

# Essai **RENATO**

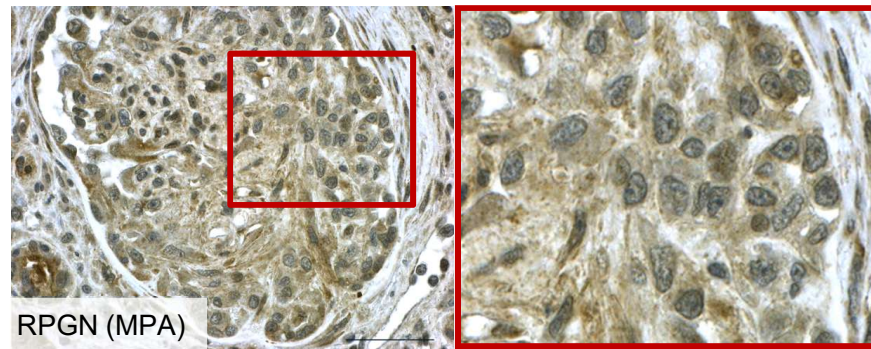
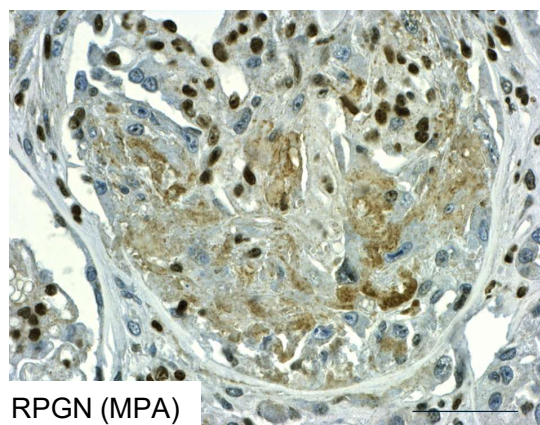
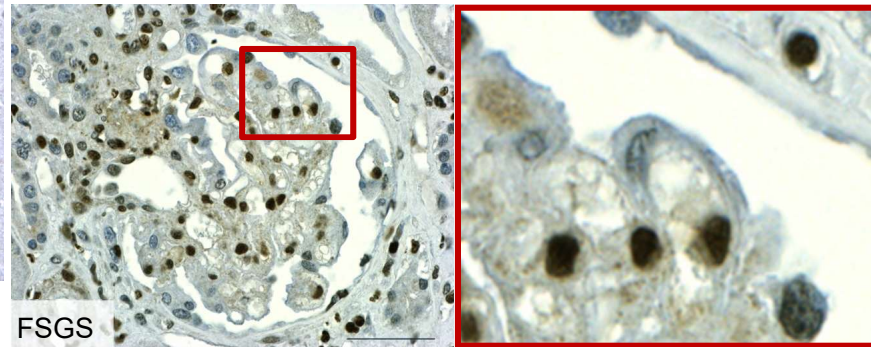
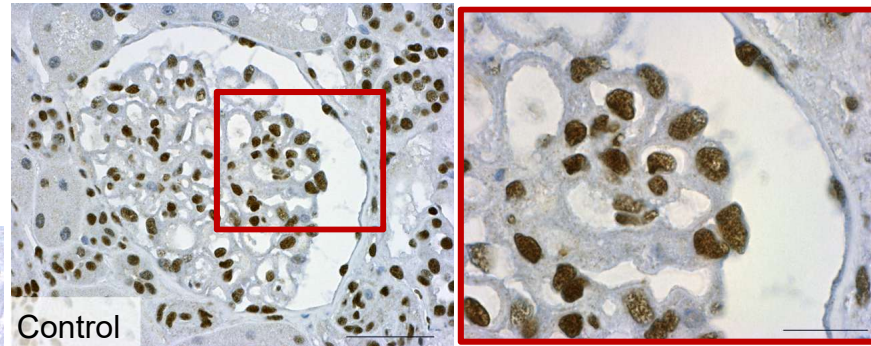
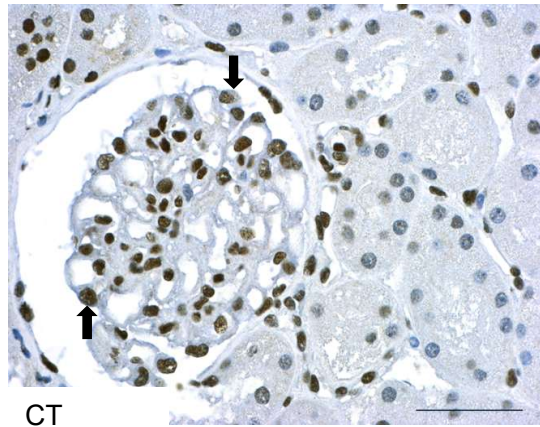
MULTICENTER **R**ANDOMIZED TRIAL TO **E**VALUATE THE  
EFFICACY OF PIOGLITAZONE TO PROMOTE **RENAL**  
**T**OLERANCE IN ANCA-ASSOCIATED VASCULITIS

# Introduction

Comment limiter les séquelles rénales d'une poussée rénale de VAA ?

