# MEMBRANOUS GLOMERULONEPHRITIS



Pierre RONCO
Inserm Unit 1155
and Division of Nephrology
Tenon hospital, Paris, France

# Disclosure of Interests

- Alexion (research grant)
- Amgen (research grant)
- Roche (research grant)
- Amicus (consultancy)

# KDIGO 2012: Indications of IS therapy

- We recommend that initial IS therapy be started only in patients with nephrotic syndrome AND one of the conditions below:

  - Ur protein > 4g/d AND remains at >50% basal value, AND does not show progressive decline during antiproteinuric therapy **during observation period > 6 months (1B)**

  - Severe, disabling, or life threatening symptoms related to nephrotic syndrome **(1C)**

  - Scr has risen by >30% within 6 to 12 months from the time of diagnosis (but eGFR > 25-30 ml/min/1.73m²) and this change is not explained bysuperimposed complications **(2C)**



*KDIGO Guidelines, Kidney Int 2012, 2:186*

# KDIGO : Initial therapy of MN

- We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents **(1B)**
- We suggest using cyclophosphamide rather than chlorambucil for initial therapy **(2B)**
- We recommend that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen



*KDIGO Guidelines, Kidney Int 2012, 2:186*

# KDIGO : Research recommendations

- Studies are needed to validate the utility of anti-PLA2R antibody in terms of its accuracy in separating primary from secondary MN



- Studies are needed to determine the most cost-effective panel of investigations for screening an underlying (covert) malignancy in the older patients with MN

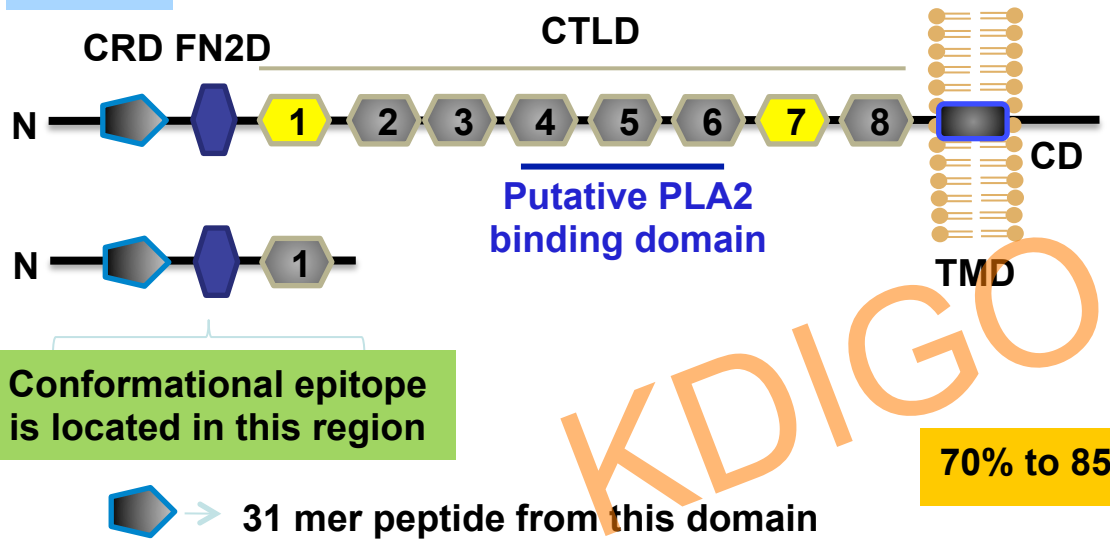
*KDIGO Guidelines, Kidney Int 2012, 2:186*

# Events since KDIGO 2012

- A wealth of studies on PLA2R
- Identification of THSD7A as a target
- Development of ELISA/IF tests (mostly EUROIMMUN)
- Two RCTs : GEMRITUX and MENTOR
- Retrospective comparisons of efficacy and safety (cyclophosphamide vs rituximab)

# A paradigm shift in diagnostic, monitoring and classification of patients with MN

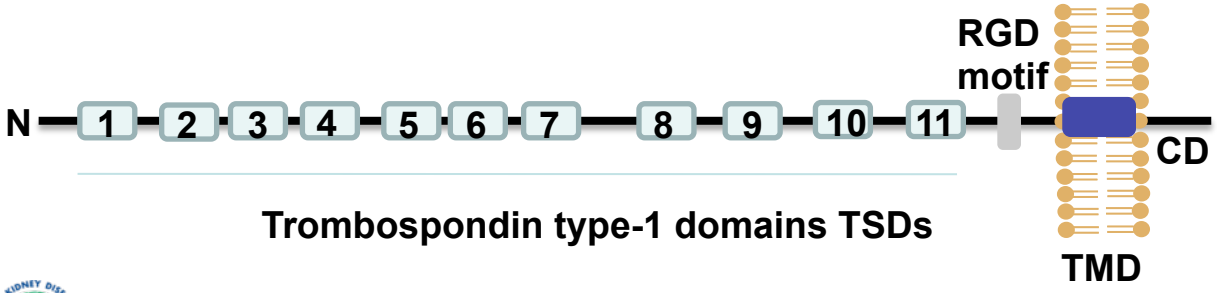
***PLA2R***




Beck et al, NEJM 2009,361:11
Kao et al, JASN 2015,26:291
Fresquet et al, JASN 2015,26:302
Seitz et al, JASN 2016, 27:1517; JASN 2017 Nov 7th (epitope speading correlated with outcome)

**70% to 85% of adult MN patients**

***Thrombospondin type-1 domain containing 7A (THSD7A)***

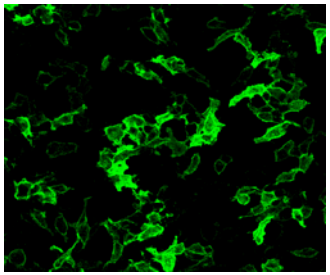



Tomas et al, NEJM 2014, 371: 2277
Tomas et al, J Clin Invest 2016, 126:2519

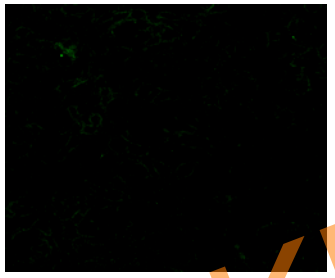
**10 % of PLA2R-negative patients with MN**

# Serological tests for the diagnosis and monitoring of patients with MN

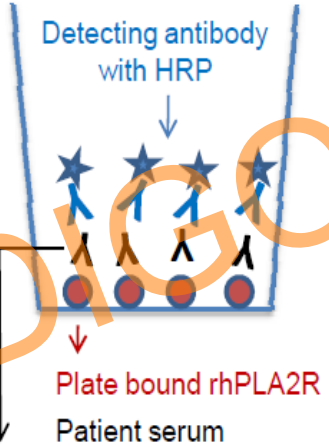
→ Indirect immunofluorescence for PLA2R and THSD7A → ELISA-PLA2R



