The role of mTOR inhibitors in Astrocytoma related to TSC

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Tuberous Sclerosis Complex (TSC)

- TSC is a rare genetic disorder with an incidence of 1 in 6000 births[1]

- The disease is caused by mutations in 1 of 2 genes
  - *TSC1* (chromosome 9) encodes hamartin
  - *TSC2* (chromosome 16) encodes tuberin

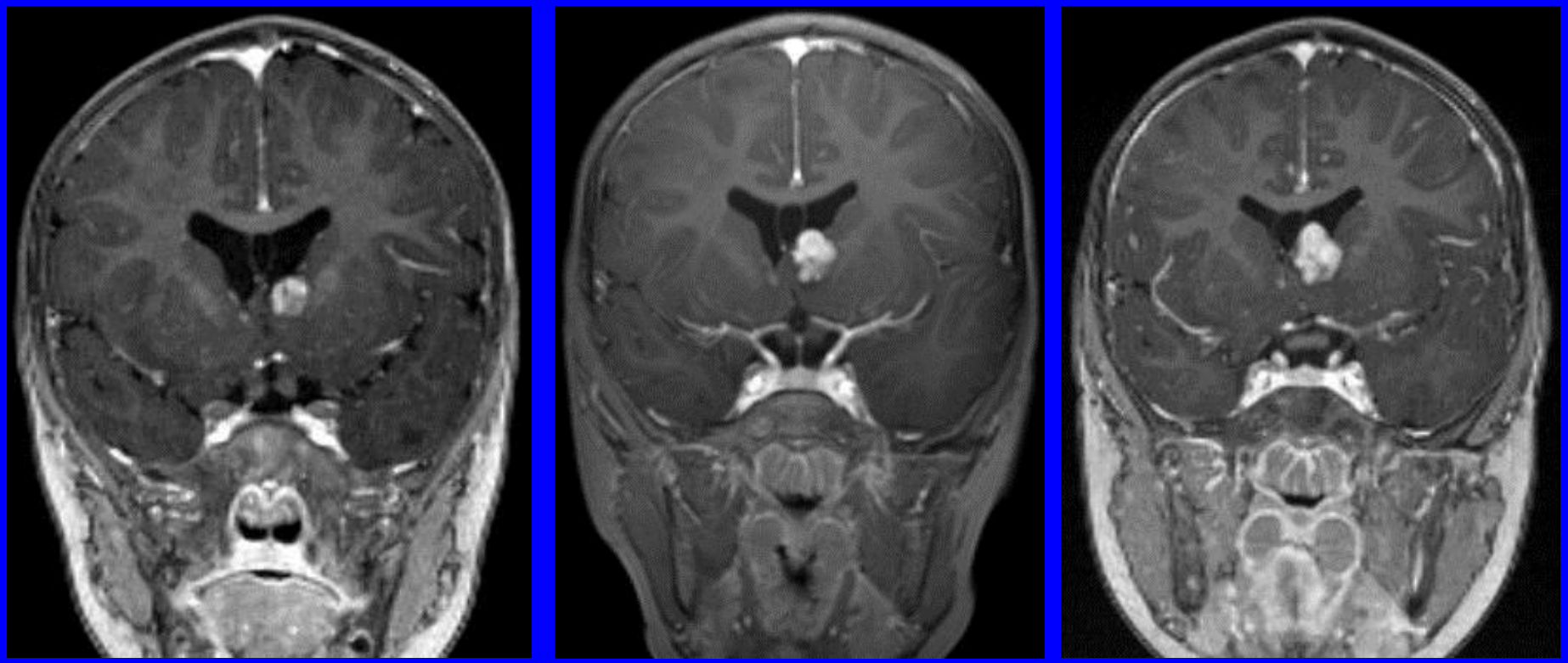
- Hamartin/tuberin complex has a crucial inhibitory role in the mTOR signaling regulating cell growth and proliferation

- The hallmark of TSC is the development of benign tumors and lesions in various organs including the skin, brain, eye, kidneys, liver, and the heart

- SEGAs are the major cause of mortality and morbidity in TSC children

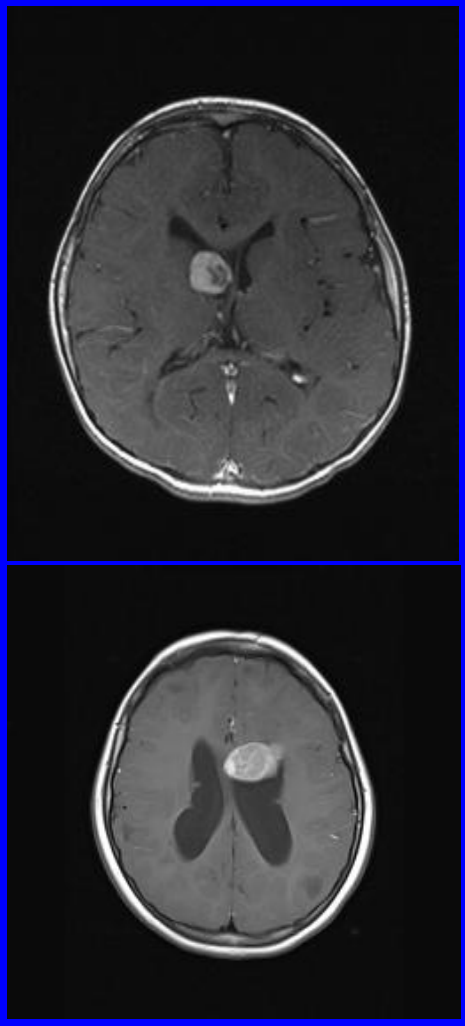
Curatolo P, et al. *Lancet* 2008;372:657-68.

SEGAs are dynamic lesions



SEGA: clinical presentation

- Occur in 6-14% of pts
- Histologically benign
- Locally invasive
- Enhanced by gadolinium
- Usually clinically silent until hydrocephalus develops
- Initial clinical symptoms of increased intracranial pressure: cognitive impairment, headache, behavioral changes
- Later symptoms: postural headache, vomiting, optic neuropathy, ataxia
- Early surgery can be curative



Management of SEGAs

- Current standard treatment for SEGAs is surgical resection; symptomatic children with SEGA (ie, those with increased intracranial pressure and hydrocephalus) undergo tumor resection or and/or ventriculoperitoneal shunting

