

# Overview of toxicity induced by Antiangiogenic drugs

## An oncologist experience...

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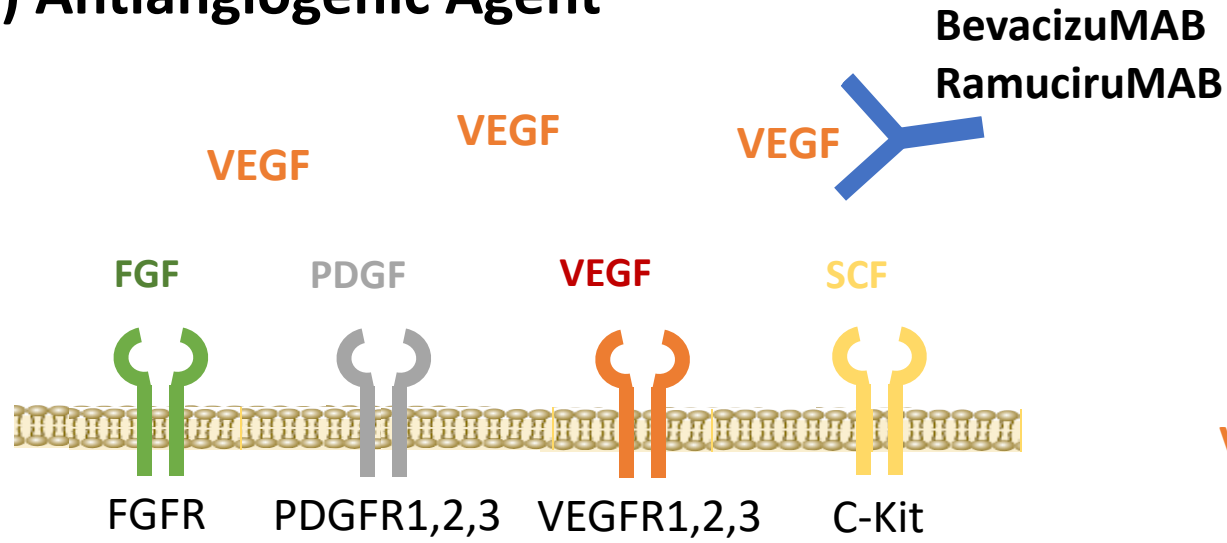
Cliniques universitaires  
**SAINT-LUC**  
UCL BRUXELLES

# Dislosures

Investigator of VASE trial (Pfizer provided sirolimus)  
Investigator of TRAMAV (Novartis provided trametinib)  
Investigator of EPIK L1 (Commercial trial)

Consultancy; fees Pfizer, Novartis, Bayer, Ipsen, BMS, Merck

# 1) Antiangiogenic Agent



Bevacizumab  
Ramucirumab

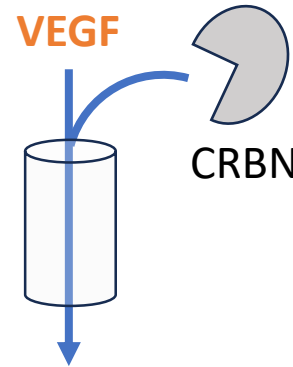
## Monoclonal Antibody

Long half-life (20 days)  
Intravenous

VEGF

## Linomide

Thalidomide  
Lenalinomide  
Pomalidomide



Proteasomal  
degradation

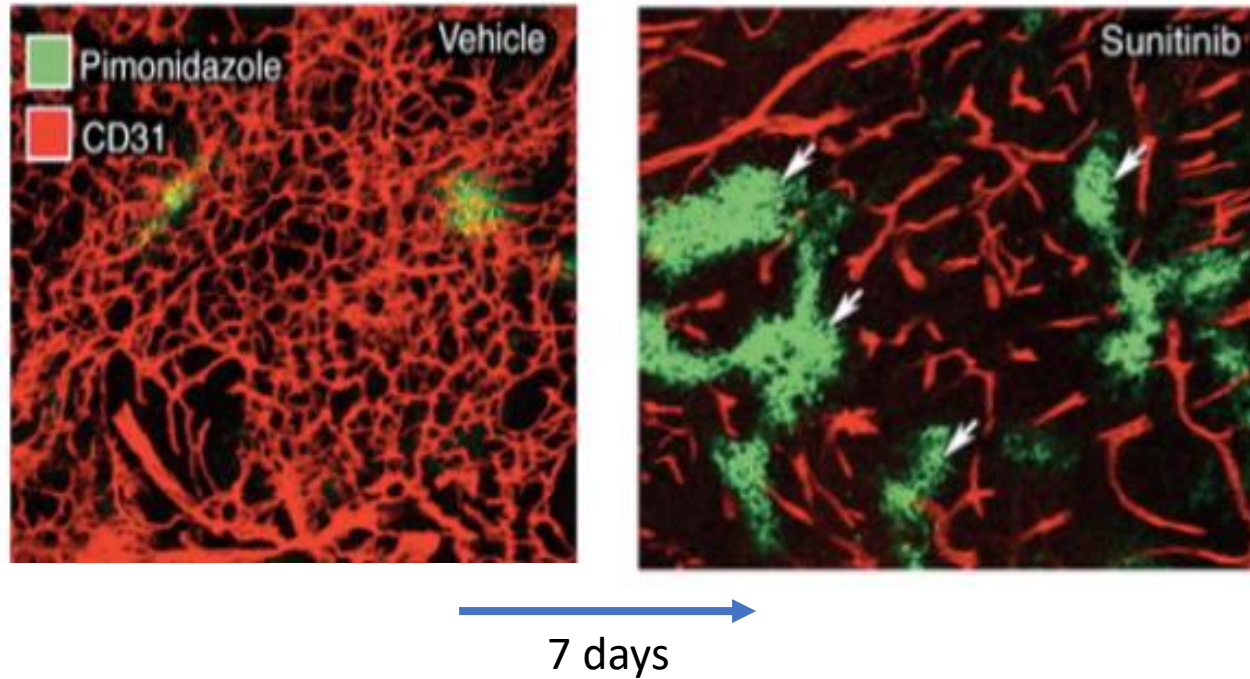
## Small tyrosine kinase inhibitors (TKI)

All with different target sensitivity  
Short half-life (8-120 h)  
Per os



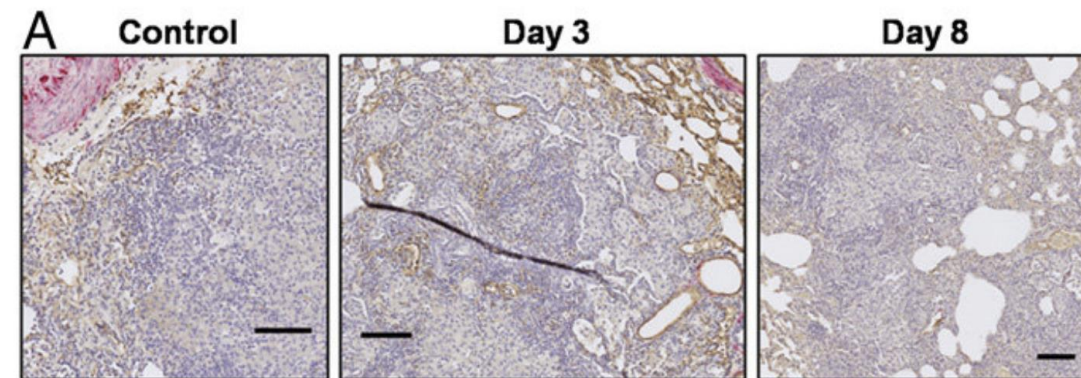
Decrease in VEGF levels  
And or decrease in downstream VEGF-VEGFR axis