HEK293 cells transfected with cDNA for PLA2R



HEK293 cells non transfected

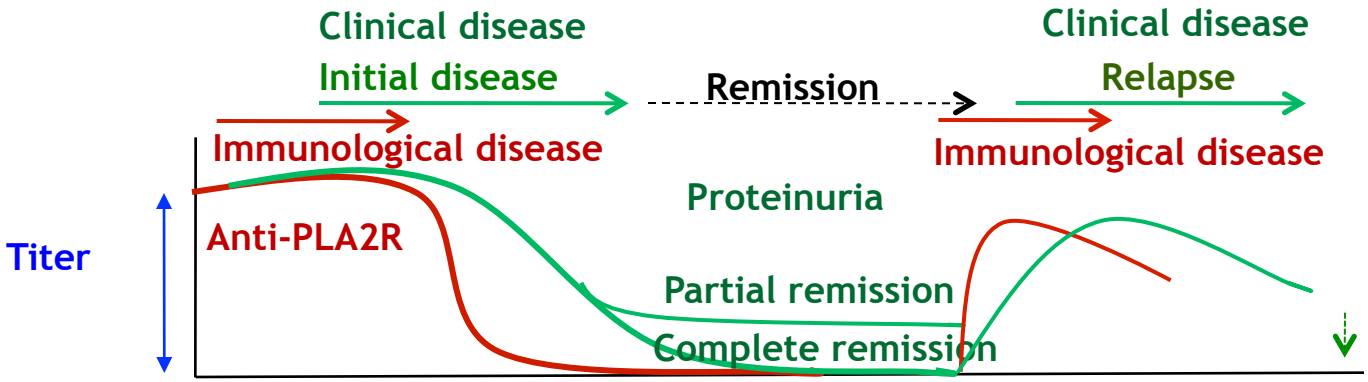





Meta-analysis (2014)

- 15 studies, 2212 patients
- **Specificity = 99%** (95% CI : 96-100%)
- **Sensitivity = 78%** (95% CI :66-87%)

*Du et al, PLoSOne 2014, 9:e104936*

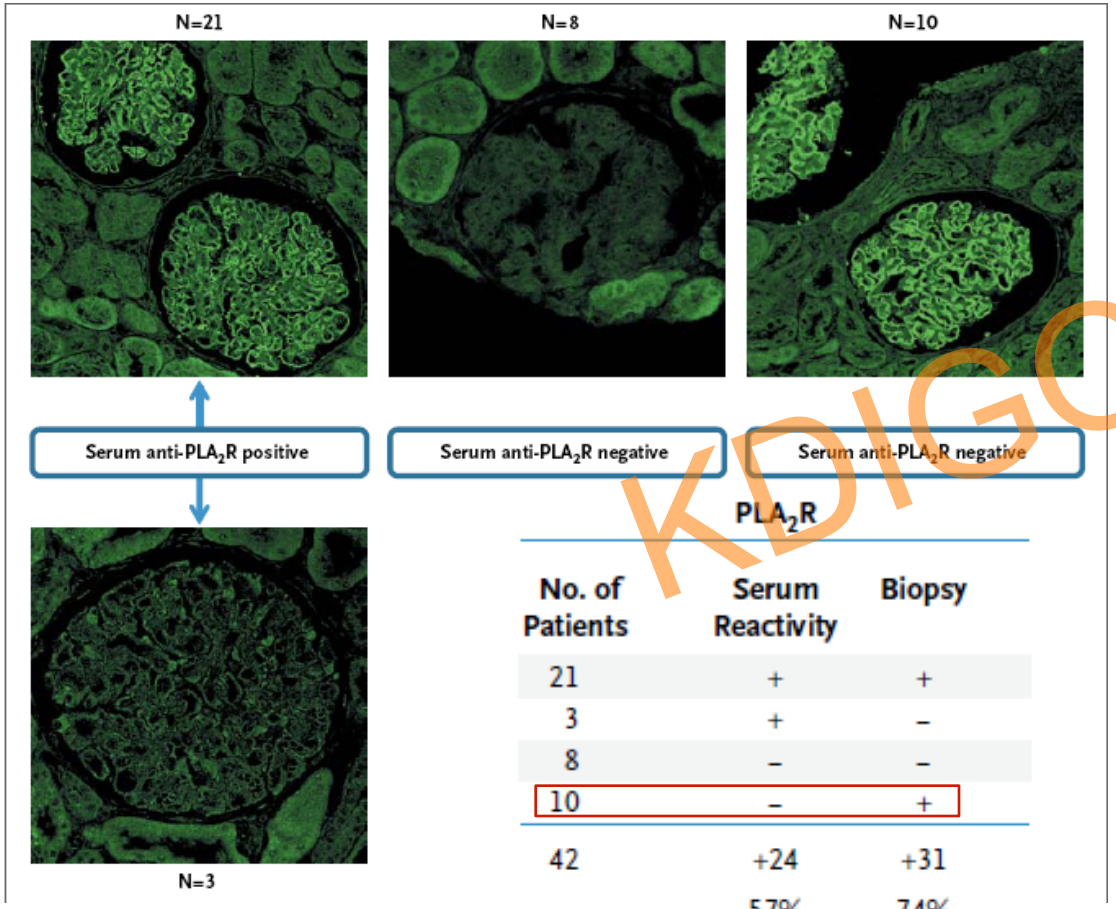


# Recommendations for a good usage of serological tests for PLA2R

- IF : screening test (more sensitive than ELISA, depends on cut-off ++)
- ELISA : monitoring
- But IF positivity persists longer, hence immunological remission requires negative IF
- Both IF and ELISA may be negative because of sink effect or immunological remission before any treatment

☞ search for antigen in kidney biopsy

# Antigen detection in biopsy is more sensitive than serology






| $PLA_2R$ | | |
|---|---|---|
| No. of Patients | Serum Reactivity | Biopsy |
| 21 | + | + |
| 3 | + | – |
| 8 | – | – |
| 10 | – | + |
| 42 | +24 | +31 |
| | 57% | 74% |

Tenon cohort 2000-2014

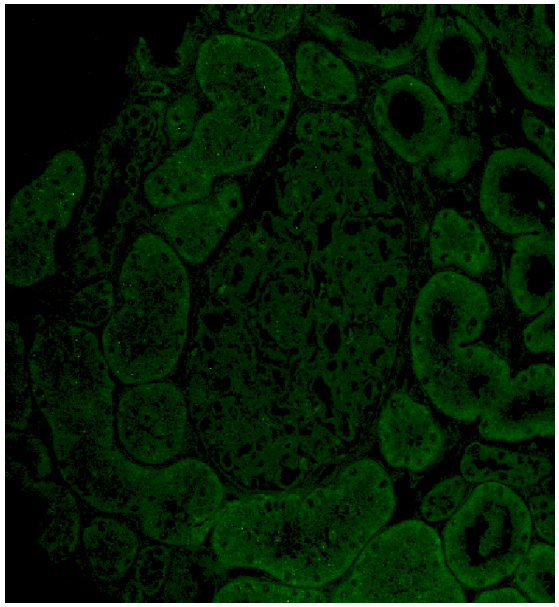
- n = 106 (84 iMN ; 22 sMN)
- sensitivity PLA2R - Ag : 86%
- ‘’ aPLA2R-Ab : 76%