- Dépister et traiter précocément les poussées...
- Améliorer les schémas d'induction pour une efficacité plus rapide ?
- Epurer les ANCA circulants ?
- Améliorer la « cicatrisation » rénale ?

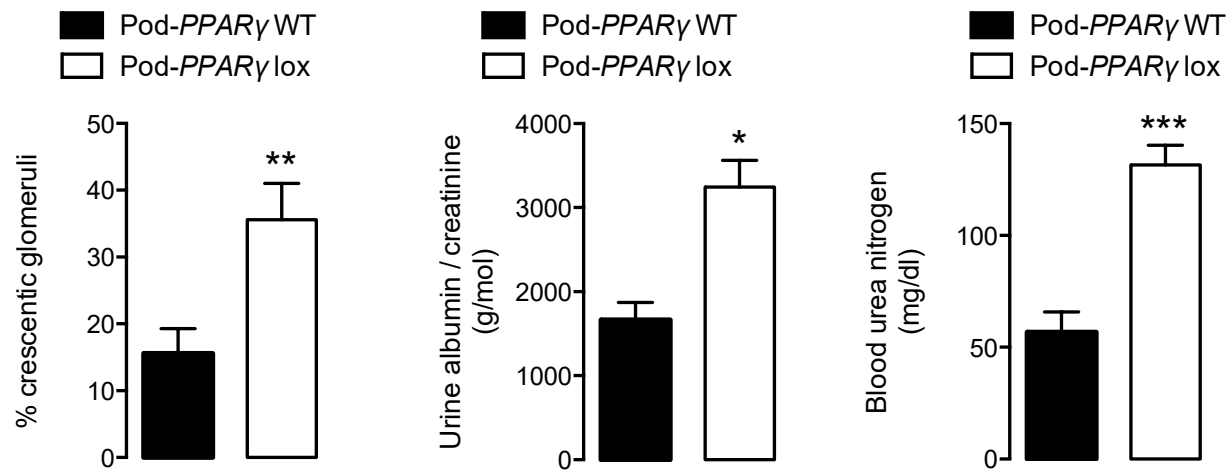
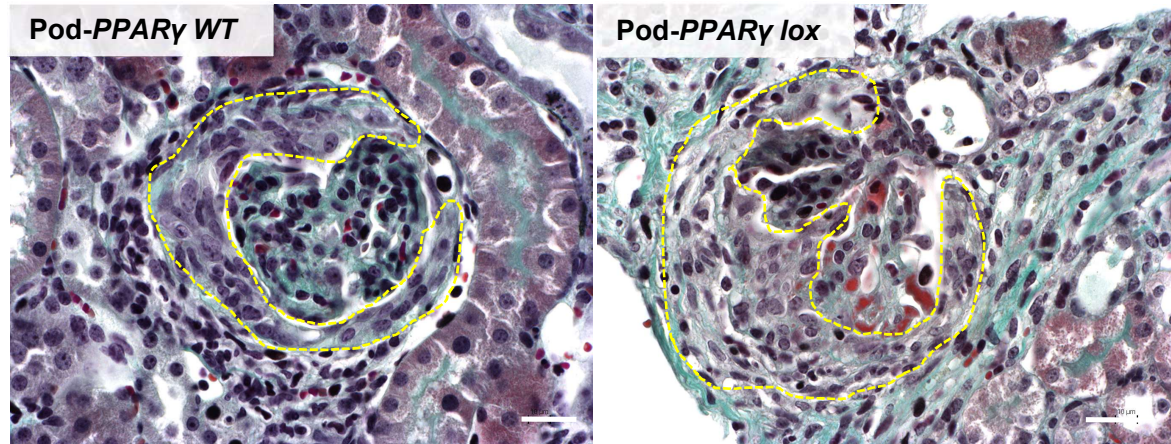
Healthy Glomerular  
Epithelial Cells express  
PPAR $\gamma$  constitutively