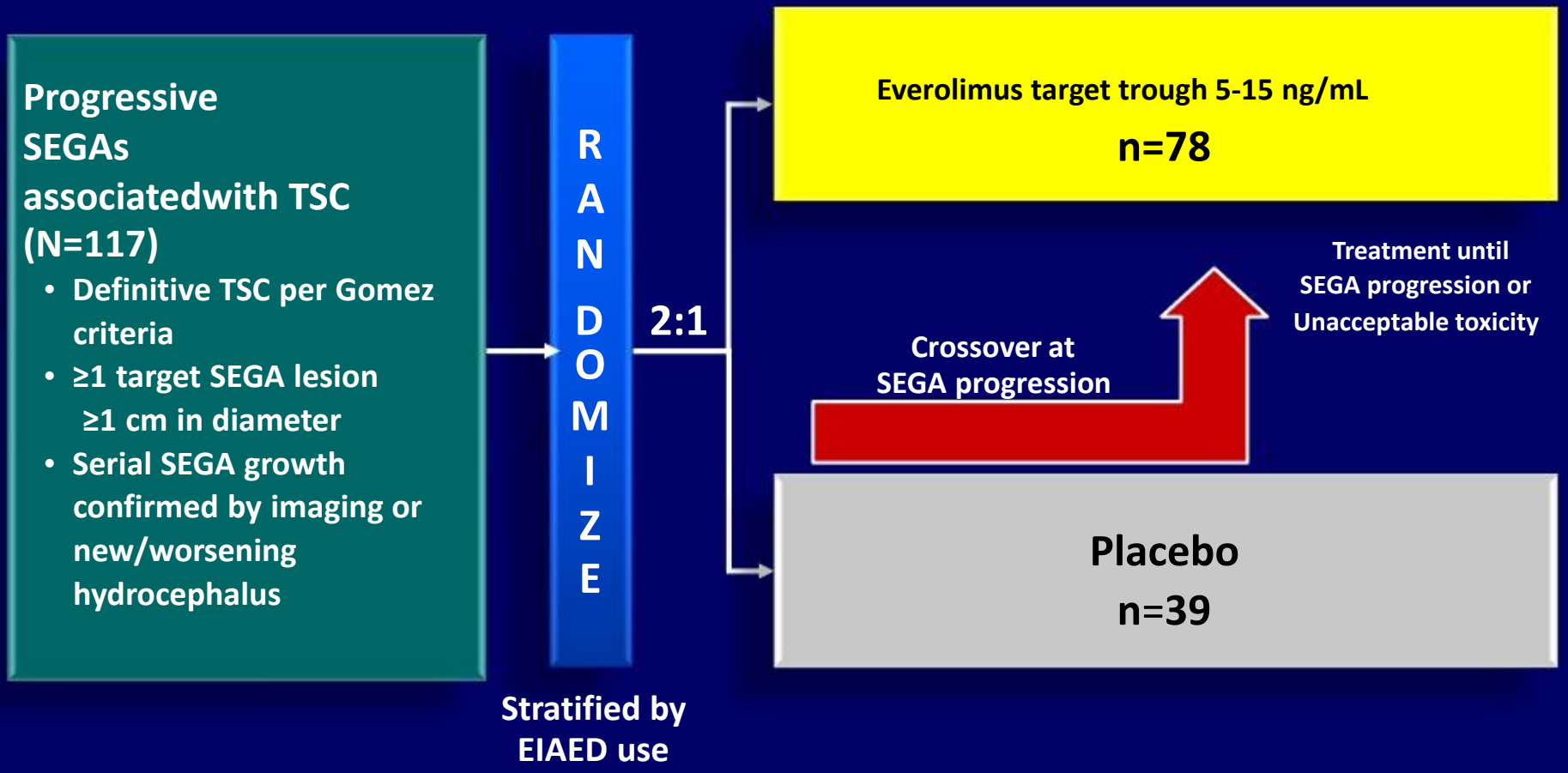
- Not all tumors are amenable to resection

- mTOR inhibitors were successfully used for the treatment of SEGAs in 4 patients with TSC in 2006

- Everolimus has been recently approved by FDA and EMA for treatment of SEGA associated with TSC

Franz DN, et al. Ann Neurol 2006; Curatolo P, Lancet 2008; Berhouma M, et al. World J Pediatr 2010

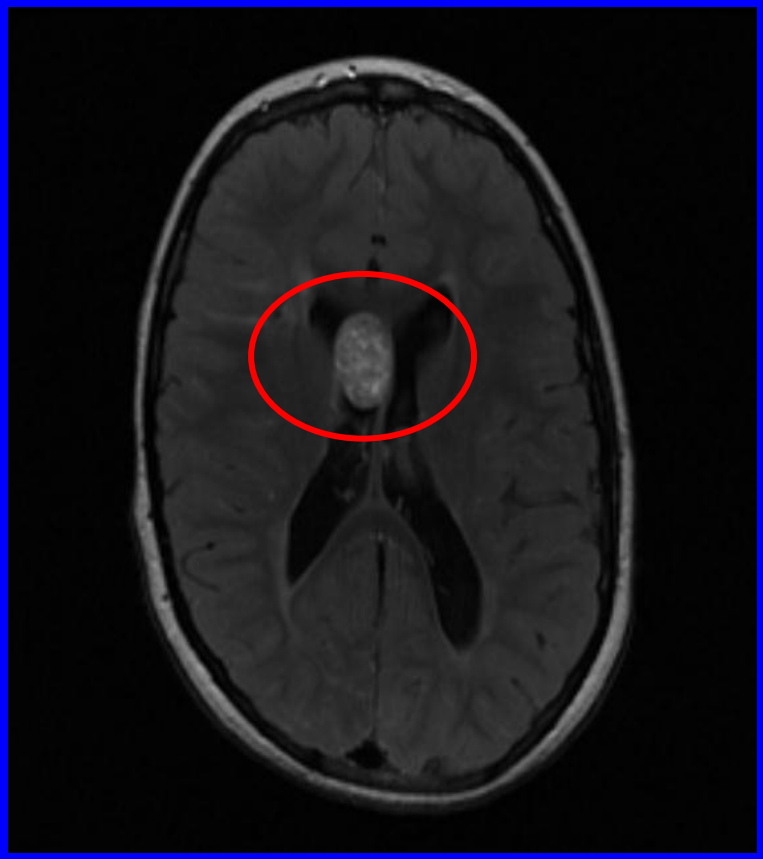
The EXIST-1 trial: Phase III Study design



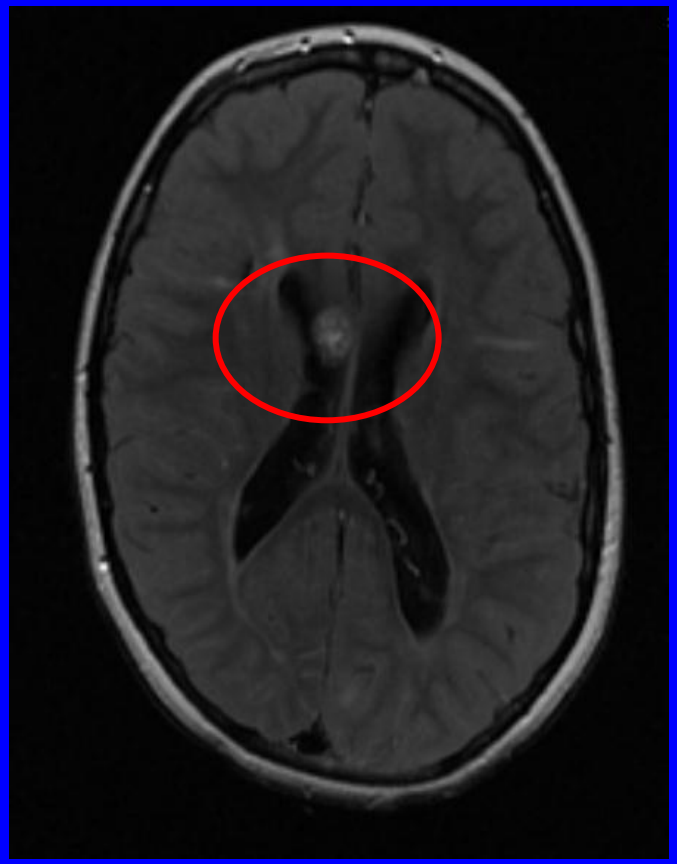
EIAED = enzyme-inducing antiepileptic drug.
Accrual between August 2009 and September 2010.
[a]Everolimus starting dose 4.5 mg/m$_2$/dayand adjusted to trough level of 5-15 ng/mL. Dose could be adjusted in cases of toxicity.
ClinicalTrials.gov identifier NCT00789828.