*Pourcine et al,* PLoS One. 2017 Mar 3;12(3)

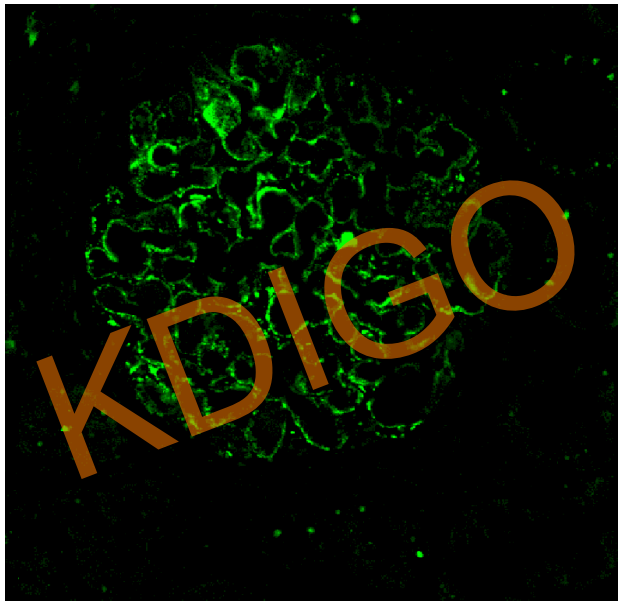
Retrospective diagnosis

*Debiec and Ronco, New Engl J Med, 2011, 364 :689 ; Svobodova et al, NDT, 2013, 28:1839 ; Hofstra et al, J Am Soc Nephrol, 2012, 23:1735 ; Ruggenenti et al, J Am Soc Nephrol, 2015, March 24*

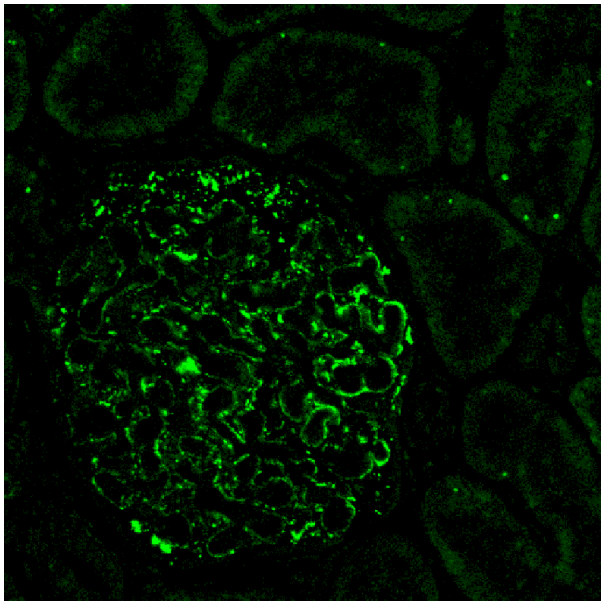
# PLA2R antigen is not specific for primary MN



**Lupus MN**




**HepB (25/39)**
**Hep C**



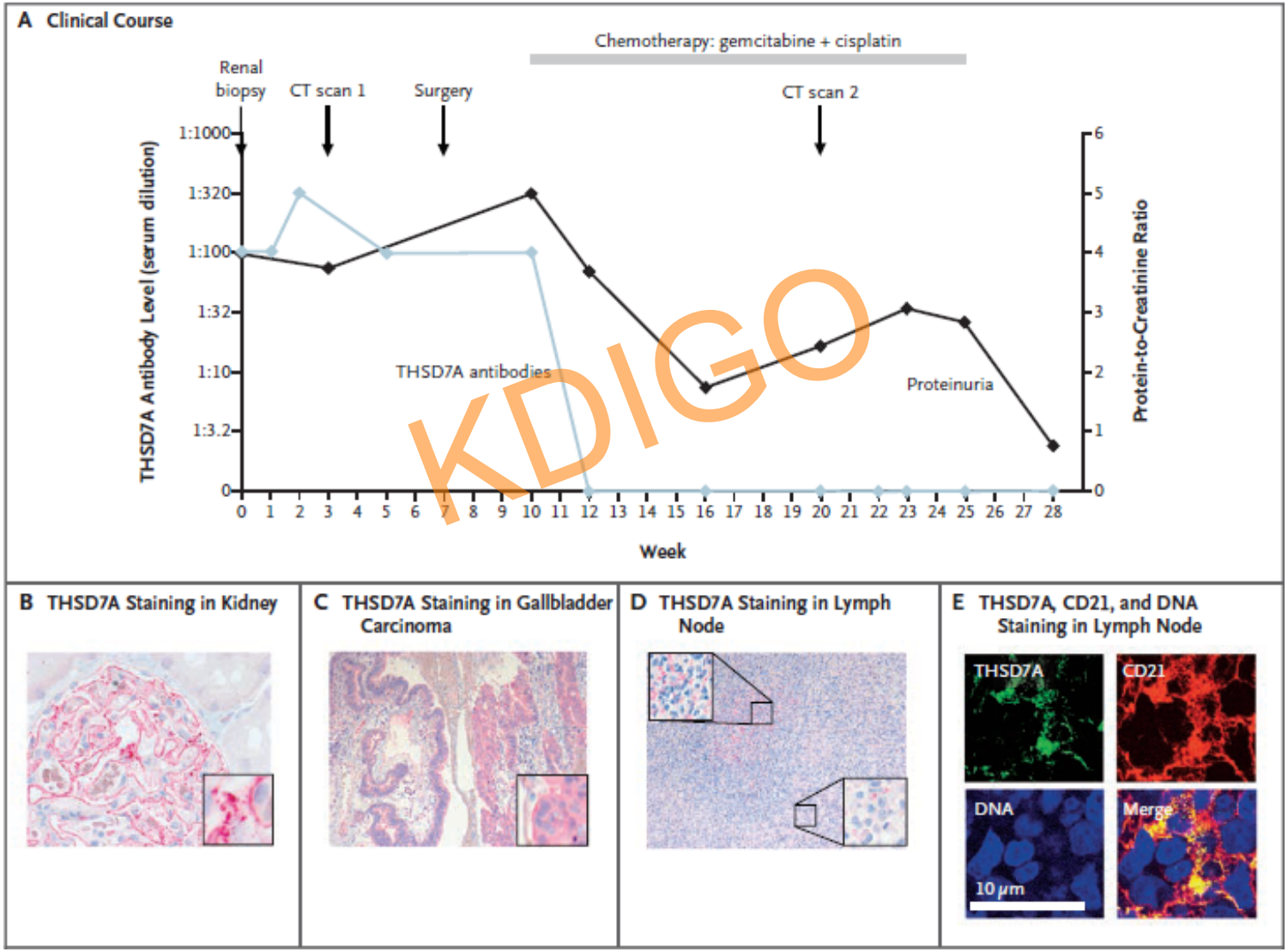
**Sarcoidosis**

Coincidence of iMN with the associated disease ?

