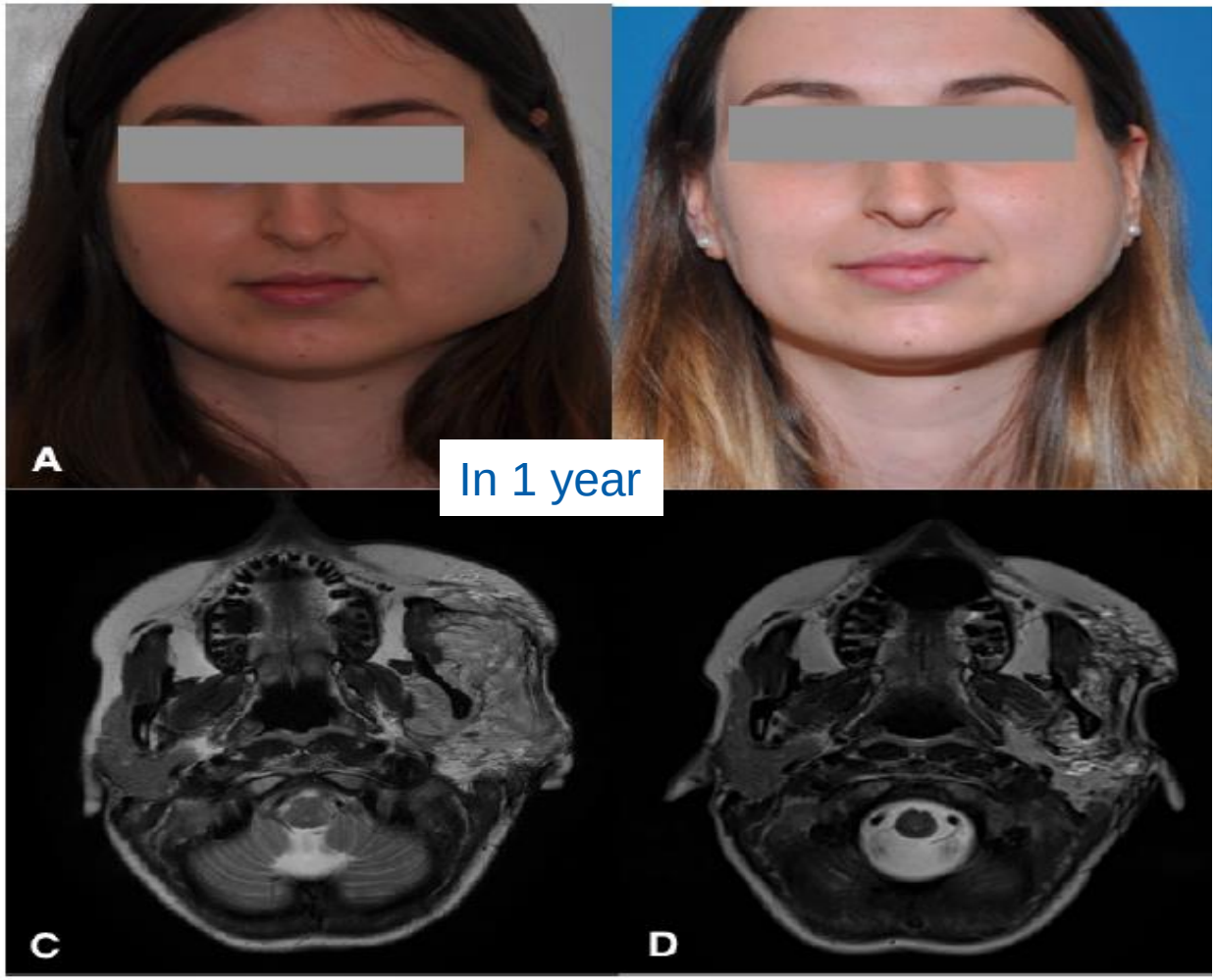
Partial response = 64 pts (93%)