Franz et al, Lancet, in press

Everolimus Effect on SEGAs
Phase 3 Study



Baseline

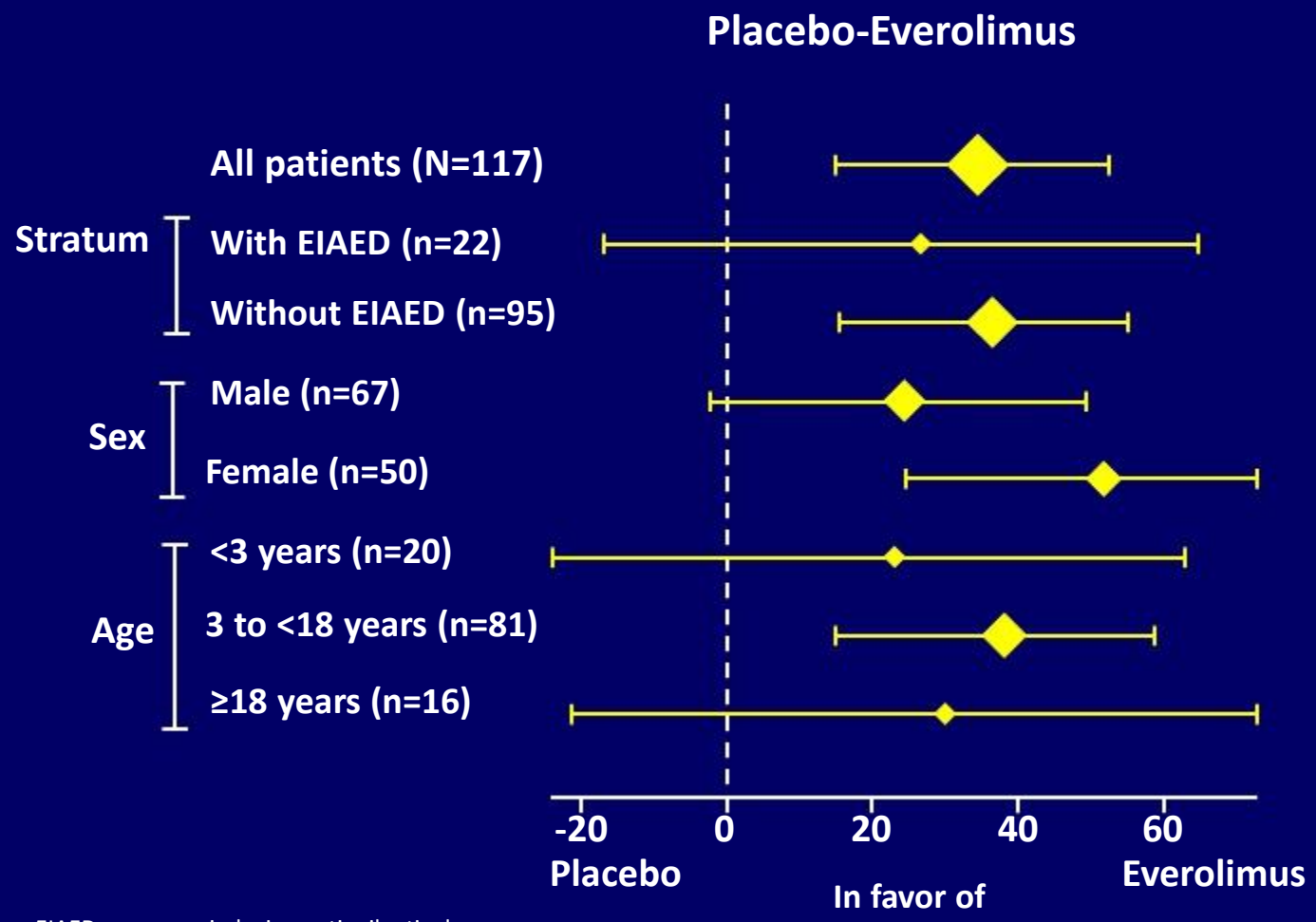


3 months

Data provided by DN Franz, University of Cincinnati College of Medicine.

The EXIST-1 trial: Phase III Study results

SEGA response rate in subgroups



	Response, n/N (%)	
	Placebo	Everolimus
All patients (N=117)	0/39 (0)	27/78 (34.6)
Stratum: With EIAED (n=22)	0/7 (0)	4/15 (26.7)
Stratum: Without EIAED (n=95)	0/32 (0)	23/63 (36.5)
Sex: Male (n=67)	0/18 (0)	12/49 (24.5)
Sex: Female (n=50)	0/21 (0)	15/29 (51.7)
Age: <3 years (n=20)	0/7 (0)	3/13 (23.1)
Age: 3 to <18 years (n=81)	0/26 (0)	21/55 (38.2)
Age: ≥18 years (n=16)	0/6 (0)	3/10 (30.0)

EIAED = enzyme-inducing antiepileptic drug.
Exact 95% confidence interval obtained from the exact unconditionalconfidence limits.
Franz et al, Lancet, in press

CASE PRESENTATION

ES (M, 25 y, TSC2 gene mutation (1831C>T, R611W))

NEUROLOGICAL MANIFESTATIONS

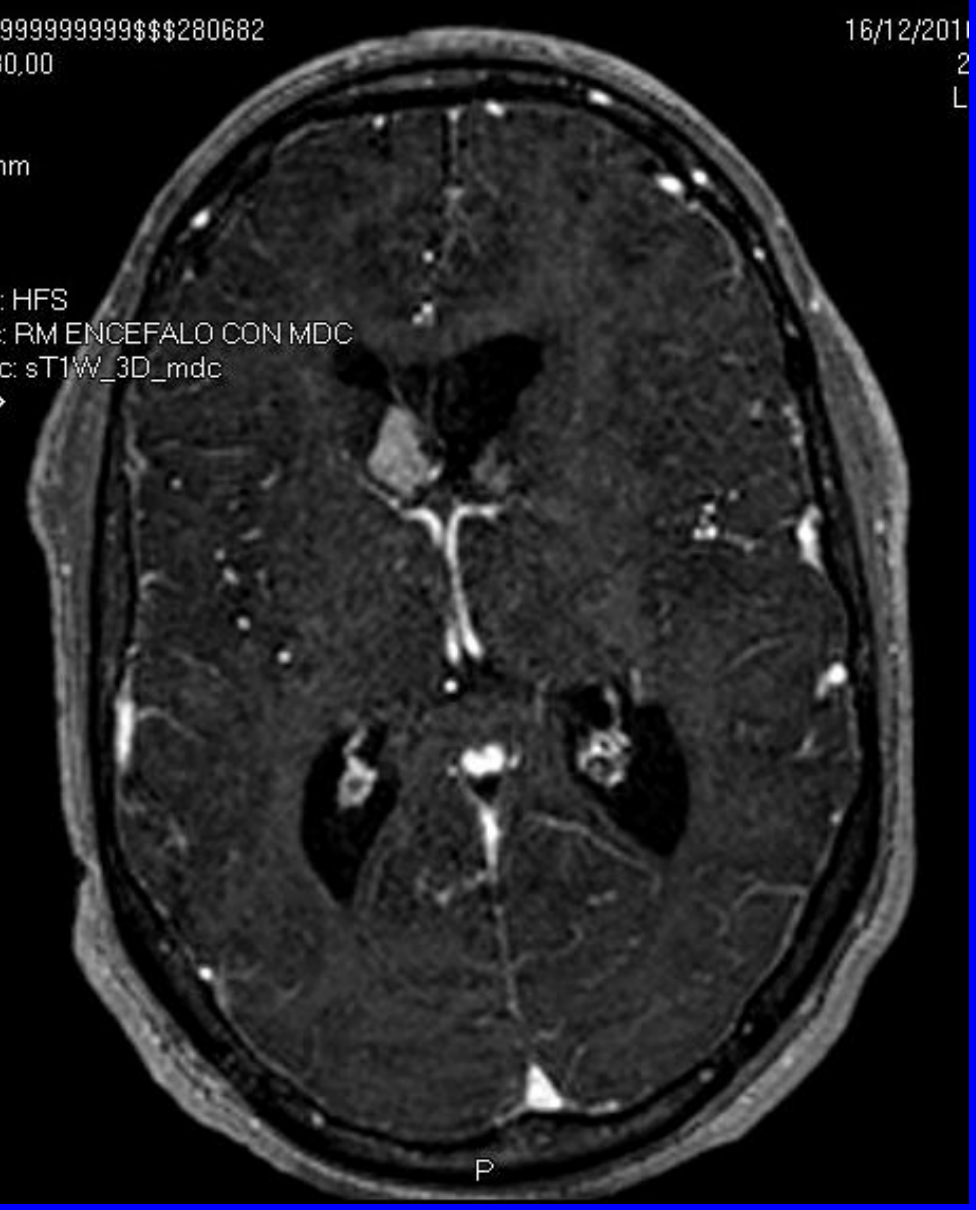
- Sz onset at 6 m, actually well controlled
- Borderline cognitive level, behavioural problems
- Cortical tubers, SENs, bilateral SEGAs