*Xie Q, Am J Nephrol 2015, 41:345 ; Stehlé T, NDT 2015, 30:1047 ; Larsen, Modern Pathol 2013, 26: 709, Berchtold L, KI Reports, 2017, in press*

# The issue of cancer association with MN is not solved

# A role for THSD7A in cancer-associated membranous nephropathy






*Hoxha et al, NEJM 2016 374:1995*

# Prevalence of PLA2R and THSD7A-Ab in cancer patients

## Hamburg/Boston series

Eight/40 patients with THSD7A-associated MN developed a malignancy within 3 months

## Chinese series

44 K-associated MN

- 1 THSD7A-Ab + (2%) Urinary blader cancer > 7 years before MN

- 18 PLA2R-Ab + (41%) Time interval < 6 months in 10/18 patients



*Wang, Cui, …, Ronco, Zhao, Clin J Am Soc Nephrol. 2017 12:164 ; Hoxha et al, JASN 2017, 28:520*

# Toward a new serology/biopsy-based classification of MN

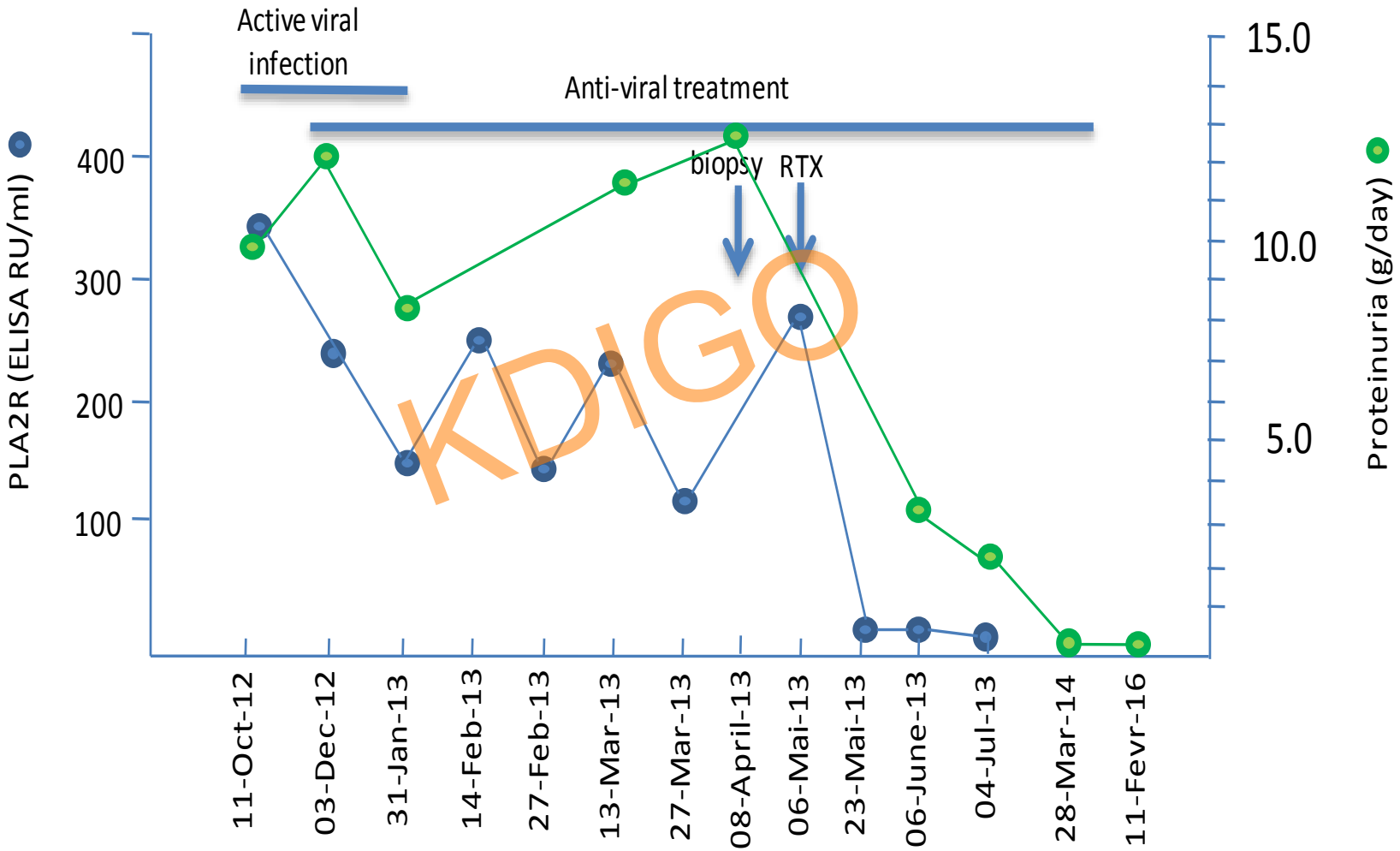
- PLA2R-related # 80 to 85%
- THSD7A-related <5%
- NonPLA2R-nonTHSD7A-related (third antigen) #10%

- Any of the above can be:
  - primary without known etiology
  - secondary: PLA2R-associated HepB, sarcoidosis
    THDSD7A-(and PLA2R-) associated cancer



☞Start with treatment of the suspected cause and shift to immunosuppresive therapy when needed

# Specific treatment of (viral) cause may not cure secondary MN




*Berchtold L et al, Kidney Int Reports, 2017, in press*

**Who and when to treat with immunosuppressive agents?**

**Can we shorten the 6-month « wait and see » period for patients at risk?**

# Is MN outcome still unpredictable ?

- Evolution follows the 3-third rule (spontaneous remission, ESKD, persisting proteinuria and altered renal function)
- Clinical predictors : age, gender, degree of proteinuria, kidney function at presentation, time-varying proteinuria
- Quality of remission: CR vs PR (elevated relapse rates, Thompson et al, JASN 2015, 26:2930)
- PLA2R (and THSD7A) antibodies

# High levels of PLA2R-Ab are correlated with:

- A lower rate of remission, either spontaneous or induced by IS treatment
- A higher risk :