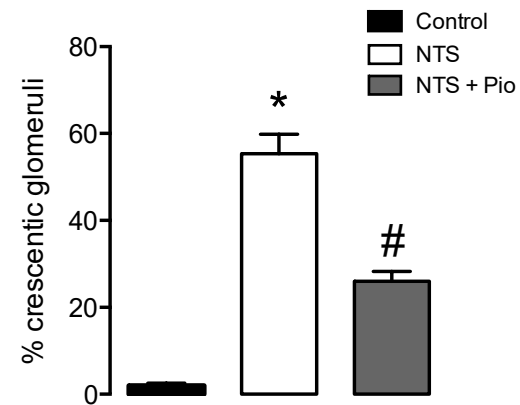
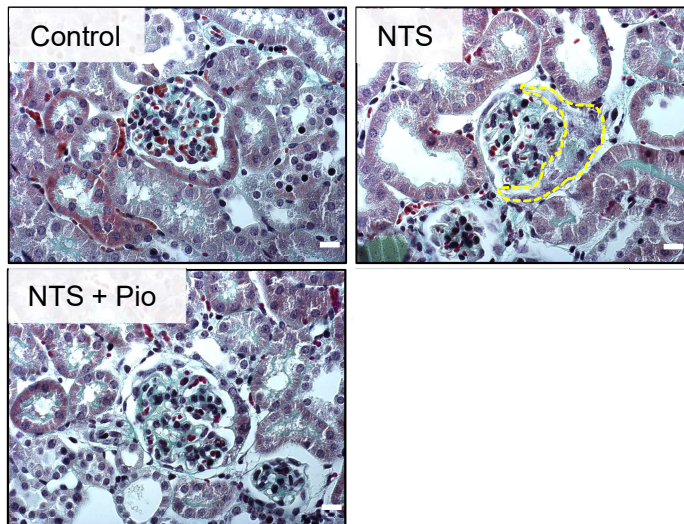
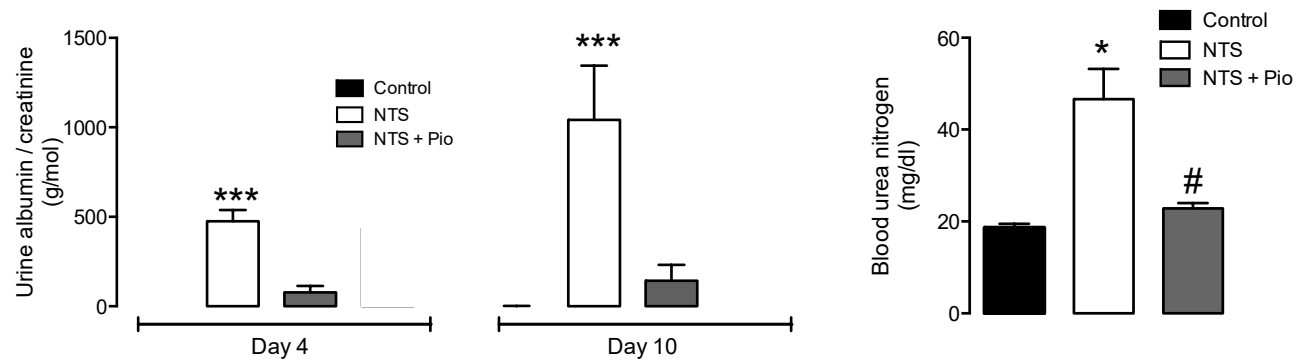
Henique et al.  
J Am Soc Nephrol. 2016

The nuclear PPAR $\gamma$   
expression is lost in  
MPA- and GPA-  
associated  
crescentic RPGN

## Podocyte Selective PPAR $\gamma$ Deficiency Aggravates Crescentic RPGN

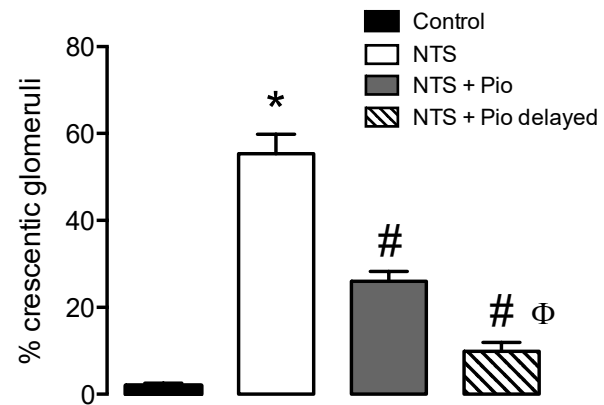
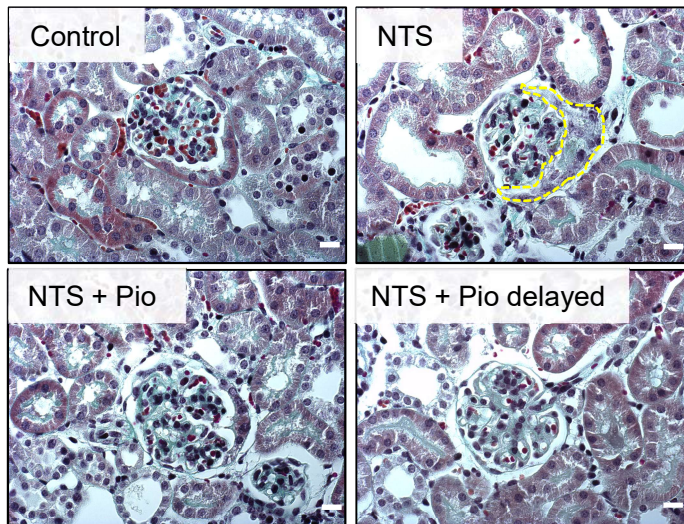
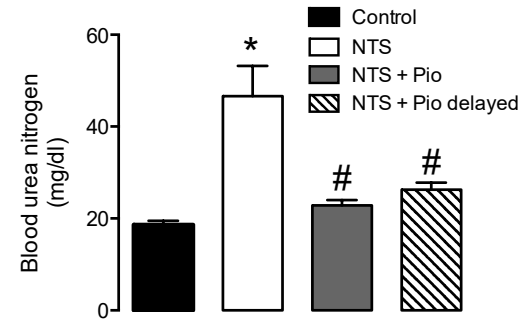
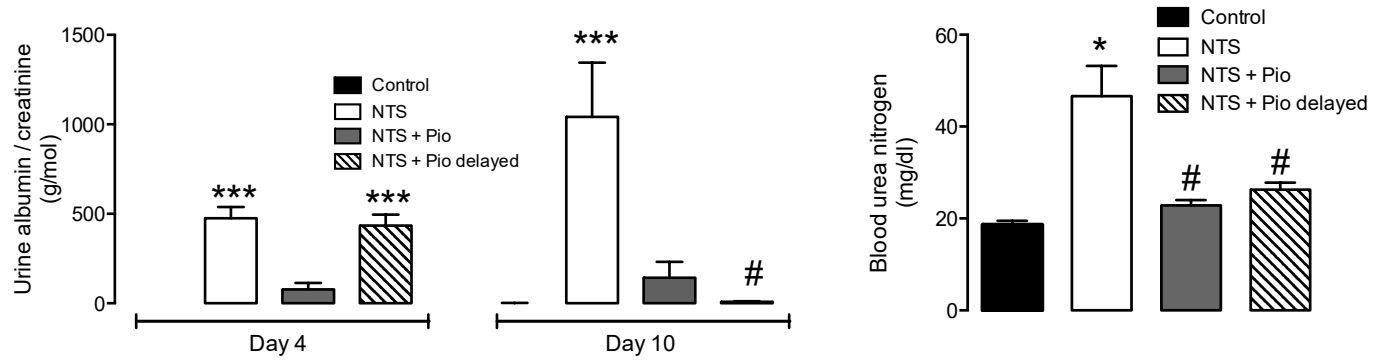