NON NEUROLOGICAL MANIFESTATIONS

- Facial angiofibroma, forehead plaque, shagreen patch (8y)
- Multiple retinal nodular hamartomas
- Renal AMLs (10 y)

Clinical history

- 2005 (17 y): hydrocephalus occurred → SEGA surgery
- 2007 (19 y): new episode of hydrocephalus → controlateral SEGA surgery
- 2011 (23 y): third episode of hydrocephalus → external derivation →Everolimus was started (10 mg/d)
- 2012 (24 y): SEGAs volumetric regression



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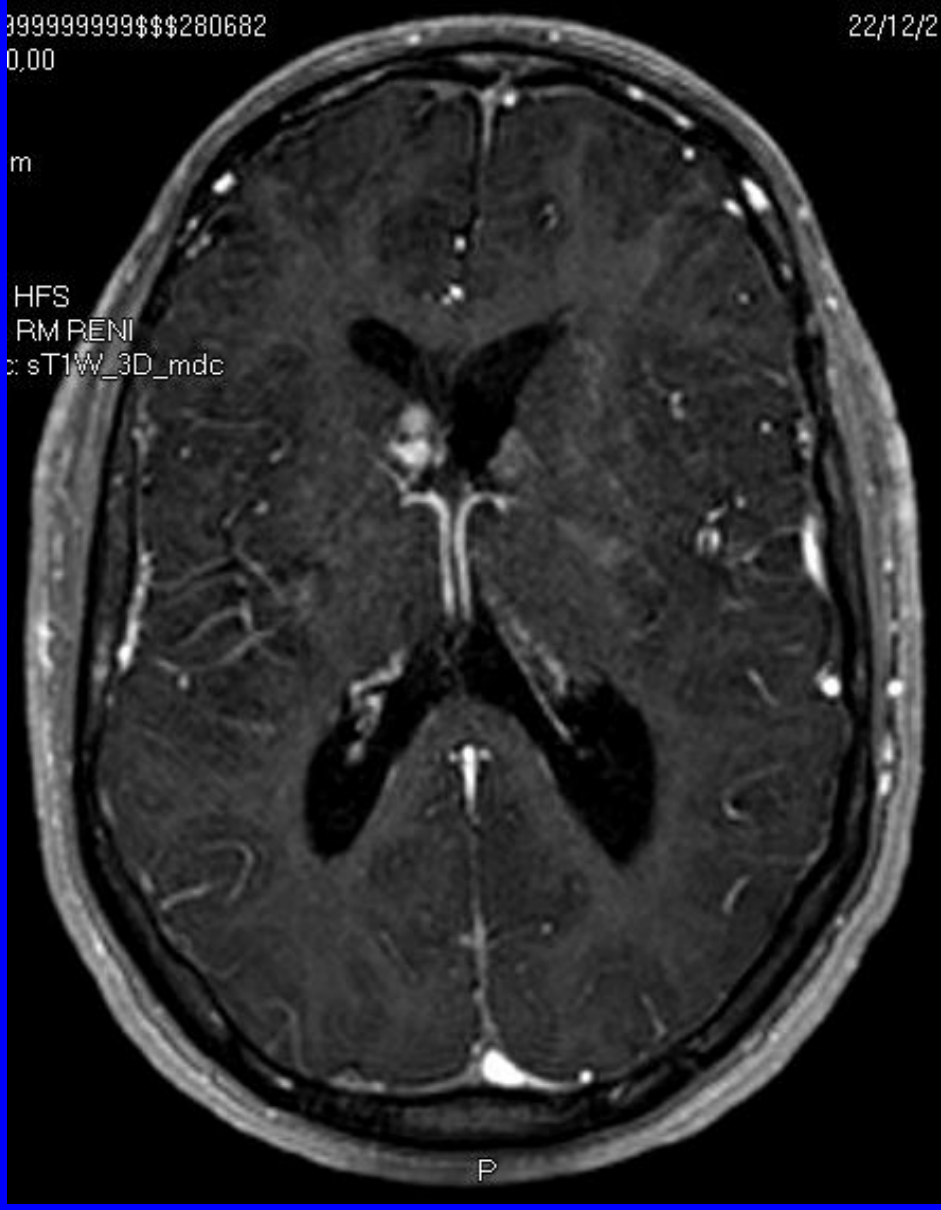
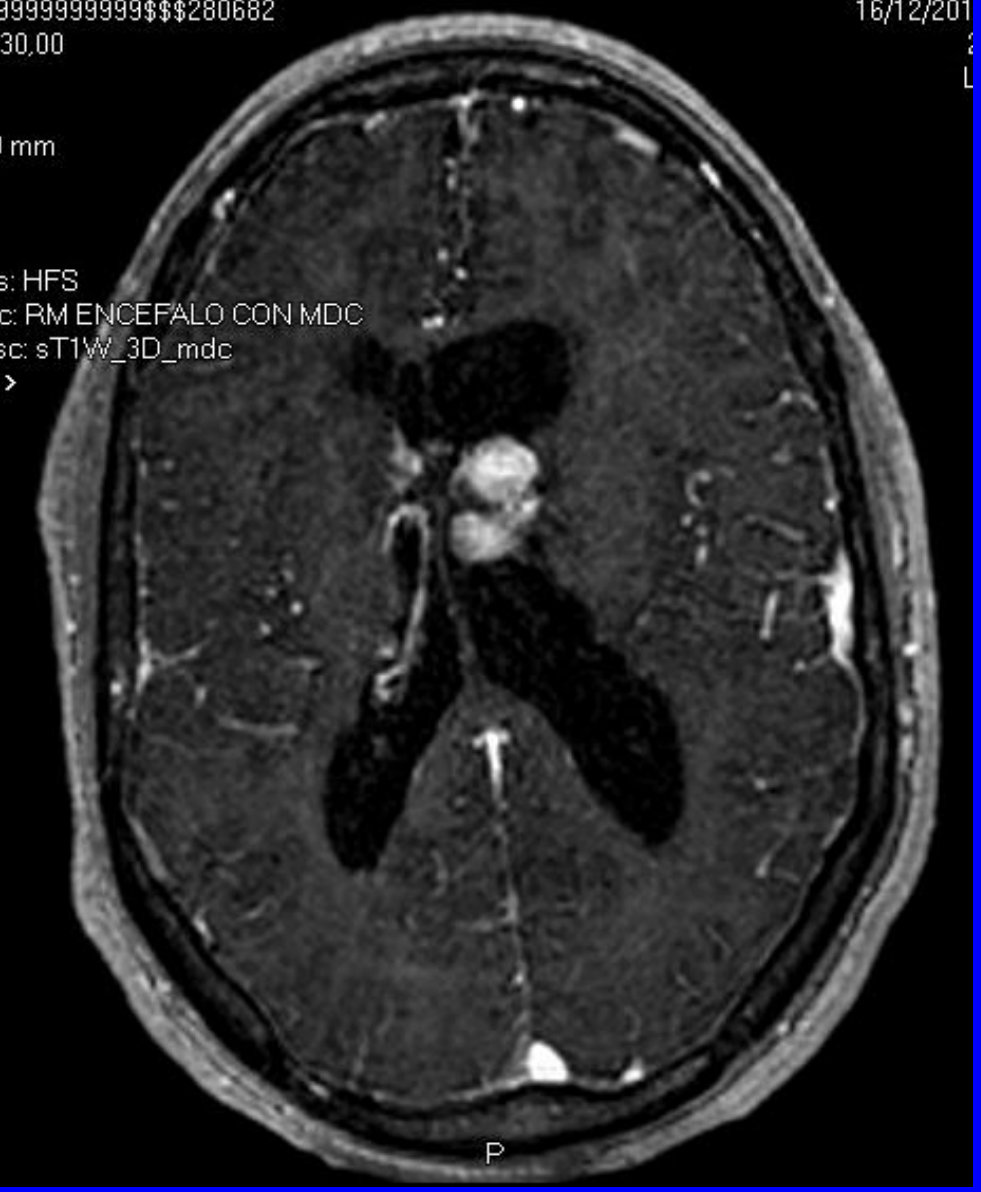