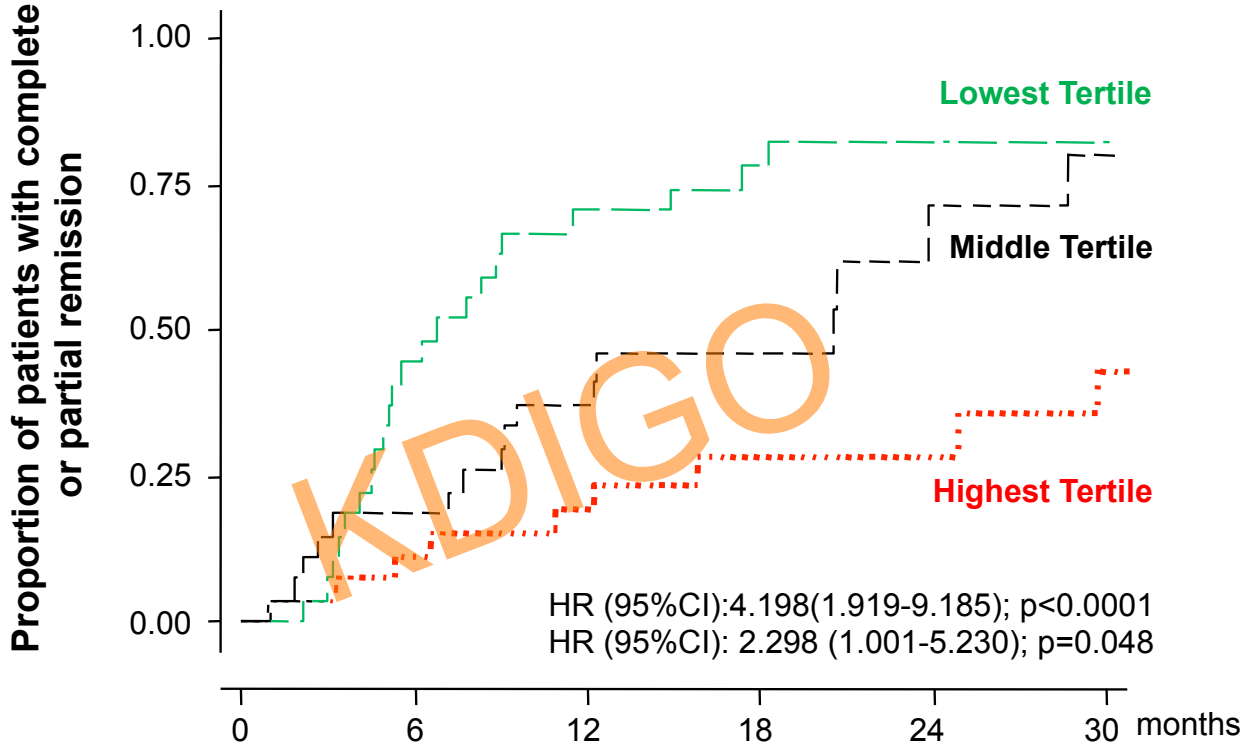
  - of occurrence of nephrotic syndrome in non-nephrotic patients

  - of renal function deterioration
- A longer time to remission under IS treatment



*Kanigicherla D et al, Kidney Int 2013 83: 940 ;*
*Hofstra JM et al, JASN 2012 23: 1735 ;*
*Hoxha E et al, JASN 2014 25:1357 ;*
*Ruggenenti P et al, JASN 2015 26:2545;*
*Hoxha E et al,PLoS One 2014 9:e110681*

# Proportion of PLA2R-positive patients with remission is strongly dependent on antibody titer



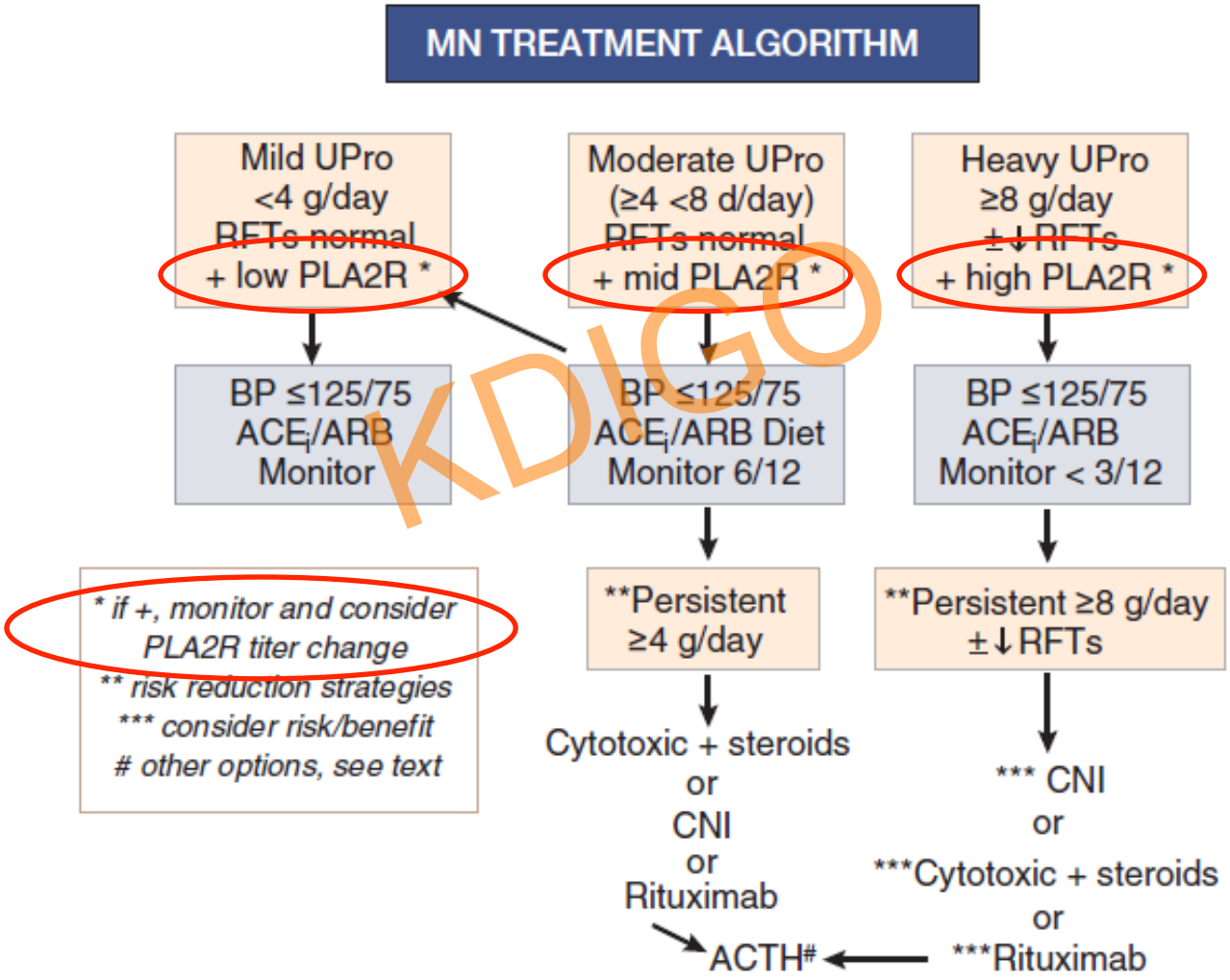

**Patients at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Lowest Tertile | 27 | 15 | 8 | 6 | 4 | 3 |
| Middle Tertile | 27 | 22 | 16 | 8 | 3 | 2 |
| Highest Tertile | 27 | 22 | 20 | 14 | 11 | 6 |

*Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 26:2545*

# Revisiting algorithms for stratifying risks

# MN treatment algorithm : The new approach



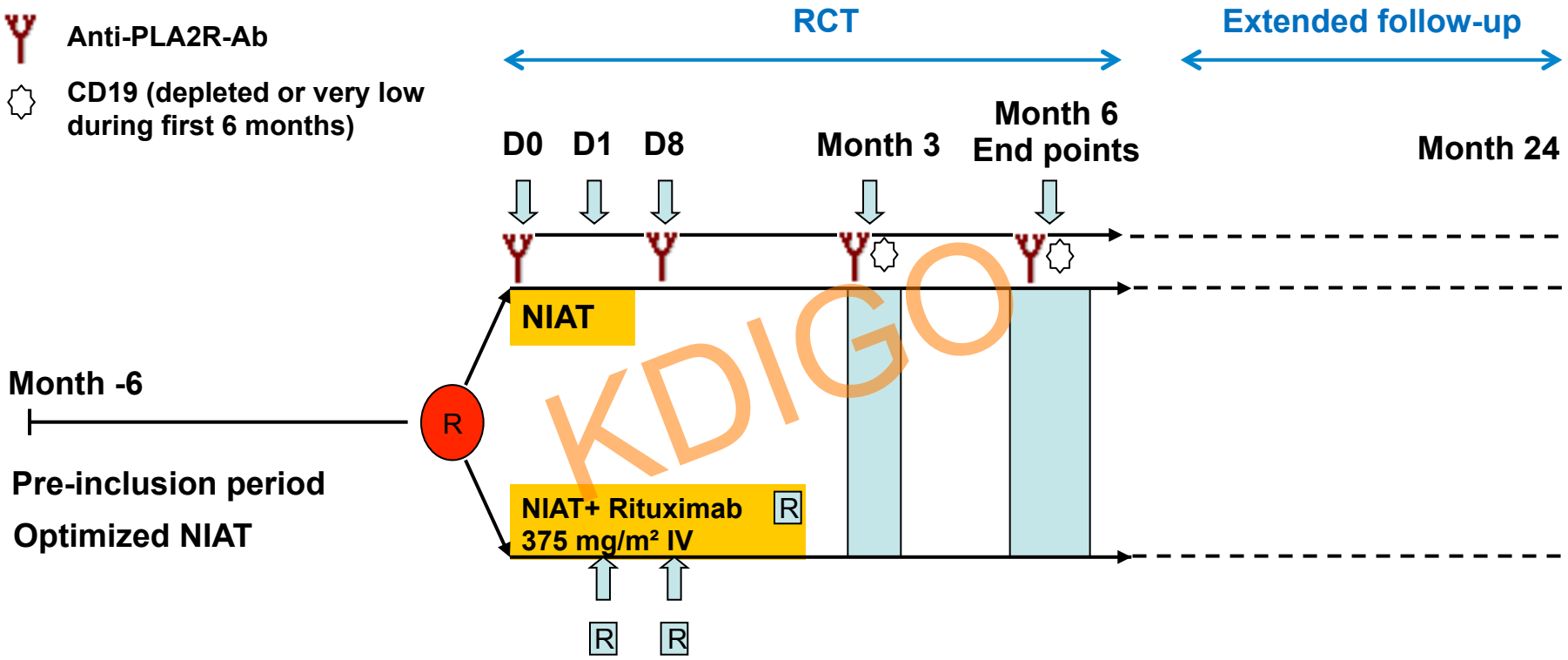

*Cattran and Brenchley, Kidney Int 2017, 91:566*

**What should be the first line therapy ?**

**Efficacy vs safety: Is this still a timely question?**

**Time for a paradigm shift ?**

# GEMRITUX protocol: 80 patients




Inclusion criteria :

- > 18 yrs
- idiopathic MN
- **persisting NS after 6 months**
- eGFR > 30 ml/min/1.73m²
- 2 determinations of proteinuria

Exclusion criteria :

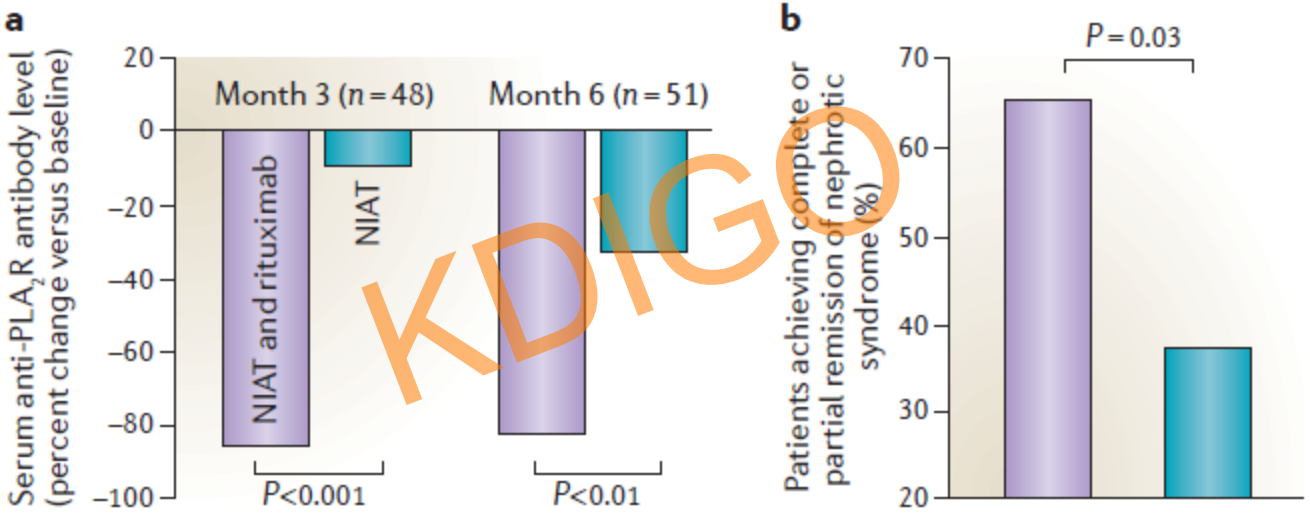
- secondary MN
- pregnancy/breast feeding
- IS in the last 3 months (4 pts>1 yr)
- active infection