# PPAR $\gamma$ Agonism before NTS administration Halts Crescentic RPGN



Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

# PPAR $\gamma$ Agonism 4 days after NTS administration Halts Crescentic RPGN



Henique et al. J Am Soc Nephrol. 2016;27(1):172-88

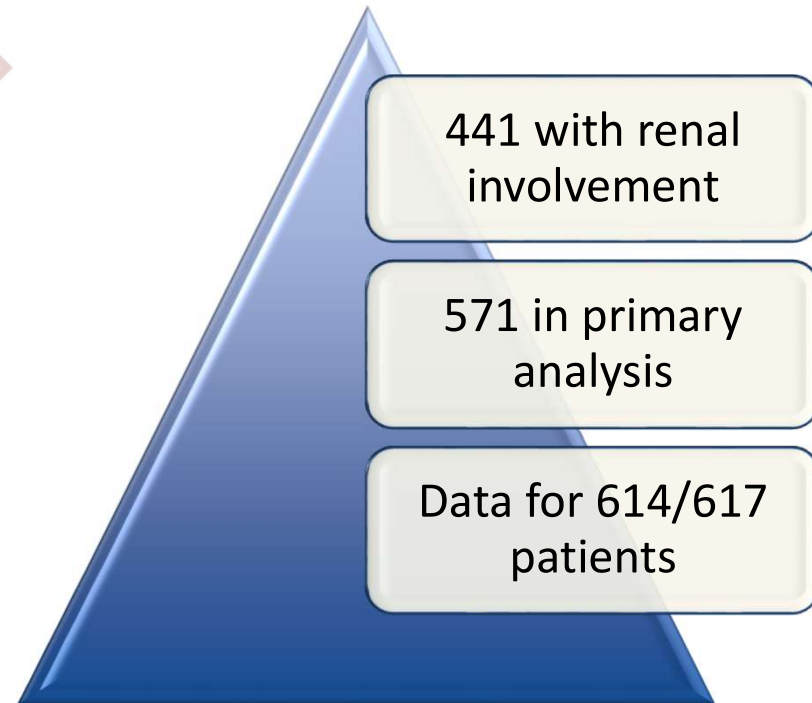
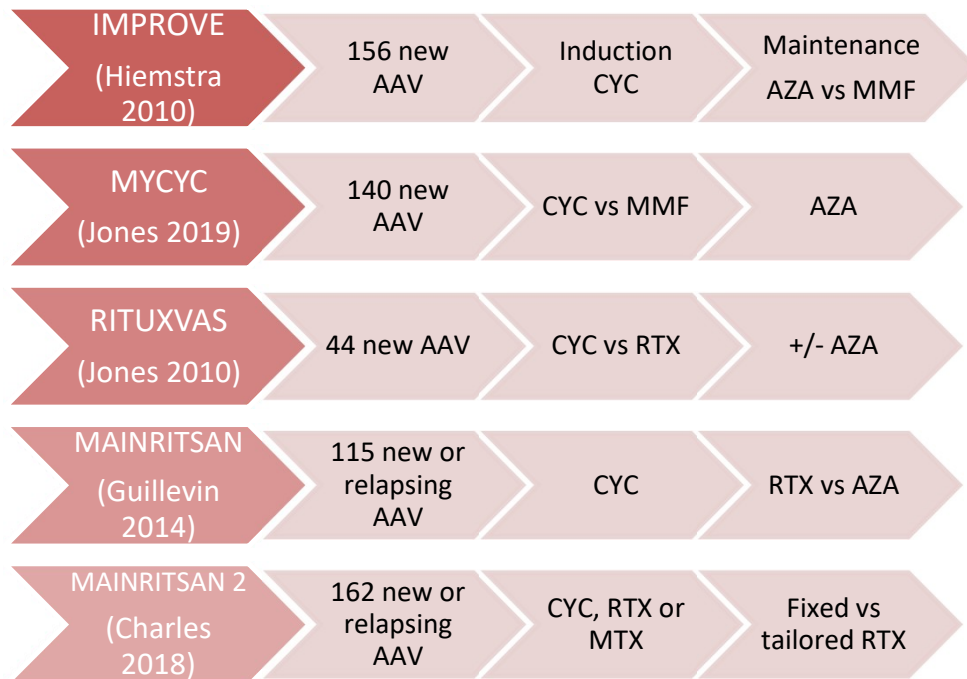
# Essai RENATO