Week 12



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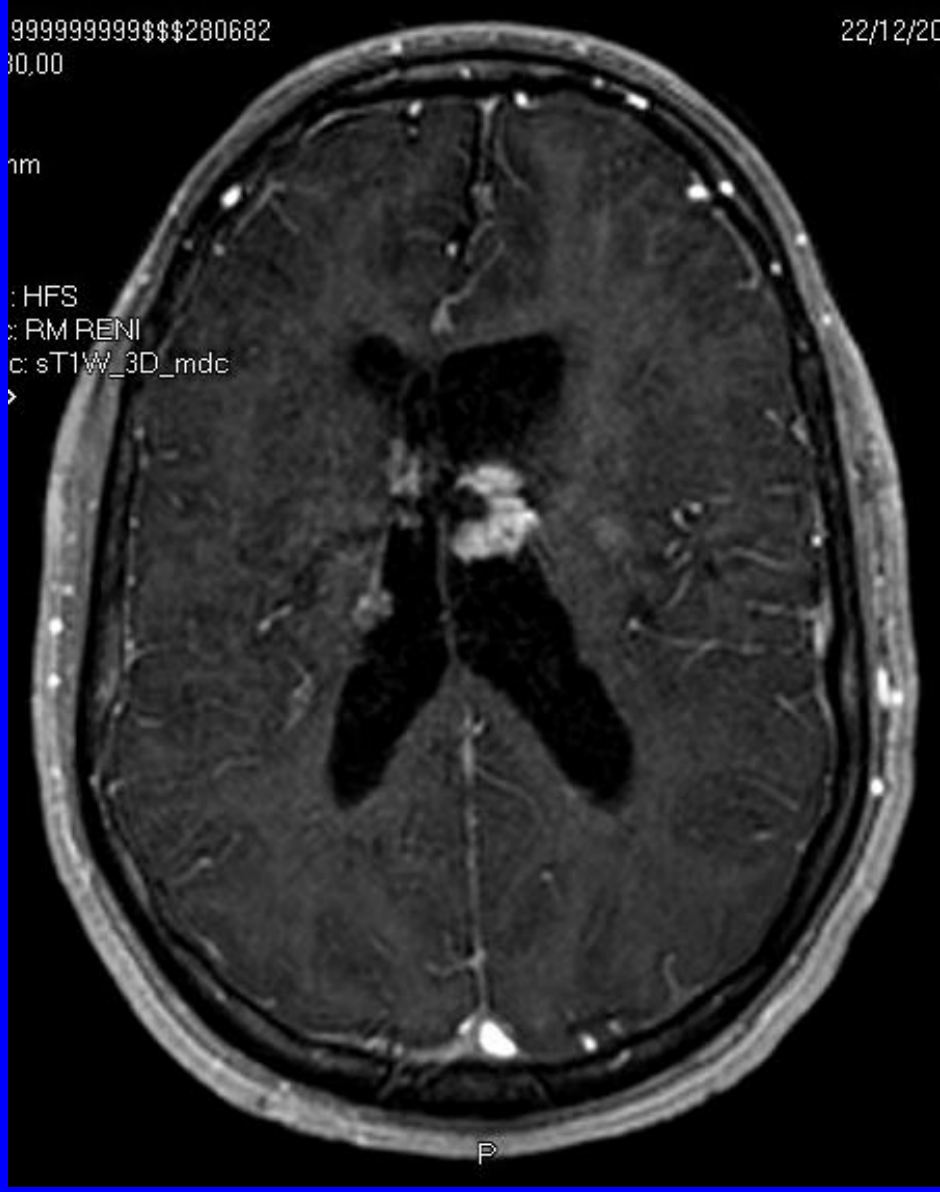