## Rapid reduction of vessels density in RCC

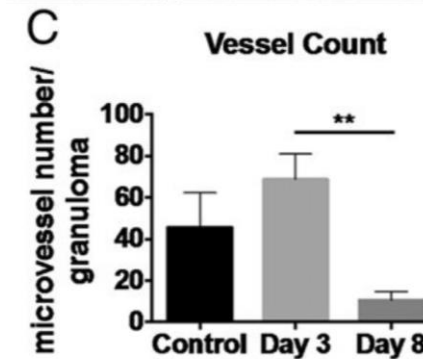


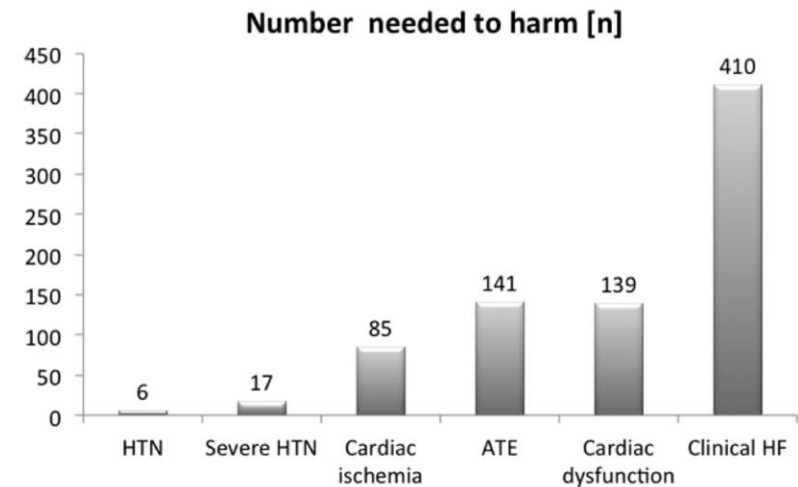
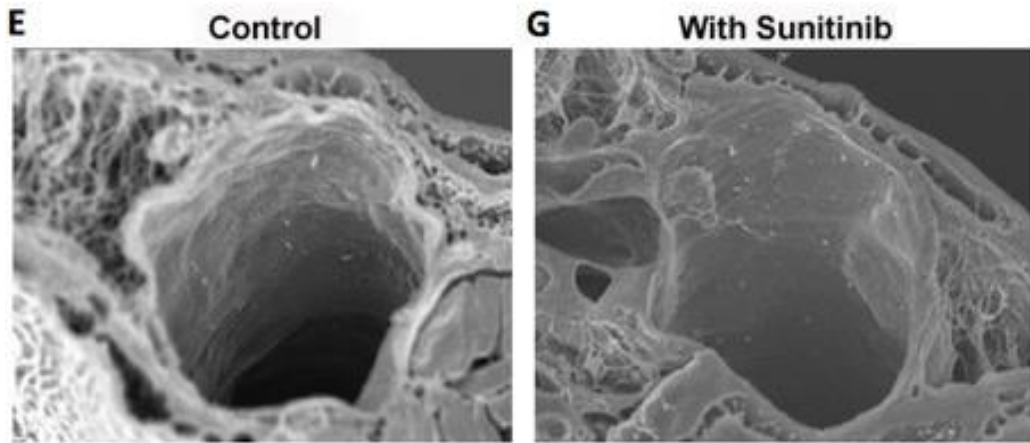
→ Highly potent agent  
in decreasing endothelial cells proliferation

But also in non-oncological fields

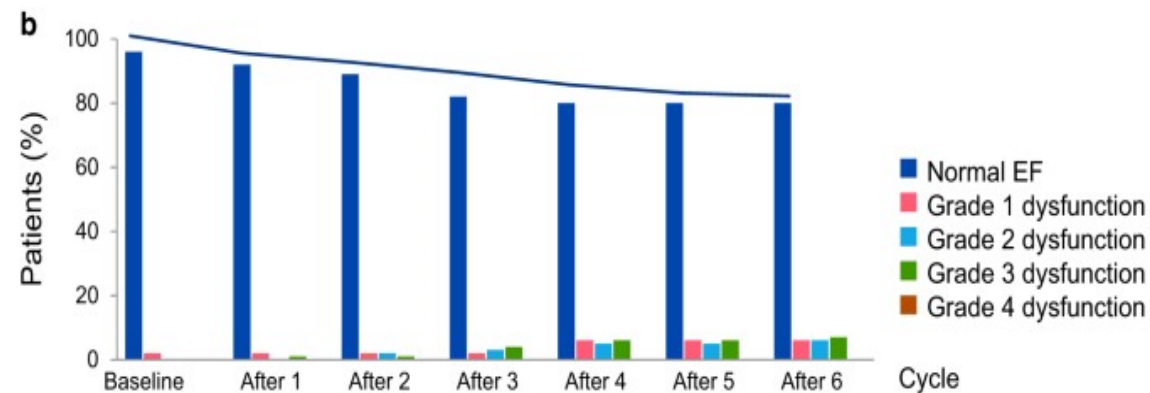
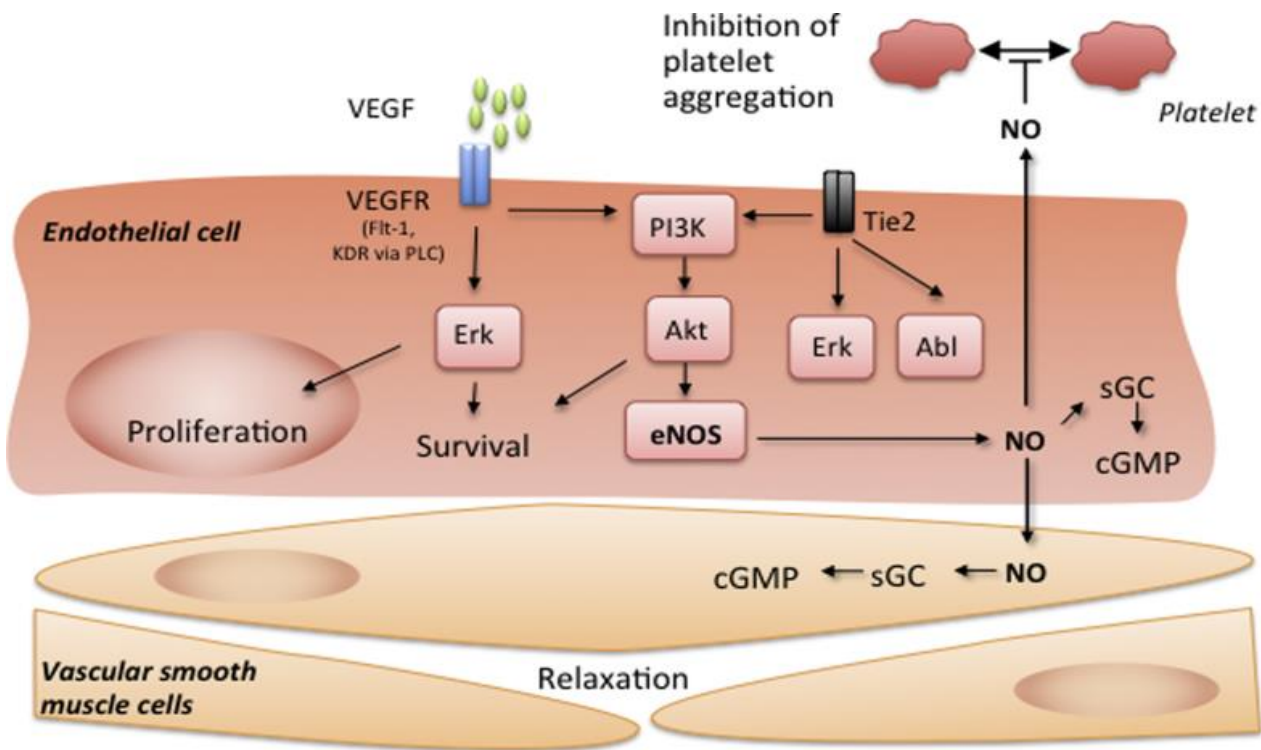


Bevacizumab





**Figure 1.** Bar graph illustrating the number needed to treat to cause one of the indicated CV events (based on data from<sup>13</sup>). HTN, hypertension; ATE, arterial thromboembolic events; HF, heart failure.