- Primary objective : to demonstrate a reduction of renal damage in ANCA-associated renal vasculitis, by pioglitazone add-on treatment on top of SOC standardized immunosuppressive regimen with glucocorticoids and rituximab.
- Secondary objectives :
  - To evaluate the efficacy of pioglitazone on long-term preservation of renal function,
  - To assess the efficacy of pioglitazone on the reduction of hypertension and metabolic side effects of glucocorticoids.
  - To describe the clinical and biological tolerance of pioglitazone in this population,
  - To measure the impact of this drug on renal and systemic vasculitis activity,

# Essai RENATO

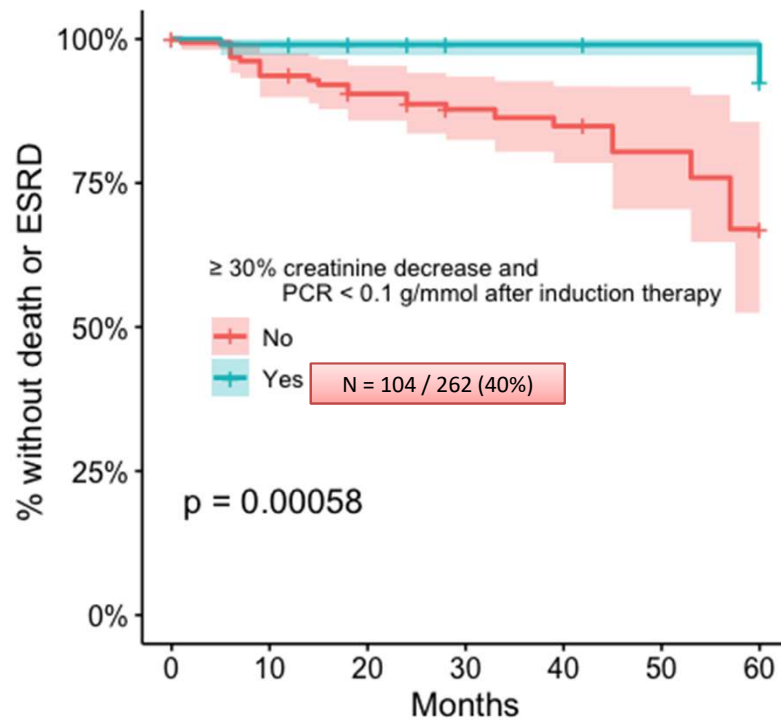
- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.