*Dahan et al, JASN 2017, 28;348*

# Key findings from the GEMRITUX trial

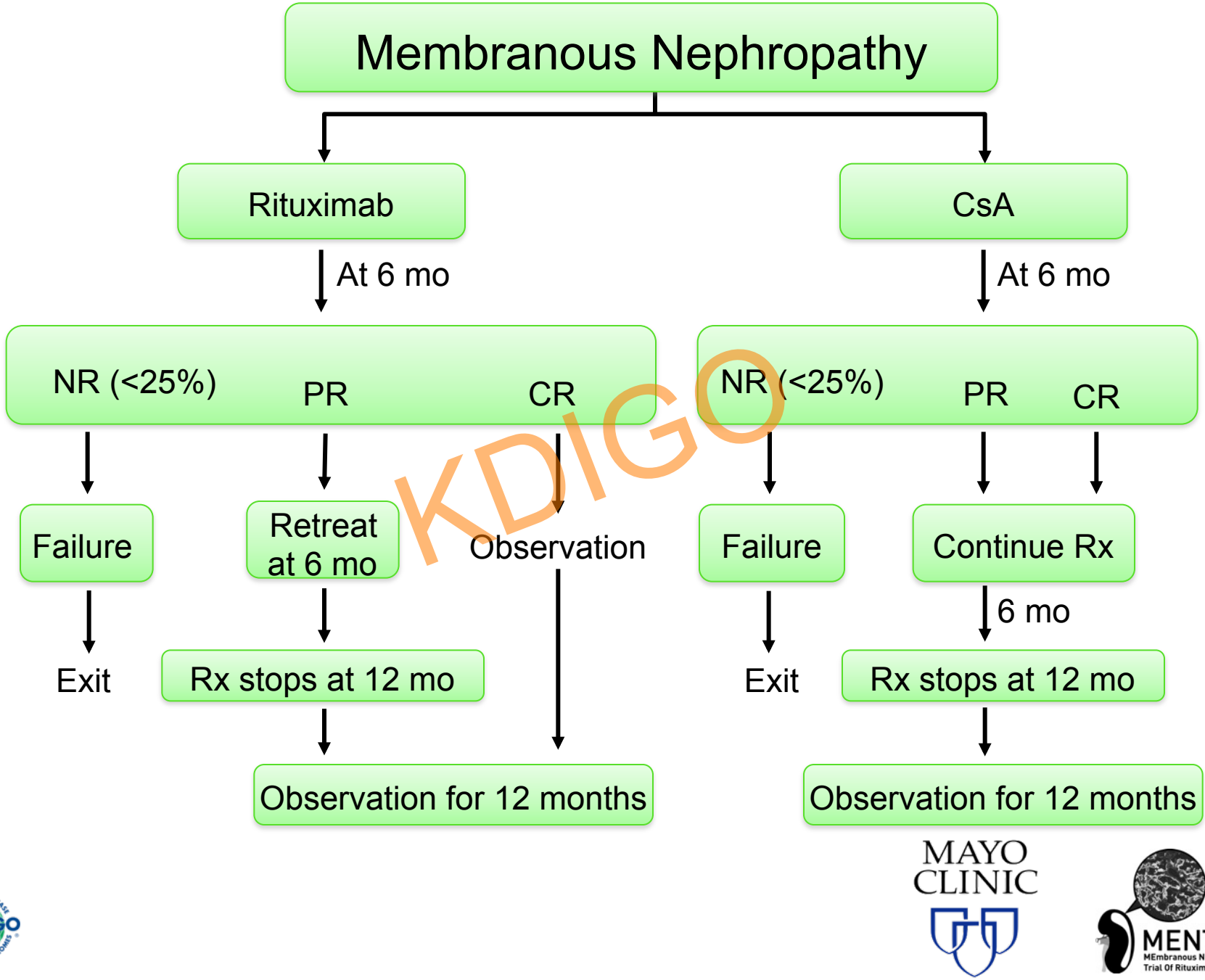
**PLA2R1-Ab**

**Clinical remission (last FU)**

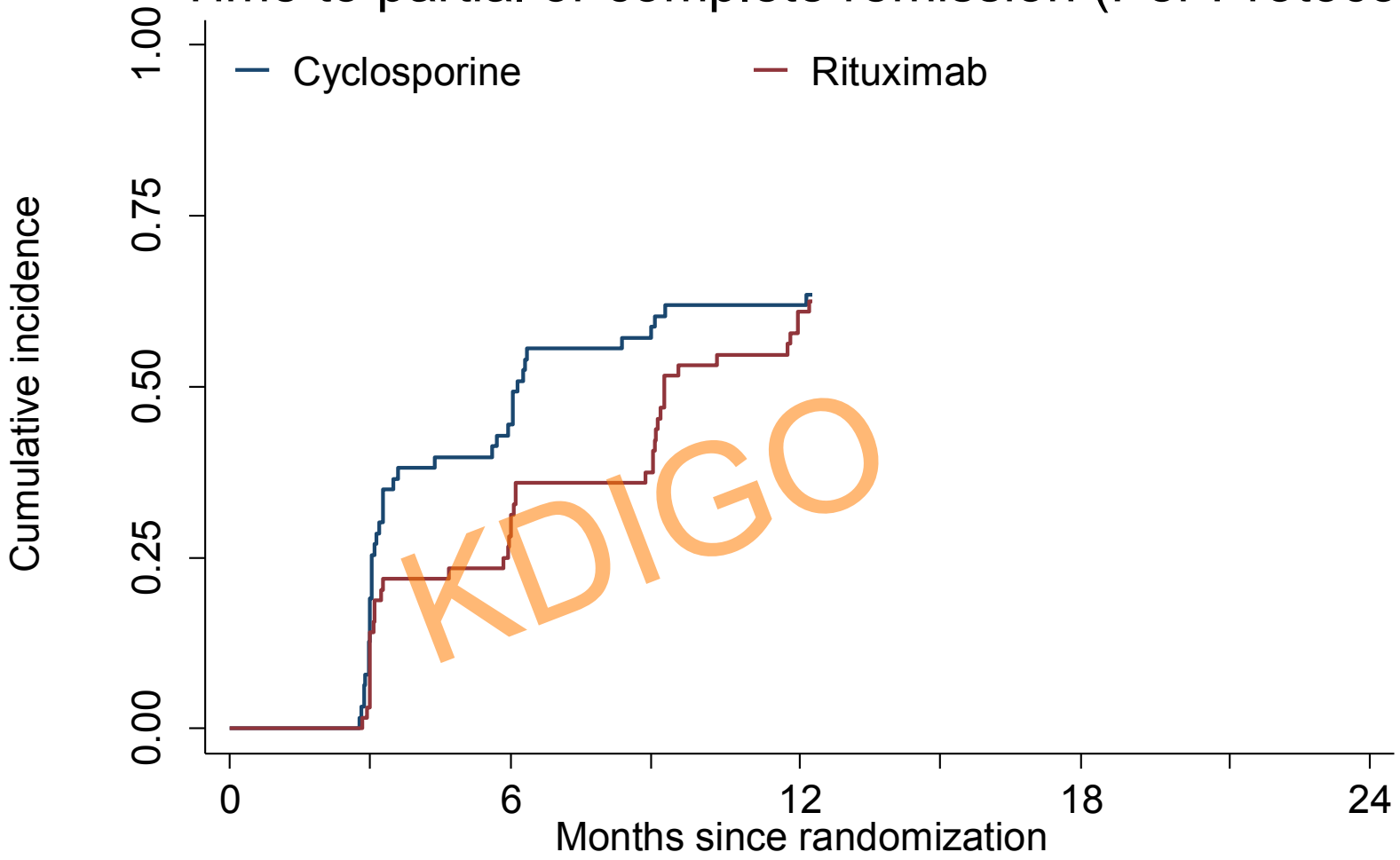





*Dahan et al, JASN 2017, 28;348*
*Drawn by Ruggenenti et al, Nature Reviews 2017 july 3rd*