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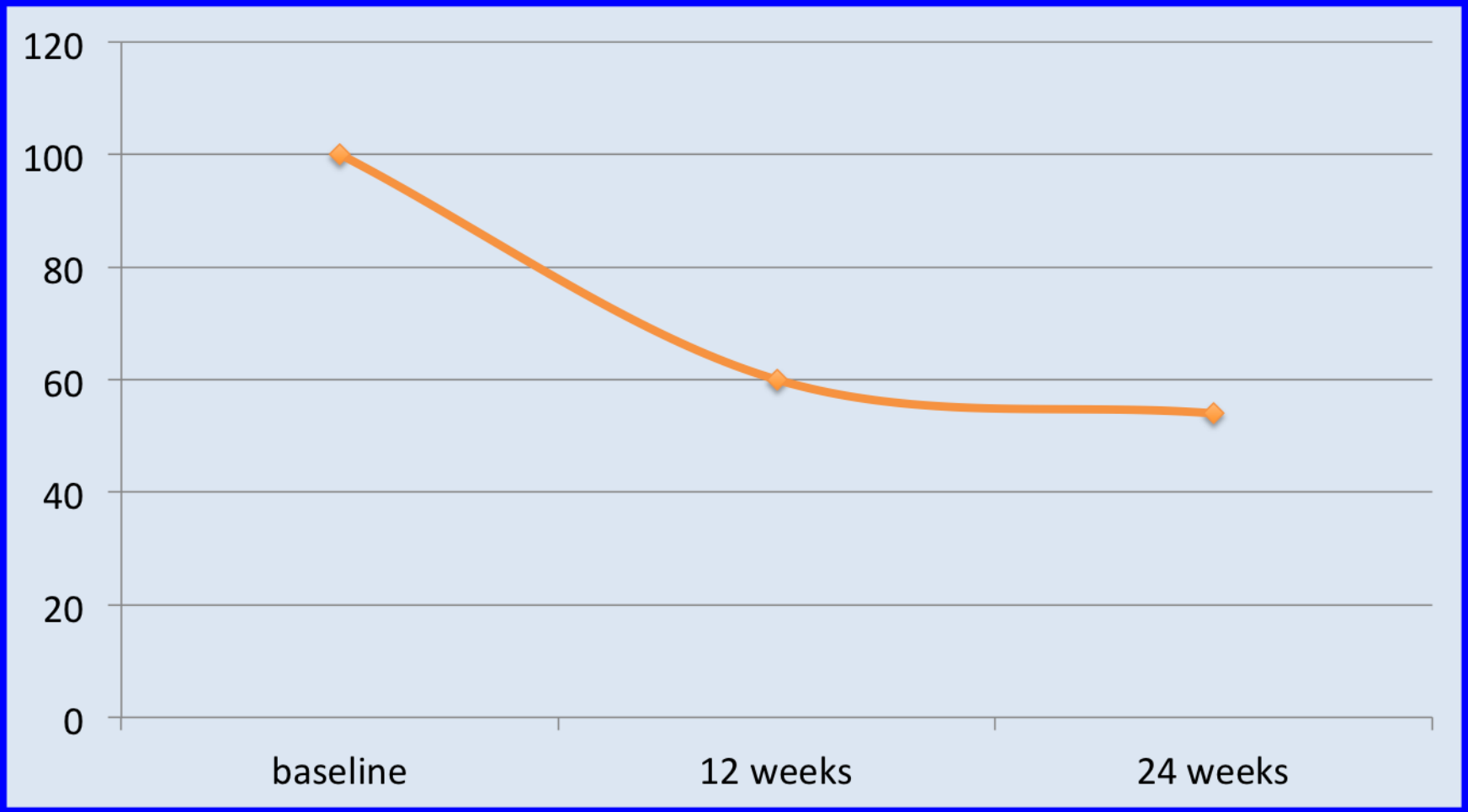
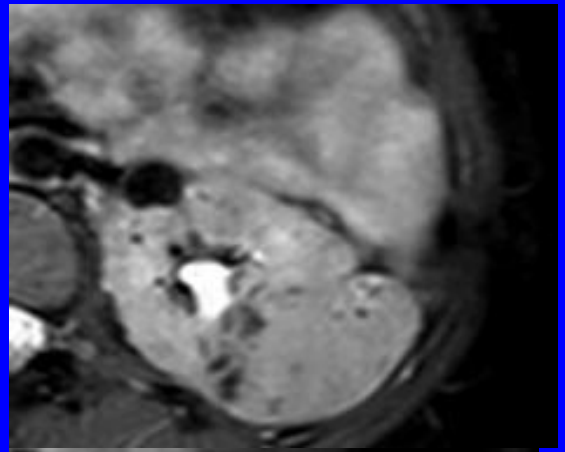
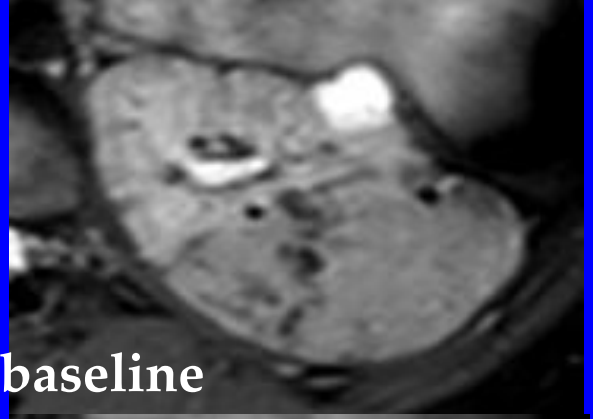