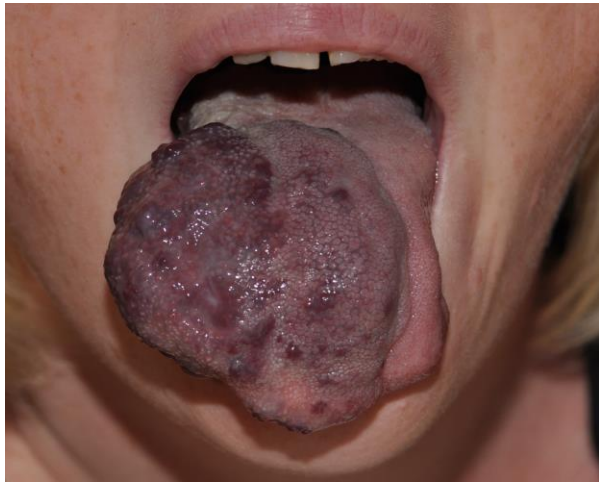
Reduction in size (clinical and/or radiological), improvement of symptoms and/or QoL.

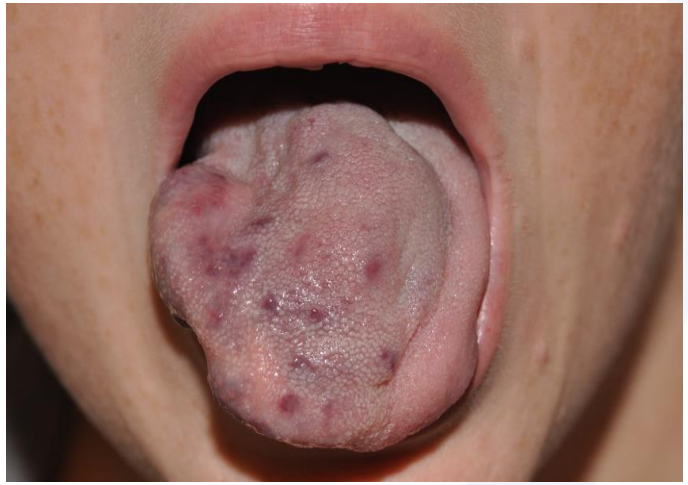
Pain decrease rapidly	within first month	(median VAS 7 ==> 2)
Decreased bleeding, oozing, infection	within first month	
Functional improvement	within three months	
Physical change	within 6-12 months	
Quality of life increase	**within two months**	**(20-100% improvement)**

Absence of response = 5 pts (7%)

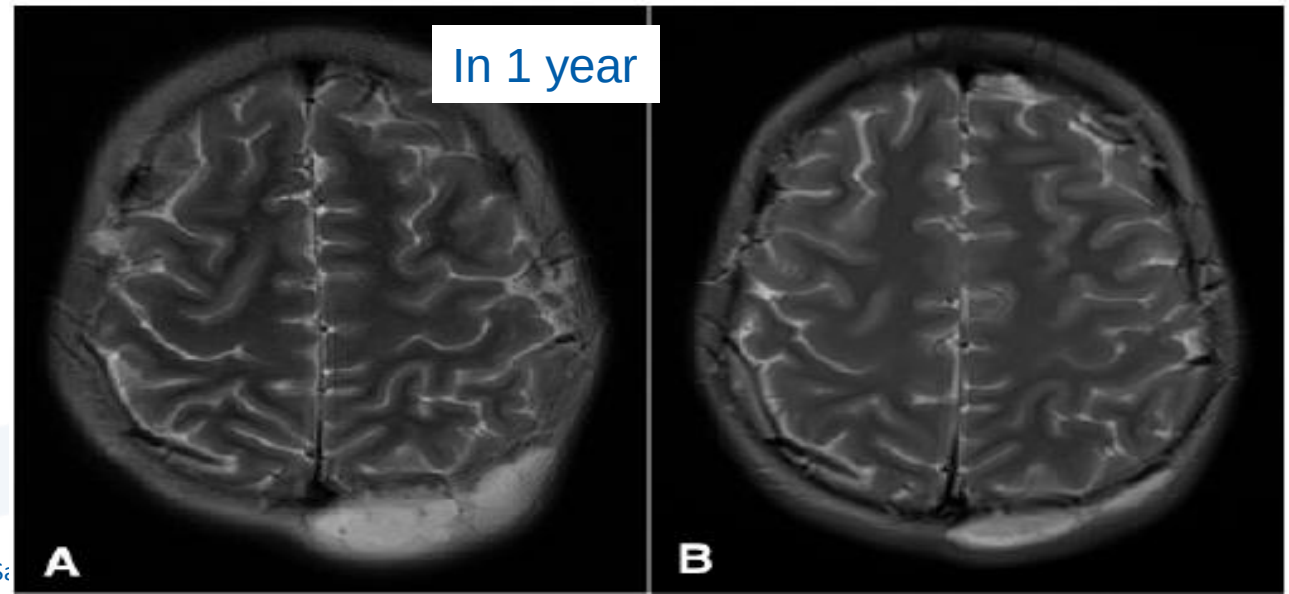
Progressive disease (increase in size, symptoms and decreased QoL) or disease stability (no change).