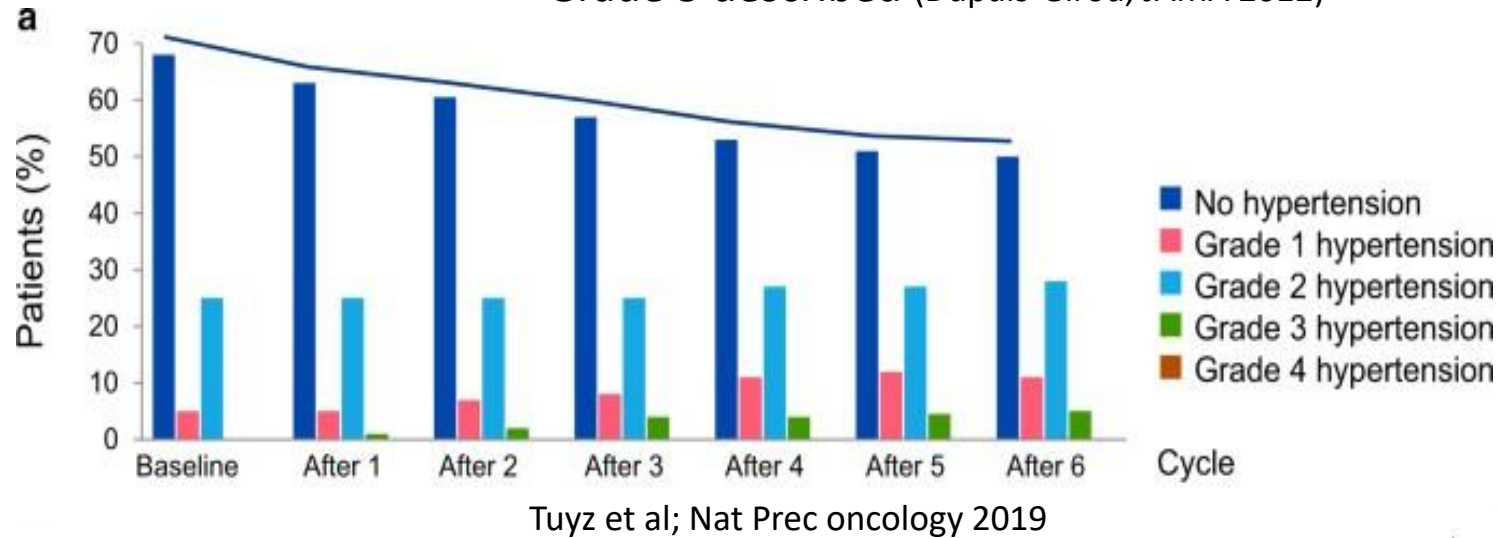


# HTA : FREQUENT

Frequent in Ca = 20-60% (Neves et al, Clin Sc 2020)

Frequent in VaM = 7-20% (Buscarini et al, J Orphan J 2019)

Grade 3 described (Dupuis-Girod, JAMA 2012)



- Monitoring

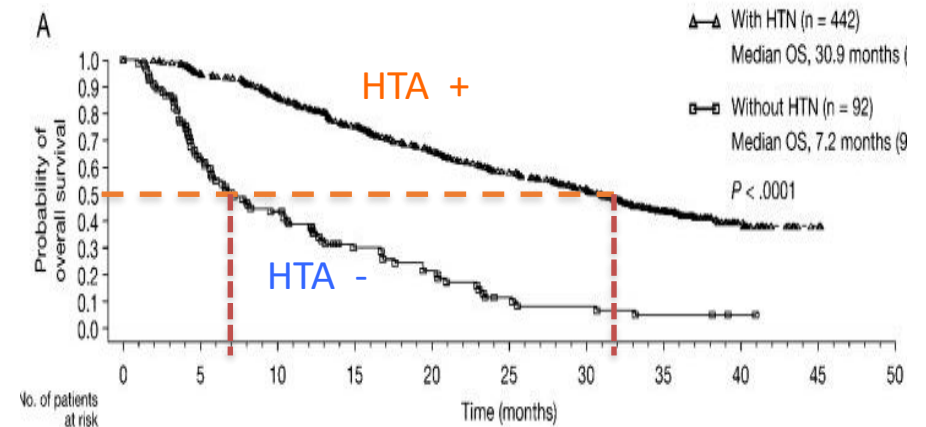
→ weekly

- Which anti HTA ?

→ IEC ou un sartan

→ Calcium antagonist= amlodipine

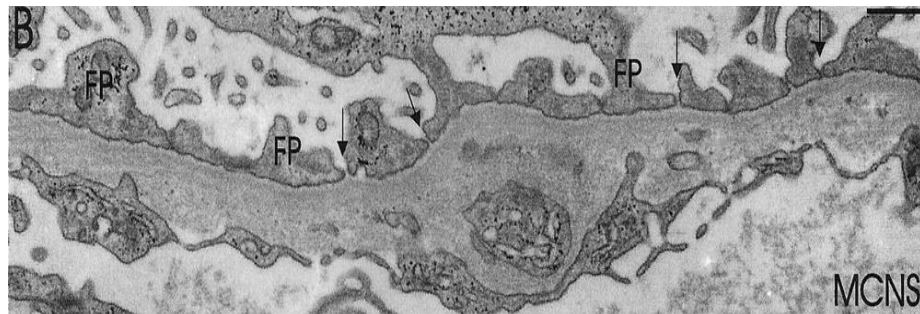
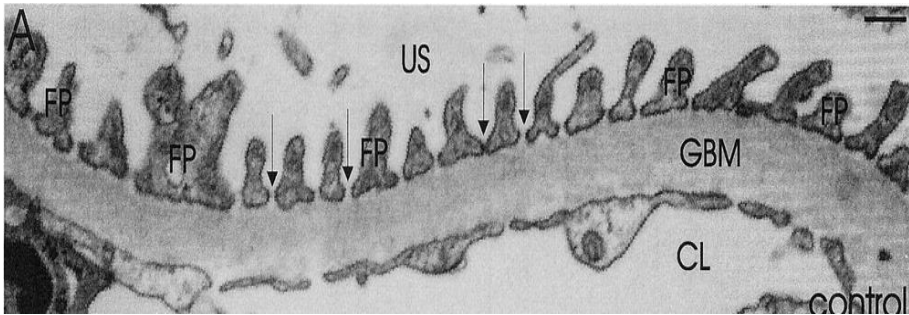
- Predictive of response in RCC?