Volume reduction (percentage) of subependimal giant cells astrocytomas in a 25 y old patient treated with Everolimus (10 mg/d)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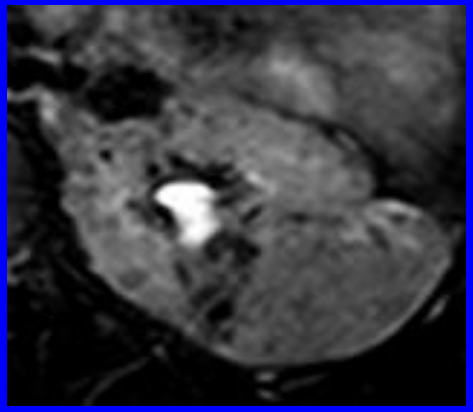
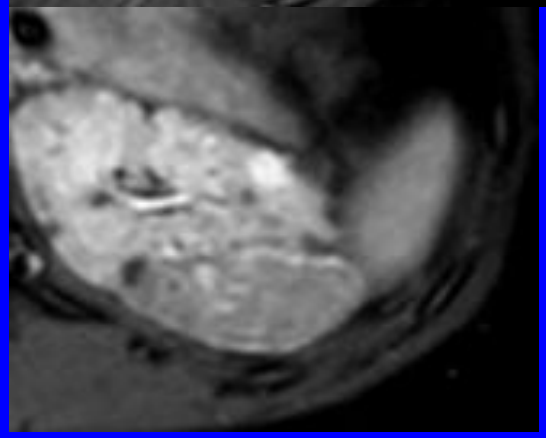
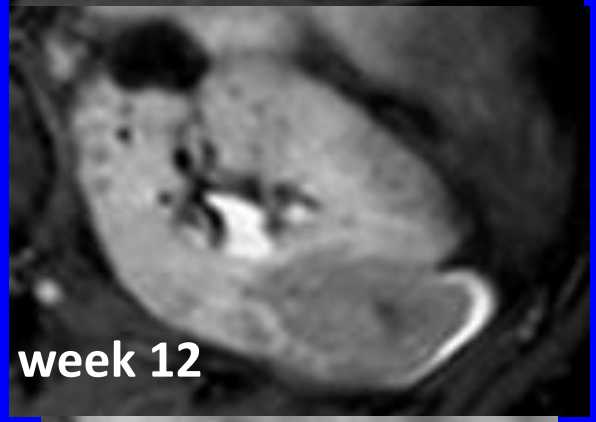
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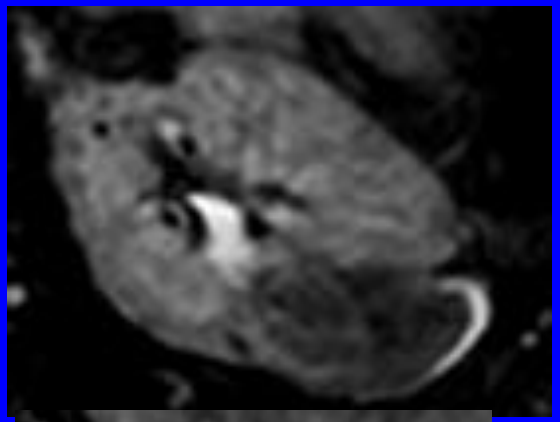
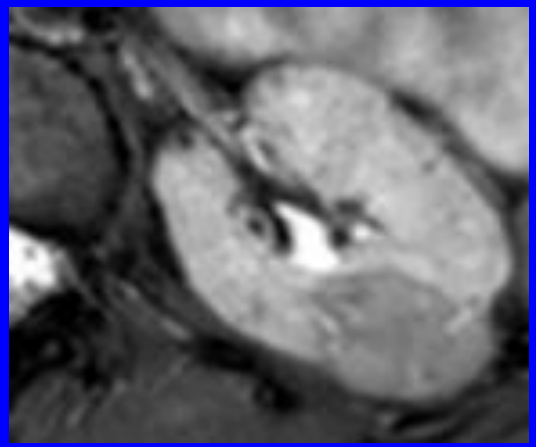
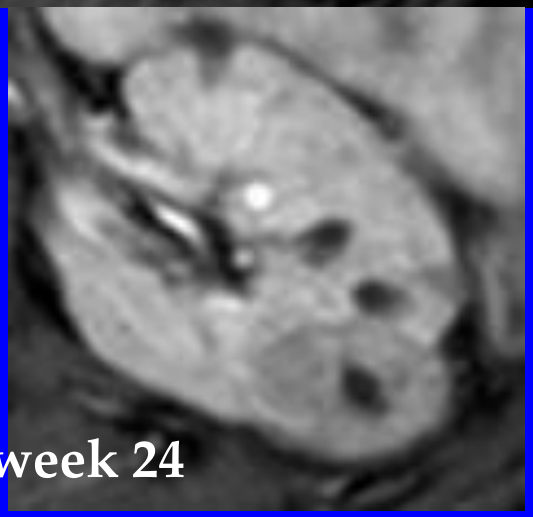
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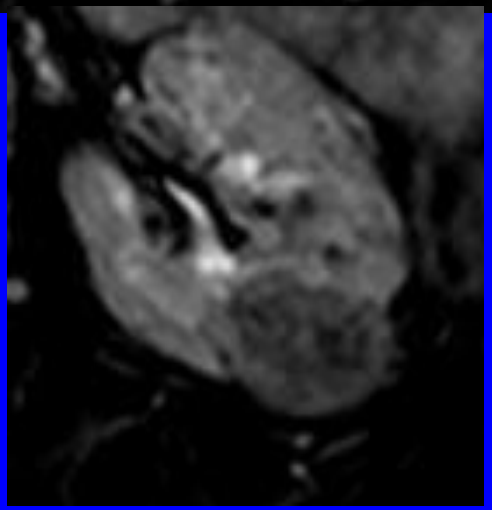
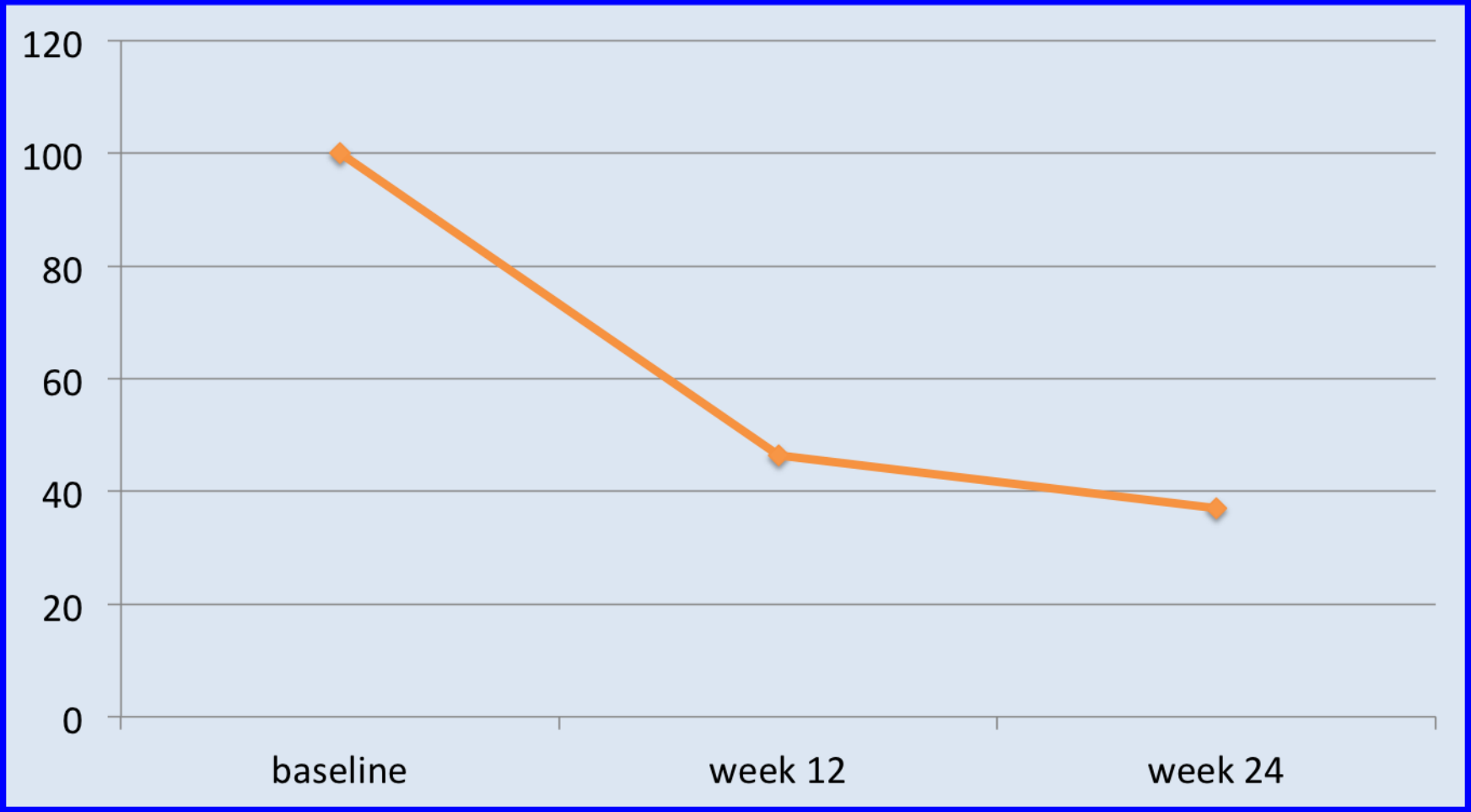
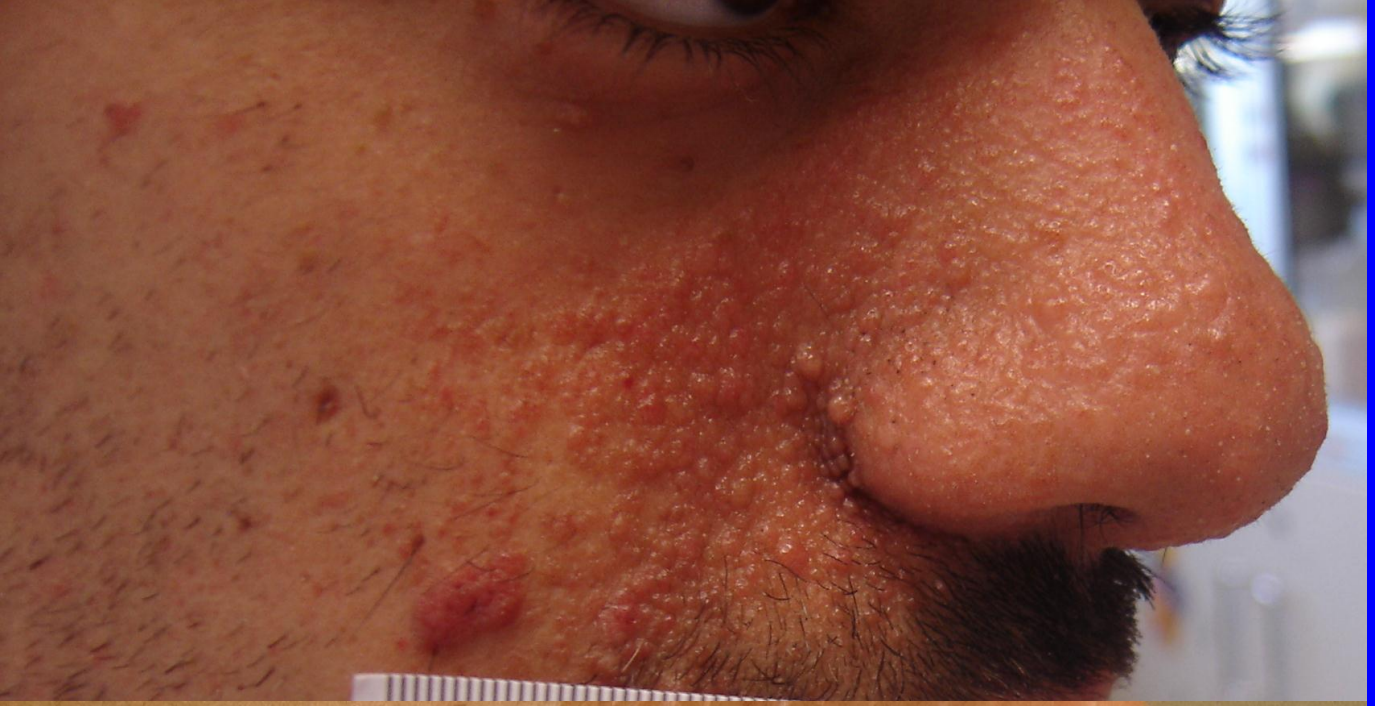
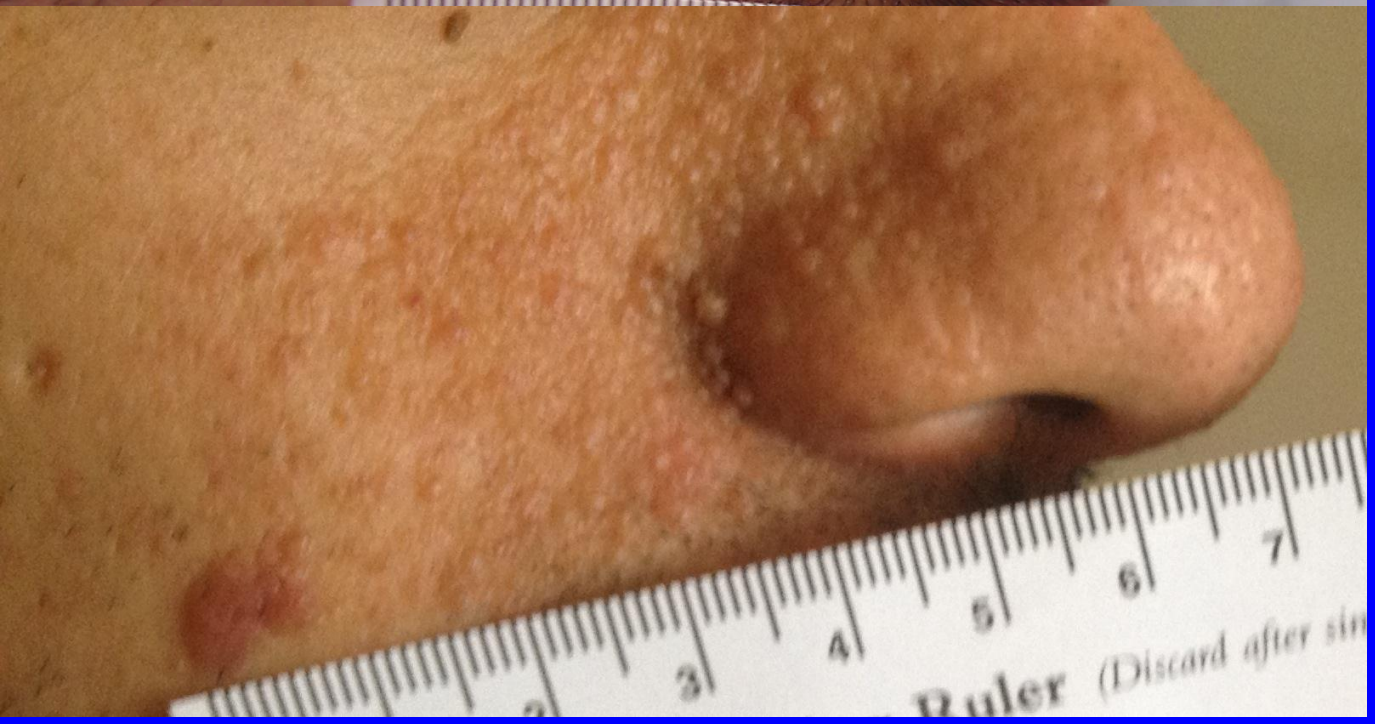