# Prognostic value of persistent proteinuria and hematuria after induction therapy in ANCA-associated vasculitis



## Outcome : Death or ESRD

Patients with sCreat > 130 umol/L at diagnosis



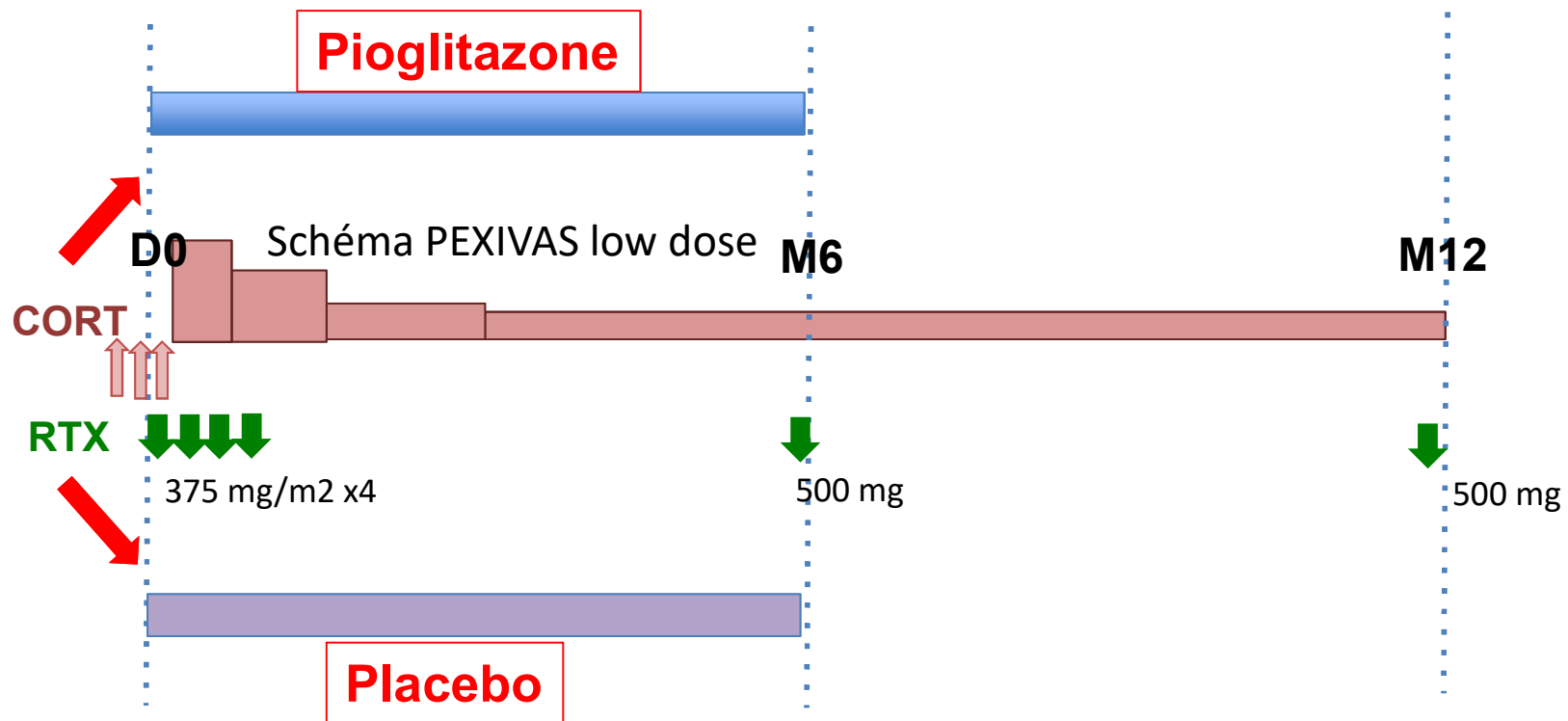
Multivariate Cox Analysis	Adjusted HR	95% CI	p value
Male sex	1.03	0.42 - 2.50	0.955
Age	1.01	0.98 - 1.05	0.391
ANCA type (ref: PR3)			
Negative	1.19	0.25 - 5.75	0.830
MPO	2.09	0.82 - 5.38	0.124
eGFR at flare diagnosis	<b>0.96</b>	<b>0.92 - 0.99</b>	<b>0.015</b>
Hematuria after induction therapy	2.01	0.88 - 4.58	0.098
Proposed surrogate endpoint (≥ 30% creatinine decrease and PCR < 0.1 g/mmol after induction)	<b>0.11</b>	<b>0.02 - 0.46</b>	<b>0.003</b>

Benichou N, Karras A, ASN 2020

# Essai RENATO

- Primary composite endpoint :
  - Improvement of serum creatinine (Delta sCreat) >30% of baseline value **AND** urine proteine-to-creatinine (uPCR) <1g/g at week 26.
- Secondary endpoints :
  - sCreat, Delta sCreat, eGFR, renal survival (off-dialysis) and proteinuria (UPCR) at W4, W12, W26, W52
  - BVAS and ANCA positivity at W4, W12, W26, W52, Relapse rate
  - Renal vasculitis activity (urinary MCP-1, KIM-1, Calprotectin, CD163 ) at W4, W12, W26, W52.
  - Damage score (VDI ) at W26, W52 and Glucocorticoid Toxicity Index (GTI) at W12, 26, 52
  - Blood pressure (ABPM and n of antihypertensive drugs), Diabetes (HbA1c), Lipid profile
  - Safety profile of pioglitazone

# RENATO trial



# Essai RENATO

- Inclusion criteria :
  - Newly-diagnosed or relapsing AAV (GPA /MPA), with an active disease defined as a BVAS  $\geq 3$
  - Presence of proteinuria (UPCR  $>300$  mg/g), haematuria ( $>10$  RBC/hpf) and eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> at inclusion
  - Recent ( $<4$  weeks) renal biopsy that confirms renal involvement of ANCA-associated vasculitis
  - Patients aged of 18 to 80 years