# Proteinuria: FREQUENT

Frequent in Ca = 20-60% (Launay-Vacher et al, Anticancer drug 2019)

(Less) Frequent in Va Malf = 1-8% (Buscarini et al, J Orphan J 2019)



Follow-up with urinary bandelet

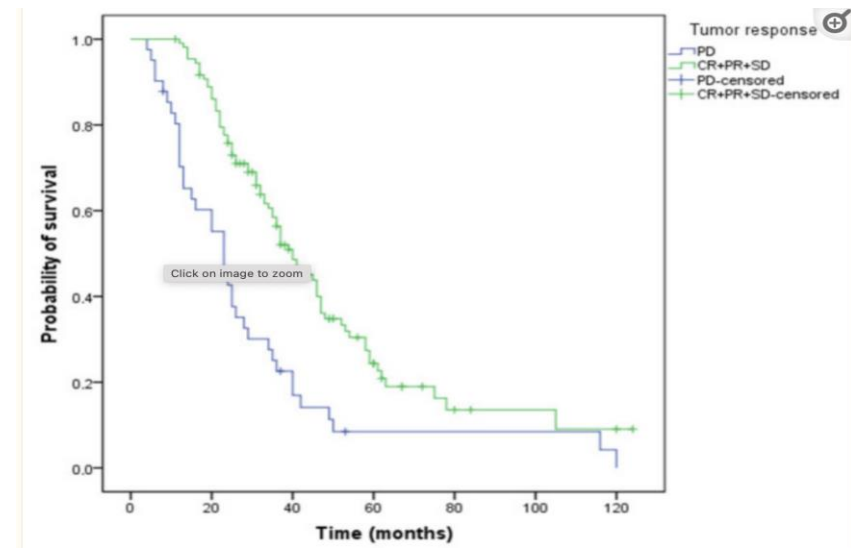
- 1<sup>st</sup> mont= every 2 weeks
- And then every month

If proteinuria = 0 or + → continue treatment

If proteinuria ≥ ++ → 24h collect

→ IEC ou un sartan

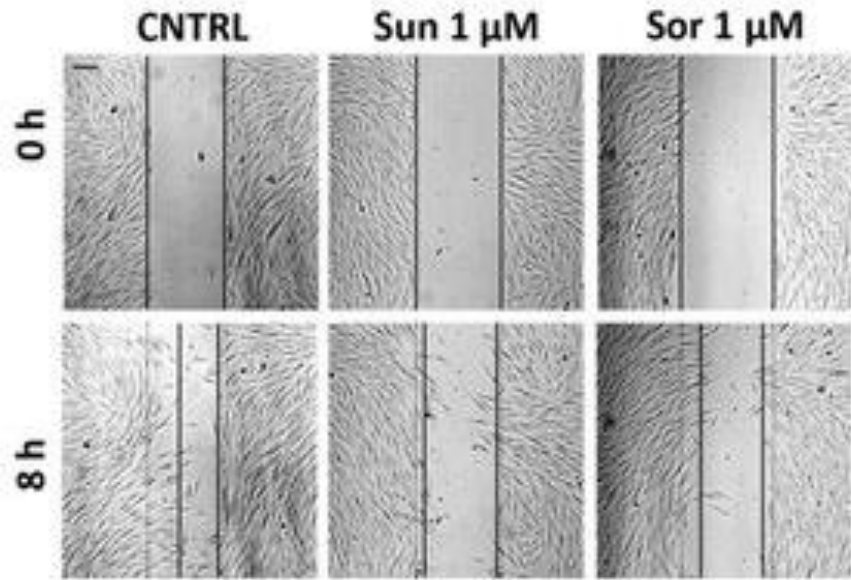
- Predictive of response in mCRC ?



Moisuc et al, Curr Oncol 2022

Tuyz et al; Nat Prec oncology 2019

# Wound healing: be cautious



Fiorio Pla, BMC 2014

## In Va Mal

Bevacizumab in 46 pts with HHT

--> Wound healing in 3 patients → amputation in 2

Guilhem et al, PLoS one 2017

**Antiangiogenic should be interrupted if heavy surgery !**

**EXCEPT for**

- Sirolimus in order to prevent LIC → DIC (Dompmartin et al, JAMA 2008)
- Thalidomide for AVM to prevent VEGF release (Boon et al, Nat CVR 2022)

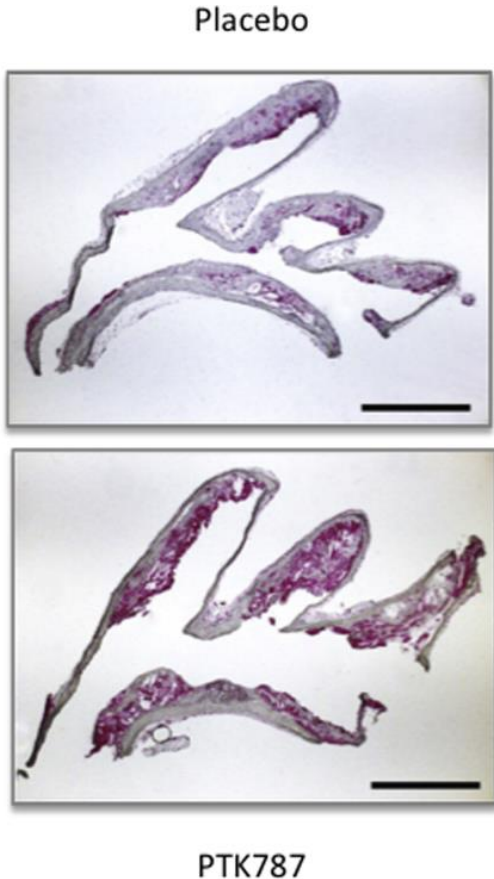
**Caution in case of surgery with high risk of bleeding !**

**Example of Renal Cancer (Carvalho, Sci Rep 2019)**

		30-Day Complication		90-Day Complication		
		HR (95% CI)	p Value	HR (95% CI)	p Value	
Unadjusted	TKI (ref=control)	2.73 (1.09, 6.80)	0.03	1.76 (0.98, 3.16)	0.06	
Adjusted <sup>a</sup>	TKI (ref=control)	2.93 (1.17, 7.36)	0.02	1.84 (1.02, 3.32)	0.04	
	Charlson Comorbidity Index (ref=0)	1	0.71 (0.36, 1.41)	0.33	0.93 (0.59, 1.47)	0.76
		2	2.41 (1.44, 4.02)	0.001	2.23 (1.51, 3.29)	<0.0001



# Endothelial destabilisation leading to severe complications



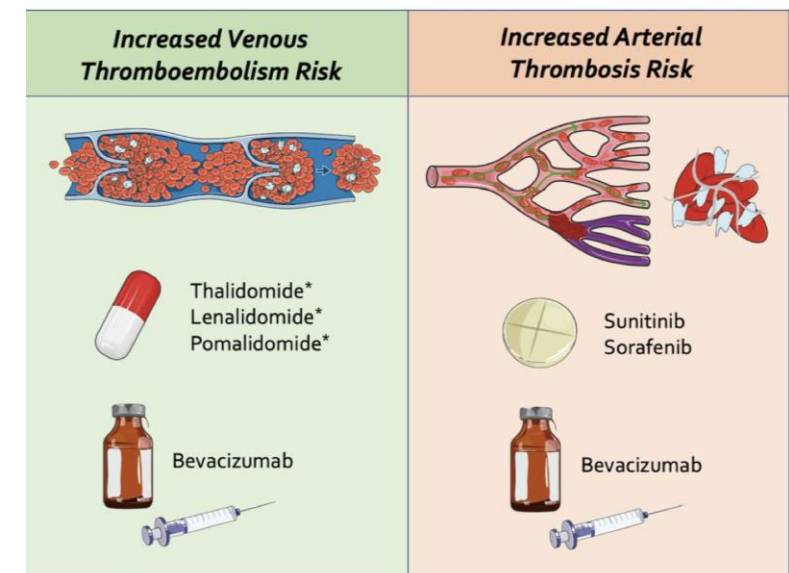
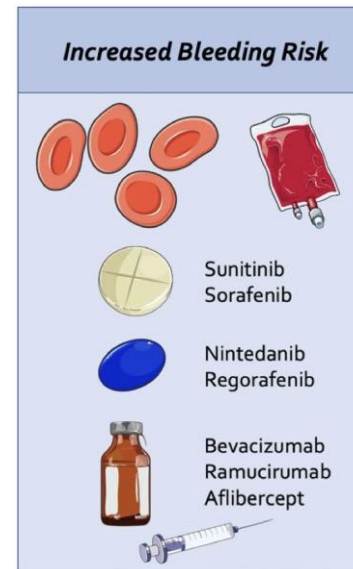
Touyz RM, et al. JASH. 2018