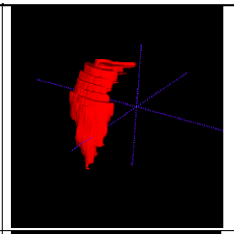
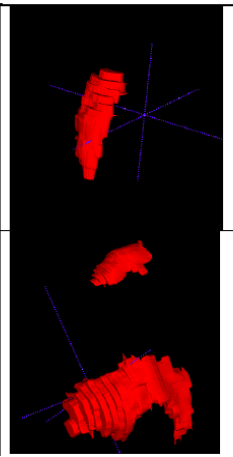
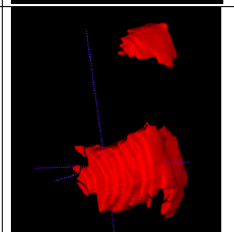


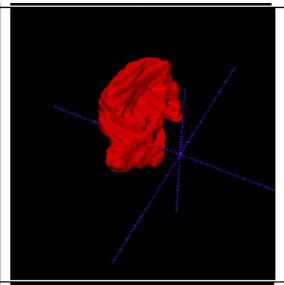
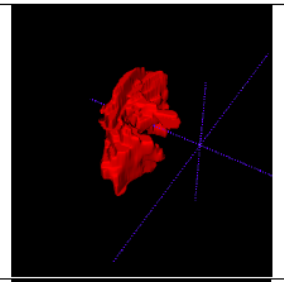
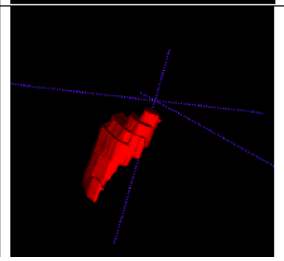
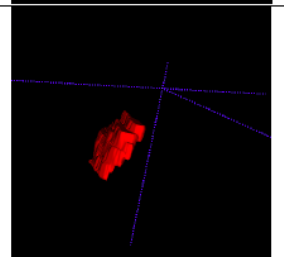


In 2 months



- Size reduction >10% in 50% of patients at 1-year

Patients	Image pré-R/	Image post-R/	Volume pré-R/ (cm^3)	Volume post-12 mois R/ (cm^3)	Pourcentage de modification
101003			30,13	24,69	-18%
101007			99,01	69,72	-29,6%

101009			128,7	80,61	-37,4%
101029			21,23	10,54	-50,4%

- Biomarker analysis (*TIE2* and *PIK3CA)* currently ongoing
- Too early to evaluate response maintenance in patients who stopped sirolimus regarding protocol
- Toxicity profile is safe