# Essai RENATO

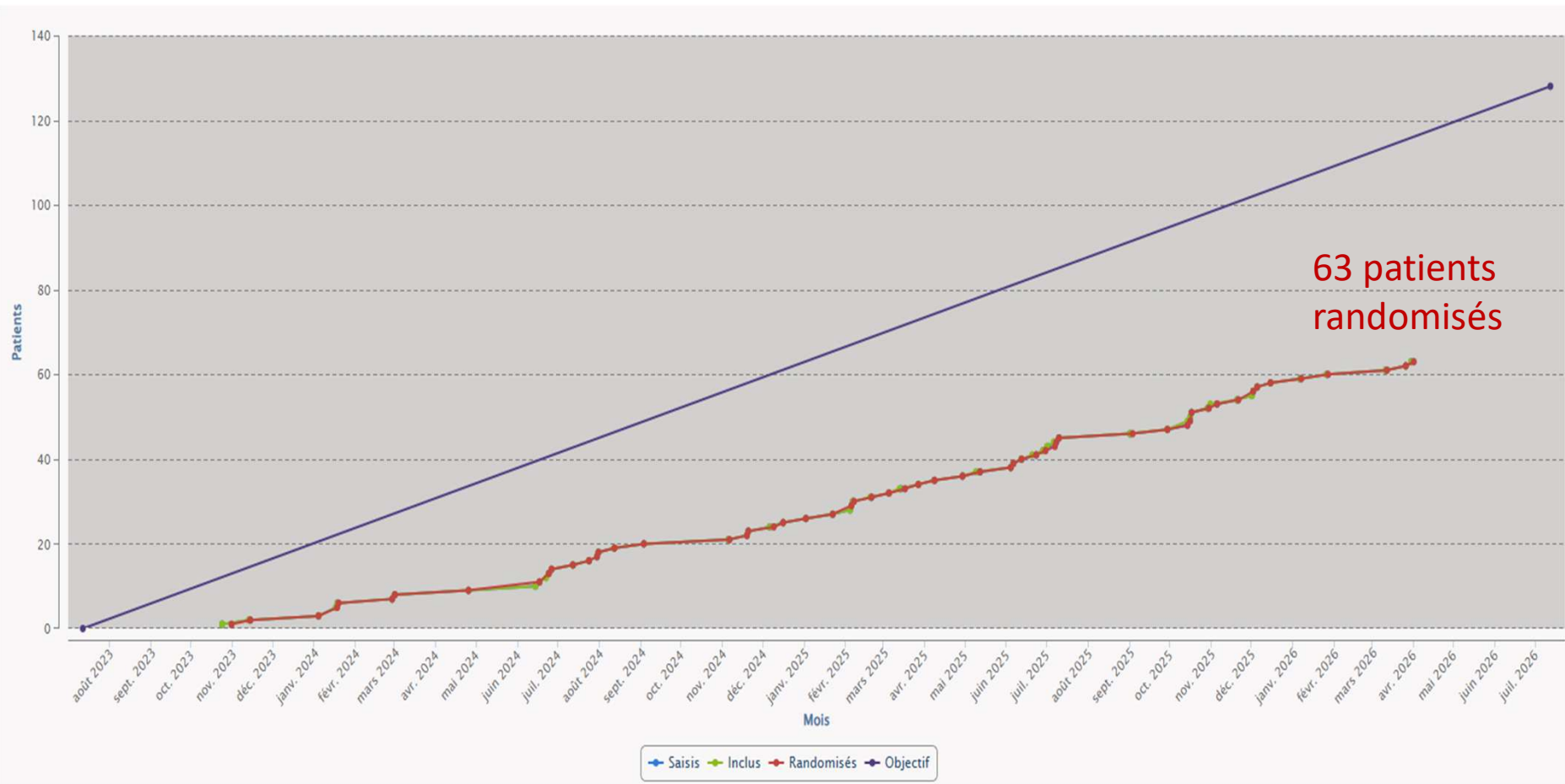
- Non-inclusion criteria :
- Severe kidney injury with eGFR <15 ml/min/1.73m<sup>2</sup> or dialysis therapy at inclusion
- Alveolar haemorrhage requiring pulmonary ventilation support at inclusion
- Active cancer (except non-melanoma skin cancer) within the past 24 months
- Past history of bladder or urinary tract cancer
- History of Class 3/4 congestive heart failure symptoms, Class 2 heart failure symptoms within the past 3 months and ejection fraction <40% on recent echocardiography
- Chronic liver disease
- Positive serology for HIV, HBV (Ag HBs positivity), HCV at inclusion
- Pregnant or breast-feeding women, or desire to become pregnant within 12 months
- Severe neurologic or psychiatric disease (e.g., dementia or schizophrenia)
- Kidney transplant recipients
- Cyclophosphamide or rituximab use within 26 weeks prior to screening
- Indication for avacopan therapy