## Hemorrhagic events

## AtheroThrombotic events

TABLE 2 Risks of thrombotic and hemorrhagic events for biologic VEGF/VEGFR inhibitors in cancer patients estimated by large published meta-analyses for each agent

Therapy	All-grade Bleeding Events – % [RR (95% CI)]	Grade 3–5 Bleeding Events – % [RR (95% CI)]	Venous Thromboembolism – % [RR (95% CI)]	Arterial Thrombosis – % [RR (95% CI)]
Bevacizumab	30.4% [2.48 (1.93–3.18)] <sup>28</sup>	3.5% [1.91 (1.36–2.68)] <sup>28</sup> ; 2.8% [1.60 (1.19–2.15)] <sup>29</sup>	11.9% [1.33 (1.13–1.56)] <sup>20</sup>	3.3% [1.44 (1.08–1.91)] <sup>22</sup>
Ramucirumab	13%–44% [1.98 (1.77–2.21)] <sup>21</sup>	1.04 (0.78–1.39) <sup>34</sup>	1%–13% [0.83 (0.52–1.35)] <sup>21</sup>	1.1%–10.4% [0.97 (0.62–1.52)] <sup>21</sup>
Aflibercept	22.1% [2.63 (2.07–3.34)] <sup>96</sup>	4.2% [2.45 (1.62–3.72)] <sup>96</sup>	7.2% [1.00 (0.67–1.51)] <sup>31</sup>	-



Watson et Al-Samkari; J Thromb Haemost 2021

TABLE 4 Thrombosis and bleeding events associated with systemic bevacizumab for hereditary hemorrhagic telangiectasia

Study	Study Design	Dosage	Number of Patients	Bleeding Adverse Events <sup>a</sup>	Thrombotic Adverse Events
Dupuis-Girod et al. (2012) <sup>97b</sup>	Single-center prospective	5 mg/kg	25	0	0
Thompson et al. (2014) <sup>98</sup>	Single-center prospective	0.25 mg/kg	9	0	0
Epperla et al. (2016) <sup>99</sup>	Single-center retrospective	5 mg/kg	5	0	0
Guilhem et al. (2017) <sup>82</sup>	Multicenter retrospective	5 mg/kg	46	1 patient (2%)	1 ischemic cholangitis, 1 mesenteric thrombosis (4%)
Iyer et al. (2018) <sup>81</sup>	Single-center retrospective	5 mg/kg	34	0	Stroke: 1 patient (3%)
Buscarini et al. (2019) <sup>83</sup>	Multicenter retrospective	2.5 mg/kg or 5 mg/kg	69	1 GI bleed, 1 pulmonary bleed (2.8%)	1 arterial thrombosis (1.4%)
Al-Samkari et al. (2019) <sup>100</sup>	Single-center retrospective	5 mg/kg	13	0	0
Al-Samkari et al. (2020) <sup>17</sup>	Multicenter retrospective	92% of patients dosed at 5 mg/kg, range of doses: 1-7.5 mg/kg	238	0	VTE: 5 patients (2%)

Watson et Al-Samkari; J Thromb Haemost 2021

### Caution in pts with CV risk factors

- cholesterol
- smoking
- daily activity
- familial history ...

→ TA profile  
→ Statin

### Caution in pts with large central Va Malf (cerebral or mediastinal)

As life-threatening bleeding has been described (as in cancer)

## Beva vs Thalidomide in HHT

**Table 7** Main AEs' rates (for grades 1–5) in present series compared to literature data on BZB and TH in oncology (or other) settings

	Present study %	Literature [64–72] %
<b>Bevacizumab</b>		
Hypertension	7.2	5–19
Bleeding	2.8	1.7–6.7
Proteinuria	2.8	0.7–7.4
Arterial thromboembolism	1.4	0.7–4.4
Peripheral neuropathy	Not described	6.3
<b>Thalidomide</b>		
Somnolence/drowsiness	16	2–23
Peripheral neuropathy	17.9	1–44
Thromboembolic event	2.9	1–6
Cardiac failure	1.4	1–8
Bleeding	1.4	Not described

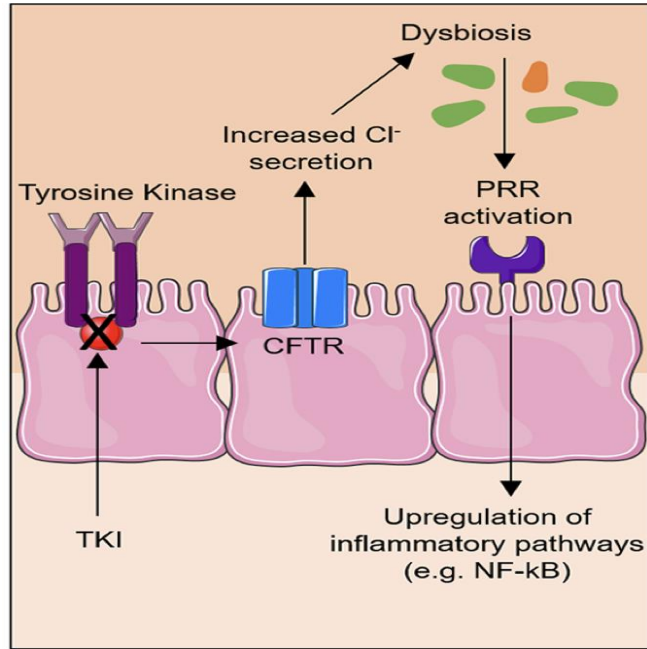
Buscarini E, et al. Orphanet J Rare Dis 2019.