  60% of patients presented Grade1-2 related toxicity (mucitis, skin dryness, fatigue)

  BUT… these toxicities were **easily manageable, transitory and reversible**

In conclusion

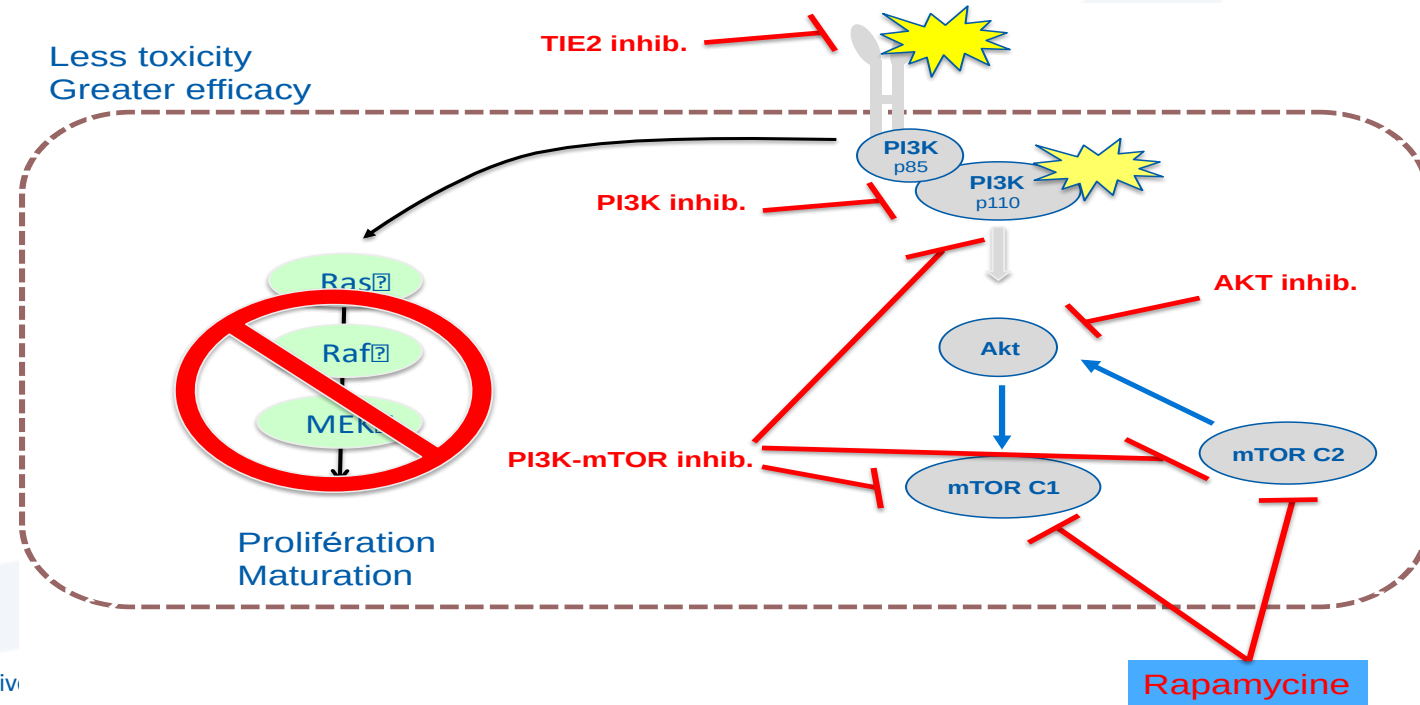
➔ Sirolimus MAY appears as a new standard in treatment of Slow-Flow malformations that are refractory to conventional treatments or for whom these are unfeasible

BUT …Prospective phase III studies, with statistical data, need to be published first!

➔ Important to evaluate the place of sirolimus in the disease course

- earlier treatment, greater benefit ?

➔ New agents under investigation



Thank you for your attention

Special thanks for such courageous patients

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Vascular Anomaly Patient Association