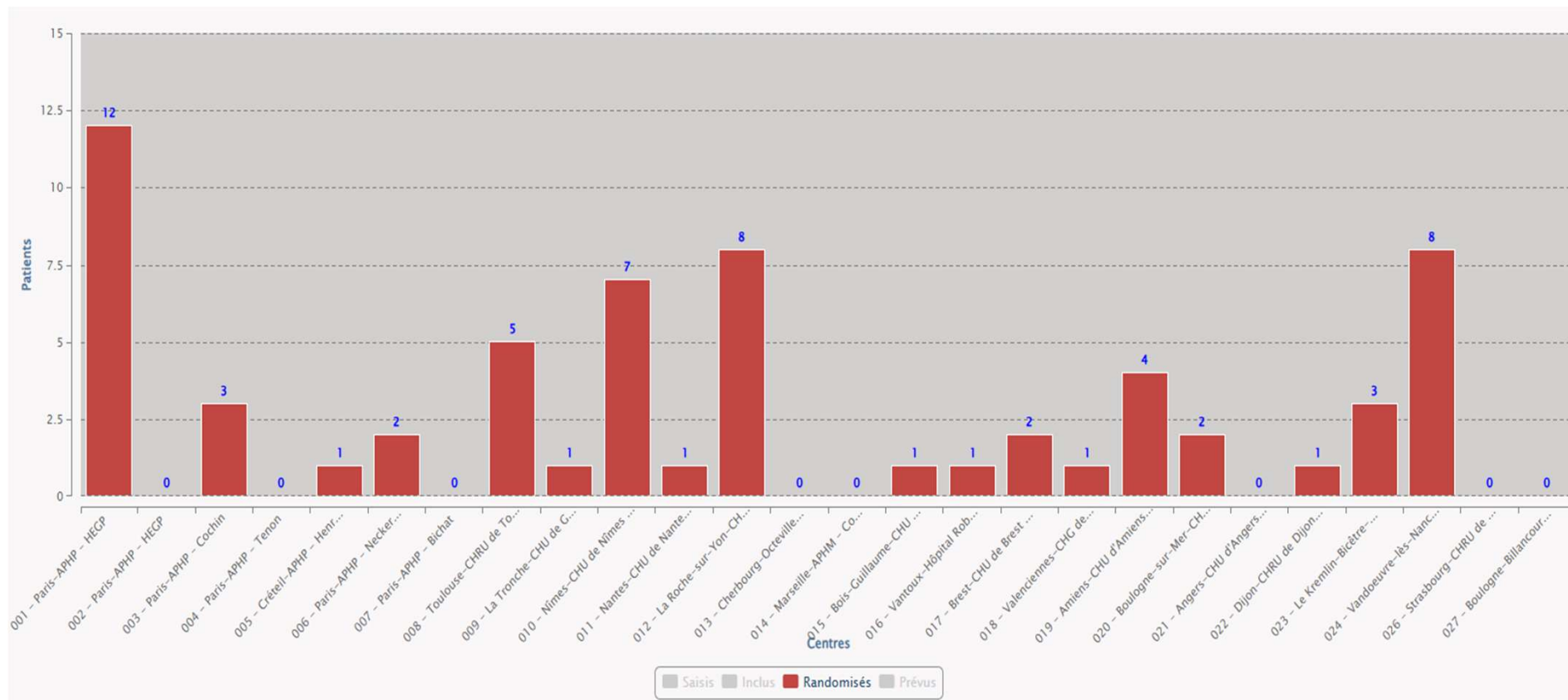
# EIG spécifiques

- Carcinomes urothéliaux
  - Pas de sur-risque confirmé sur multiples essais et métaanalyses récentes
  - Par précaution : pas de cyclophosphamide, non inclusion si ATCD
- Insuffisance cardiaque :
  - Sur-risque d'OMI et décompensation cardiaque dans qq études chez diabétique
  - Par précaution : non inclusion si ATCD d'insuffisance cardiaque classe III/IV
  - Echo cardiaque à l'inclusion et exclusion si FEVG <40%
  - Surveillance poids et BNP à chaque visite pdt 6 mois et diurétique si besoin
- Hépatite, hypoglycémie, ostéoporose fracturaire, œdème maculaire

# Traitements associés

- Traitements antihypertenseurs (ICa, diurétiques, bêtabloquants, alphabloquants) en visant TA <140/90 (135/85 sur MAPA W4 et W12)
- Débuter diurétiques en priorité si prise de poids, OMI ou élévation BNP
  - suspension pioglit/placebo si >3 kg/1 sem, doublement de BNP)
  - arrêt du traitement de l'étude si poussée d'IC congestive
- **Pas d'IEC, ARA2 ou iSGLT2 pdt les 6 premiers mois (sauf si HTA >160/95)**
- Utilisation libre des autres antidiabétiques
- Prophylaxies usuelles pneumocystose, ostéoporose cortisonique
- **Pas d'avacopan, pas d'induction par cyclophosphamide, pas d'EP**





# Essai RENATO

- 128 patients à inclure
- Durée de la période d'inclusion : **extension jusqu'en nov 2027**
- Durée du suivi : 1 an
- Première inclusion : fin 2023 (59 patients inclus à ce jour)

MERCI pour votre aide

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