**Can we consider that 3-5% is low in Va Malf?**

**Median age 25y !!**

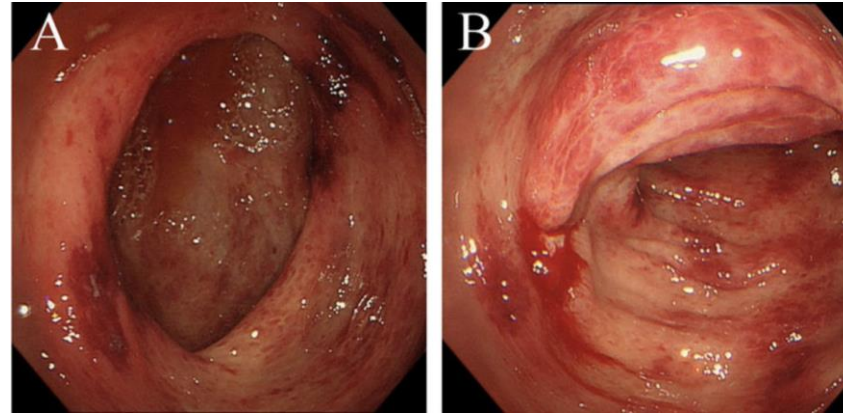
Buscarini E, et al. Dig Dis Sci 2011.  
Sehl et al. Am J Hem 2015  
Cottin et al, Eur Resp Rev 2009

# Diarrhea = FREQUENT



TKI stimulates CFTR  
 → increase permeability  
 → Dysbiose

+ Decrease in VEGF  
 → Increased fragility  
 → Impaired wound healing



!/ Suspect bowel perforation  
 in case of acute abdominal pain



Bowel perforation = 1%

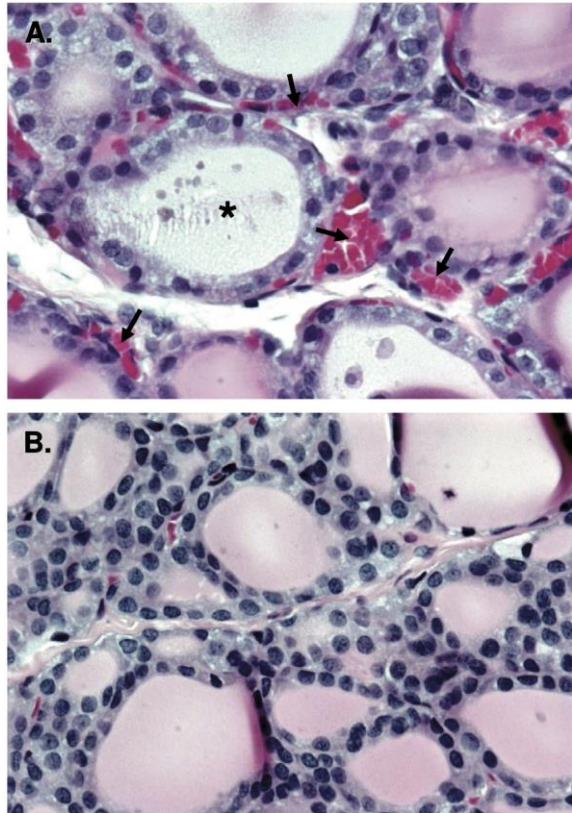
### Risk factors

- diverticulitis
- previous RT
- endometriosis
- NSAID,...

	Diarrhea incidence	
	All grades (%)	Severe, grade 3+, (%)
Sorafenib	30% to 50%	>10%
Sunitinib	30% to 50%	>10%
Regorafenib	33%	4% to 8.5%
Pazopanib	33% to 52%	2% to 4%
Axitinib	55%	11%
Vandetanib	52.1%	5.6%
Lenvatinib	45% to 67%	4% to 9%
Cabozantinib	72% to 75%	10% to 13%

Resolution of diarrhea depends of half-life !

# Hypothyroidism



- Predictive of response in RCC?

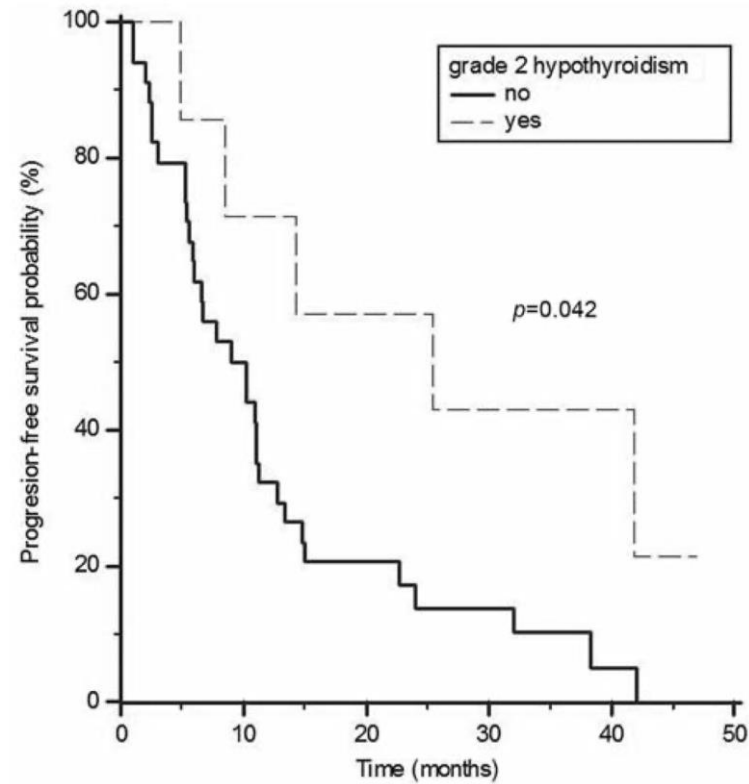


Figure 2. Association between grade 2 hypothyroidism and PFS.

Sunitinib, pazopanib > Nintedanib

Thalidomide > pomalidomide

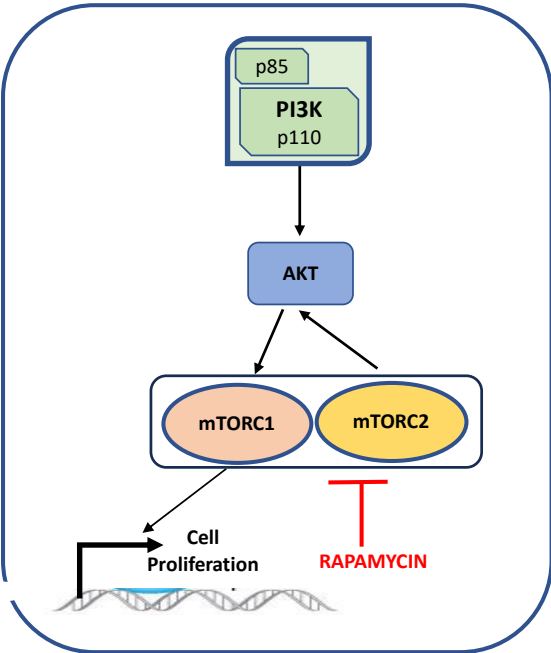
➔ Can increase CV risk

Do not also forget

**the dysphonia**

**Hypovascularization of vocal cords !**

## 2) mTOR inhibitors



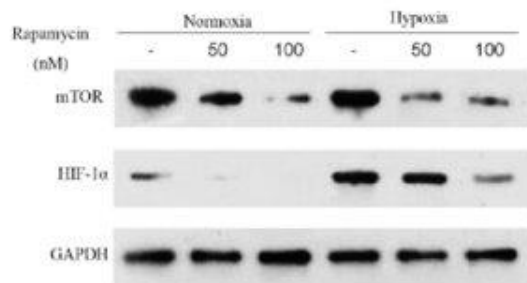
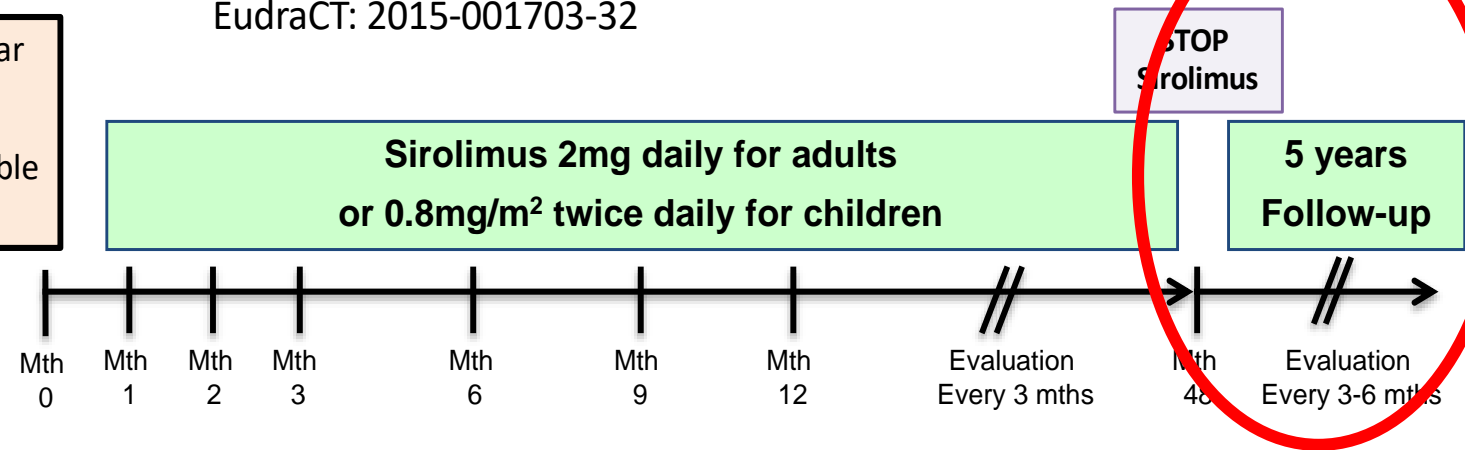
### \* Design