Volume reduction of renal AMLs (percentage) in our 25 y old patient treated with Everolimus (10 mg/d)



Baseline



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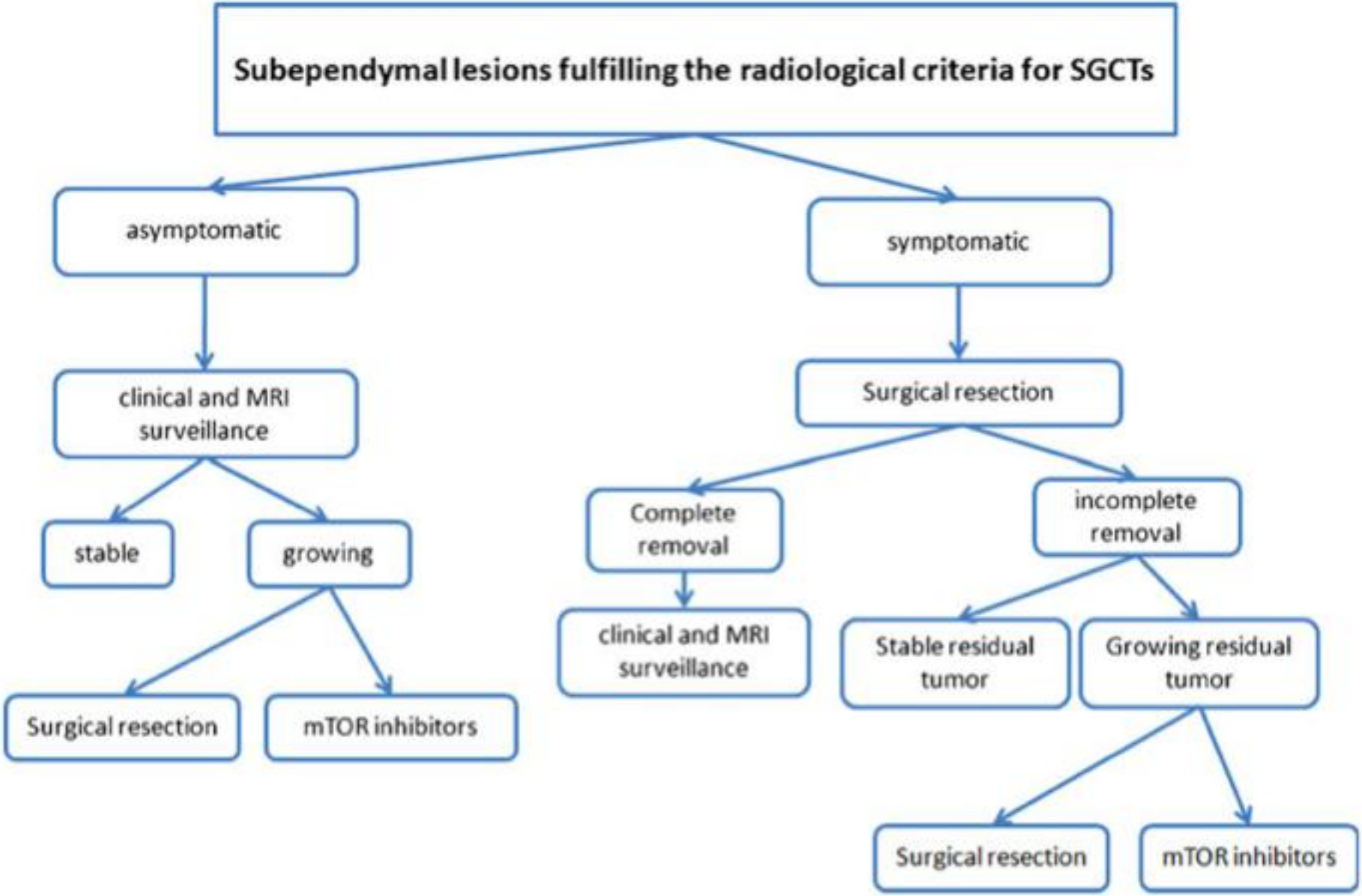

Moavero et al, Childs Nerv Syst 2011