Patients with Vascular Anomalies  
Ineffective or unfeasible conventional R/

## Multicentric European Phase III Clinical trial

Vascular Anomaly - Sirolimus – Europe (VASE)

EudraCT: 2015-001703-32



Seront E et al, BJC 2013


Seront E, ... Domp Martin A, Bisdorff A... et al JCI Insight 2023

## No Hematological toxicity

### No immunosuppressive effect in 250 patients receiving at least one dose of sirolimus

- No decrease in leucocytes (0%)
  - No severe COVID or complication (0%)
  - Development of Anti-Sras Ac (100% vaccinated pts)
  - No Pneumocystis infection despite no prophylaxis (0%)
- 
- ➔ Case by case discussion for PCP prophylaxis
  - ➔ Blood control at 1, 6 months  
and subsequently every 6 months

**Sirolimus**  
Le sirolimus, appelé également rapamycin, est classé également parmi les immunosuppresseurs.  
le tacrolimus, est classé également parmi les immunosuppresseurs.  
Historique · Utilisation · Recherche



# Sirolimus and cancer

Among 250 patients treated with sirolimus, f/u ranging from 1 year to 12 years)

- 1 **lymphoma** in a 11yo patient; probably not related due to non EBV relation
- 1 **non melanoma skin cancer**; in a 65yo patient with previous history of basal cell carcinoma
- 1 **breast cancer** in a 45yo patient; probably not related due to early appearance
- 1 **pancreatic cancer** in a 51yo patient; discovered early with blood tests; probably not related

Vol. 10, 2109–2119, March 15, 2004

Clinical Cancer Research 2109

## Rapamycin-Induced Endothelial Cell Death and Tumor Vessel Thrombosis Potentiate Cytotoxic Therapy against Pancreatic Cancer

JUBMB *Life*, 59(11): 717–721, November 2007

Christia

informa  
healthcare

[Cancer Med.](#) 2015 Sep; 4(9): 1448–1459.

Published online 2015 Jun 24. doi: [10.1002/cam4.487](https://doi.org/10.1002/cam4.487)

PMCID: P

PMID

### Research Communication

## Sirolimus Inhibits Human Pancreatic Carcinoma Cell Proliferation by a Mechanism Linked to the Targeting of mTOR/HIF-1 $\alpha$ 2/VEGF Signaling

[CANCER RESEARCH 59, 3581–3587, August 1, 1999]

Yu Wang<sup>1</sup>, Qiu Zhao<sup>2</sup>, Songli

*Advances in Brief*

## Regulation of Cell Growth and Cyclin D1 Expression by the Constitutively Active FRAP-p70<sup>S6K</sup> Pathway in Human Pancreatic Cancer Cells<sup>1</sup>

Martin Grewe, Frank Gansauge, Roland M. Schmid, Guido Adler, and Thomas Seufferlein<sup>2</sup>



**I am reassured as oncologist !**  
**Always propose standard screening**  
**-breast , prostate, colon, cervical...**

# Sirolimus and fertility : a need for prospective clinical trial

Many papers suggested infertility problems with sirolimus

But ...Case series, retrospective, renal transplant pts ,...

[The Rapamycin-Sensitive Complex of Mammalian Target of Rapamycin Is Essential to Maintain Male Fertility.](#)

33  
Cite Schell C, Kretz O, Liang W, Kiefer B, Schneider S, Sellung D, Bork T, Leiber C, Rüegg MA, Mallidis C, Schlatt S, Mayerhofer A, Huber TB, Grahammer F.  
Share Am J Pathol. 2016 Feb;186(2):324-36. doi: 10.1016/j.ajpath.2015.10.012. Epub 2015 Dec 10.

[Sirolimus may reduce fertility in male renal transplant recipients.](#)

50  
Cite Zuber J, Anglicheau D, Elie C, Bererhi L, Timsit MO, Mamzer-Bruneel MF, Ciroldi M, Martinez F, Snanoudj R, Hiesse C, Kreis H, Eustache F, Laborde K, Thervet E, Legendre C.  
Share Am J Transplant. 2008 Jul;8(7):1471-9. doi: 10.1111/j.1600-6143.2008.02267.x.

[Gonadal dysfunction and infertility in kidney transplant patients receiving sirolimus.](#)

47  
Cite Boobes Y, Bernieh B, Saadi H, Raafat Al Hakim M, Abouchacra S.  
Share Int Urol Nephrol. 2010 Jun;42(2):493-8. doi: 10.1007/s11255-009-9644-8. Epub 2009 Sep 23.  
PMID: 19774480

**Sirolimus** is an immunosuppressor of the mammalian target of rapamycin inhibitors (mTOR-I) group

[The rapamycin analog Everolimus reversibly impairs male germ cell differentiation and fertility in the mouse.](#)

15  
Cite Kirsanov O, Renegar RH, Busada JT, Serra ND, Harrington EV, Johnson TA, Geyer CB.  
Share Biol Reprod. 2020 Oct 29;103(5):1132-1143. doi: 10.1093/biolre/ioaa130.  
PMID: 32716476 **Free PMC article.**

**Sirolimus**, also known as rapamycin, and its closely related rapamycin analog (rapalog) Everolimus



## Sirolimus and fertility : observation from VASE trial

- **Less than 8% of dysmenorrhea**

  - Time of onset: median 2 months, ranging from 1 to 6 months

  - all reversible after sirolimus interruption

- **Number of Pregnancies is growing after sirolimus treatment**

Considering that we are following 120 pts aged 18-40 y

→ 10 pregnancies from 3 fathers and 3 mothers

8 occurs within the year after discontinuation of sirolimus

**No birth complication**

**No intrauterine growth retardation**

**No developmental complication**

**Child conception is rapidly feasible**

**after sirolimus treatment**

→ **Reassure the patients**

→ **Registry to be done !**

# Antiangiogenic and pregnancy

Pregnancy Category	Description
A	Appropriate human studies - no risk
B	Insufficient human studies, but animal research suggests safety <b>or:</b> Animal studies show issues but human studies show safety
C	Insufficient human studies, but animal studies show problems <b>or:</b> No animal studies, and insufficient human studies
D	Human studies, with/without animal research show fetal risks, but the drug is important to some women to treat their conditions
X	Fetal risks are evident; there are no situations where the risk/benefit justifies use

← **Sirolimus**

← **Bevacizumab**

← **Thalidomide**



[Front Pharmacol.](#) 2022; 13: 1063625.

Published online 2022 Nov 10. doi: [10.3389/fphar.2022.1063625](https://doi.org/10.3389/fphar.2022.1063625)

PMCID: PMC9684212

PMID: [36438807](https://pubmed.ncbi.nlm.nih.gov/36438807/)

Potential safety signal of pregnancy loss with vascular endothelial growth factor inhibitor intraocular injection: A disproportionality analysis using the Food and Drug Administration Adverse Event Reporting System

[Takamasa Sakai](#),<sup>1,\*</sup> [Chiyo Mori](#),<sup>1,2</sup> and [Fumiko Ohtsu](#)<sup>1</sup>

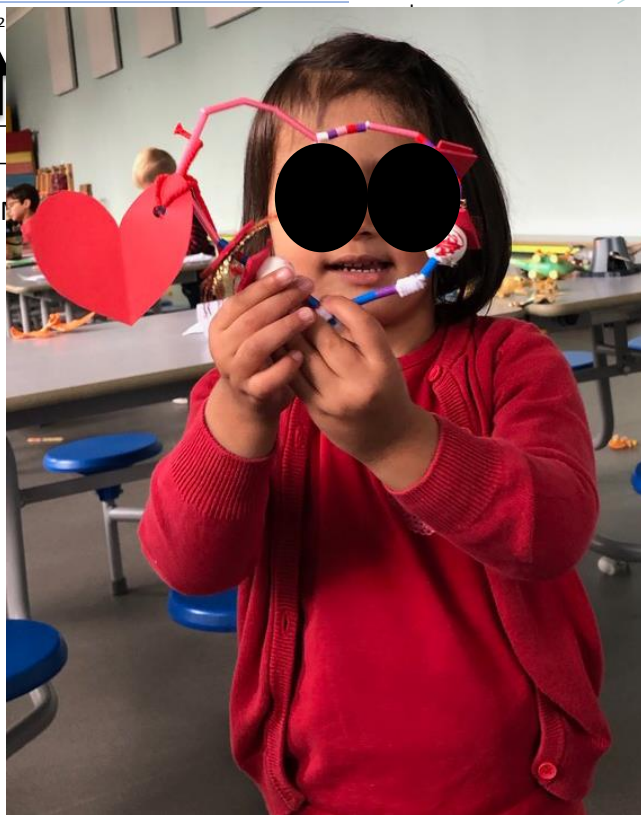
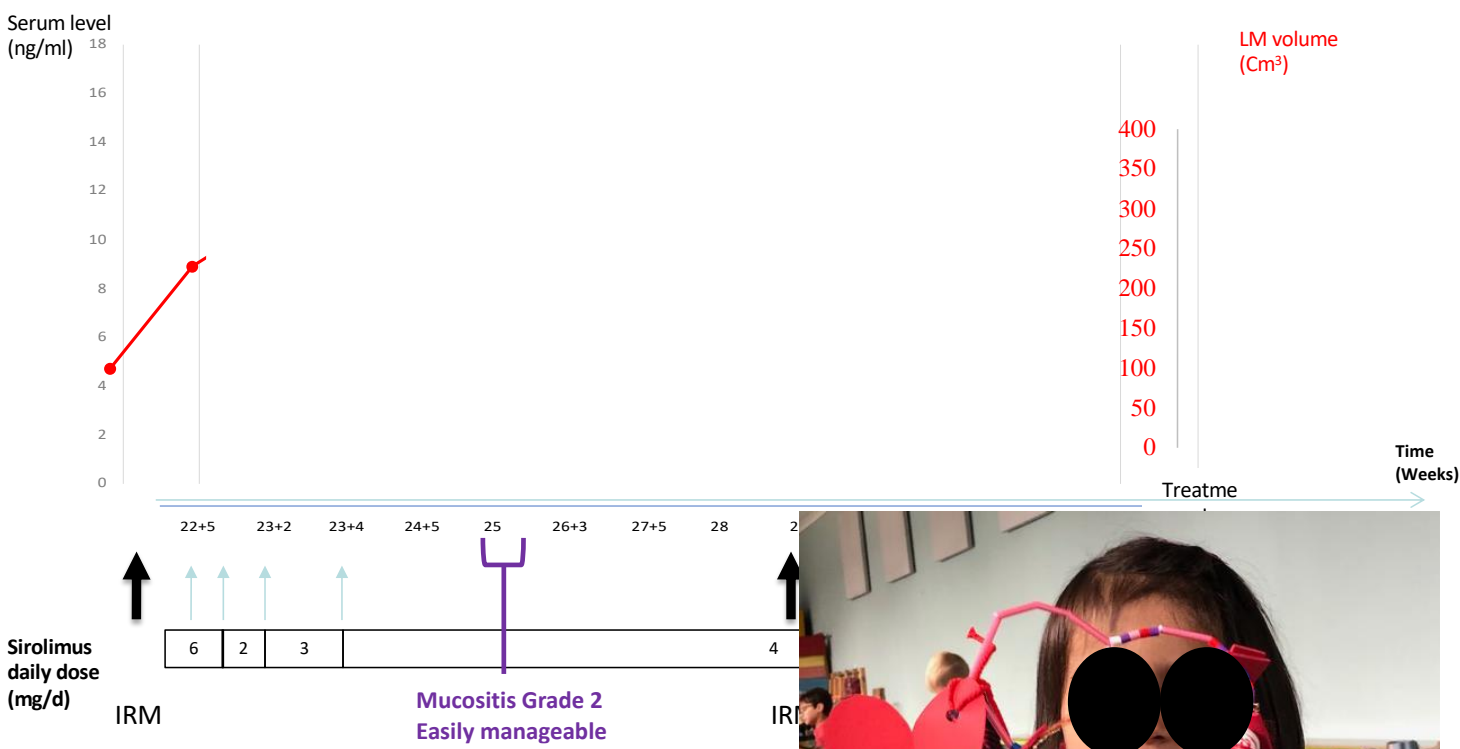
6 pregnancy loss out of 7 reported

# A case report of sirolimus use in early fetal management of lymphatic malformation

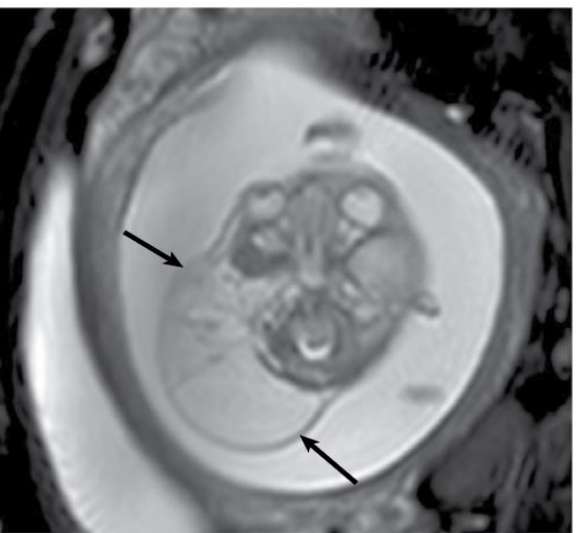
Seront E et al. Nature Card Vasc Res 2023

Maternal level of sirolimus correlates with fetal level

Sirolimus during pregnancy was not associated with developmental complication



21 weeks



Thank you for your attention

Special thanks to our courageous patients

[Emmanuel.seront@saintluc.uclouvain.be](mailto:Emmanuel.seront@saintluc.uclouvain.be)