Membranous Nephropathy
Rituximab
CsA
At 6 mo
At 6 mo
NR (<25%)
PR
CR
NR (<25%)
PR
CR
Failure
Retreat at 6 mo
Observation
Failure
Continue Rx
6 mo
Exit
Rx stops at 12 mo
Exit
Rx stops at 12 mo
Observation for 12 months
Observation for 12 months
KDIGO
MAYO CLINIC
MENTOR
MEmbranous Nephropathy Trial Of Rituximab

# Time to partial or complete remission (Per Protocol)






| Number at risk | | | |
|---|---|---|---|
| Rituximab | 64 | 46 | 25 |
| Cyclosporine | 63 | 35 | 24 |

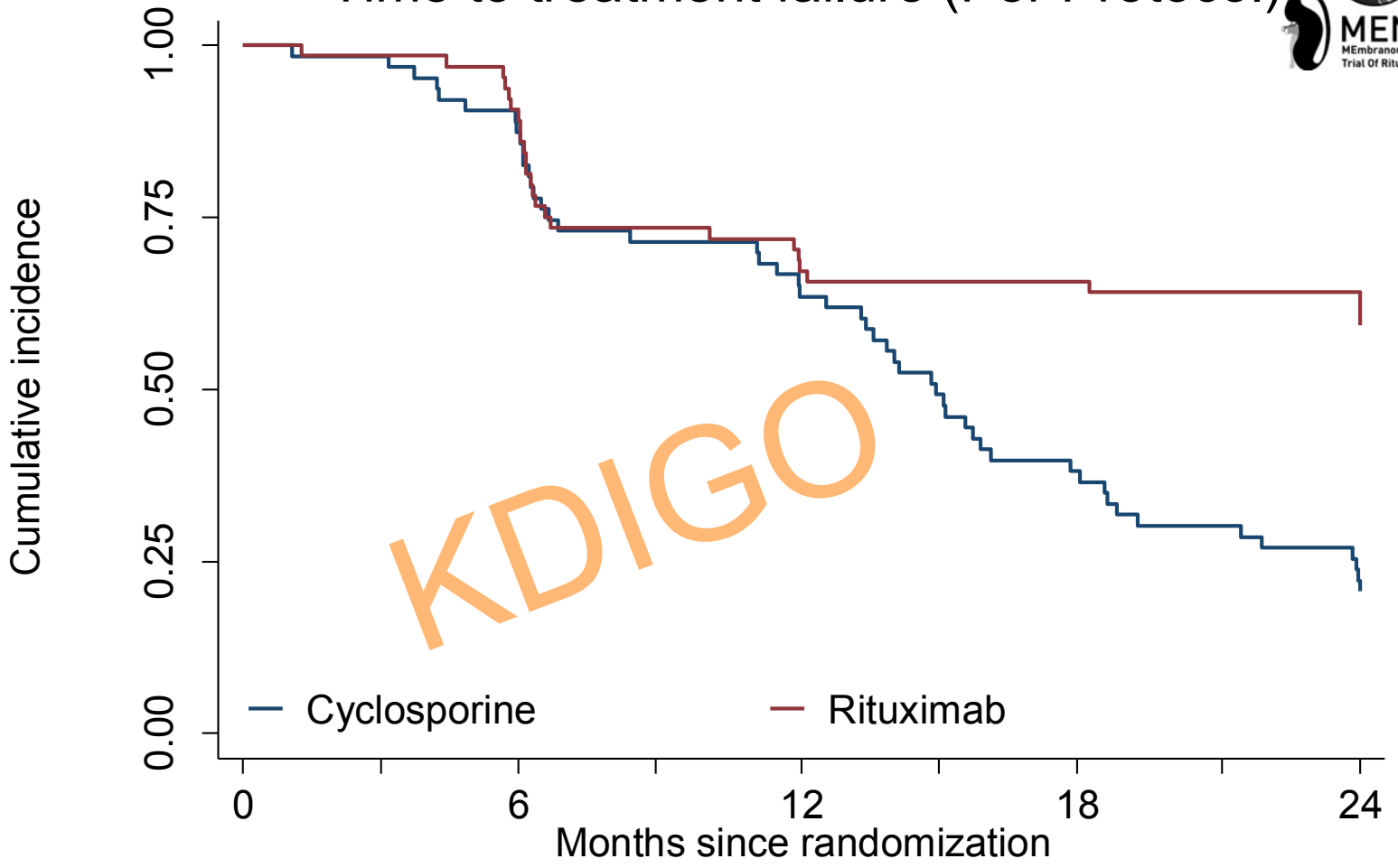
MAYO CLINIC

MENTOR
MEmbranous Nephropathy Trial Of Rituximab

MAYO CLINIC

MENTOR
MEmbranous Nephropathy Trial Of Rituximab

# Time to treatment failure (Per Protocol)






| Number at risk | | | | | |
|---|---|---|---|---|---|
| Rituximab | 64 | 58 | 43 | 42 | 41 |
| Cyclosporine | 63 | 55 | 40 | 24 | 14 |

KDIGO

# Analysis Per Protocol at 24 months

| | CSA | RTX |
|---|---|---|
| Treatment failure | 50 (79.4%) | 24 (37.5%) |
| CR/PR | 13 (20.6%) | 40 (62.5%) |



**Strong evidence against the null hypothesis of inferiority (p-value <0.0001)**

**Risk Difference is 40.3% (95%CI 24.7% to 55.9%)**

**Odds Ratio is 6.0 (95%CI 2.7 to 13.2)**

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MEmbranous Nephropathy Trial Of Rituximab

# Analysis Per Protocol at 24 months (patients that were in C/PR at 12 months)

| | CSA | RTX |
|---|---|---|
| Treatment failure | 21 (63.6%) | 1 (2.6%) |
| CR/PR | 12 (36.4%) | 37 (97.4%) |



**Strong evidence against the null hypothesis of inferiority (p-value <0.0001)**

**The estimated risk difference of being in remission between the RTX group and the Cyclosporine group is 43.856% (95% CI 28.409%, 59.302%)**

**The odds ratio of being in remission in the RTX group compared to the Cyclosporine group is 7.2065 (95% CI 3.1963, 16.2482)**

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MEmbranous Nephropathy Trial Of Rituximab

# Conclusion

- B cell targeting with Rituximab **is as effective as** Cyclosporine in inducing C/PR of proteinuria during active treatment phase
- B cell targeting with Rituximab **is non-inferior** to Cyclosporine in inducing **long-term C or PR**
- B cell targeting with Rituximab **reduces the number of relapses and increases the time to relapse** when compared with Cyclosporine
- B cell targeting with Rituximab has a **better side effect profile**



MAYO CLINIC

MENTOR
MEmbranous Nephropathy Trial Of Rituximab

# Have we made progress?

- Still 30 to 40% of patients do not achieve remission
- (Many) more partial remissions than complete ones
- Relapses more frequent in patients with partial remission
- Still severe adverse events, much less with rituximab

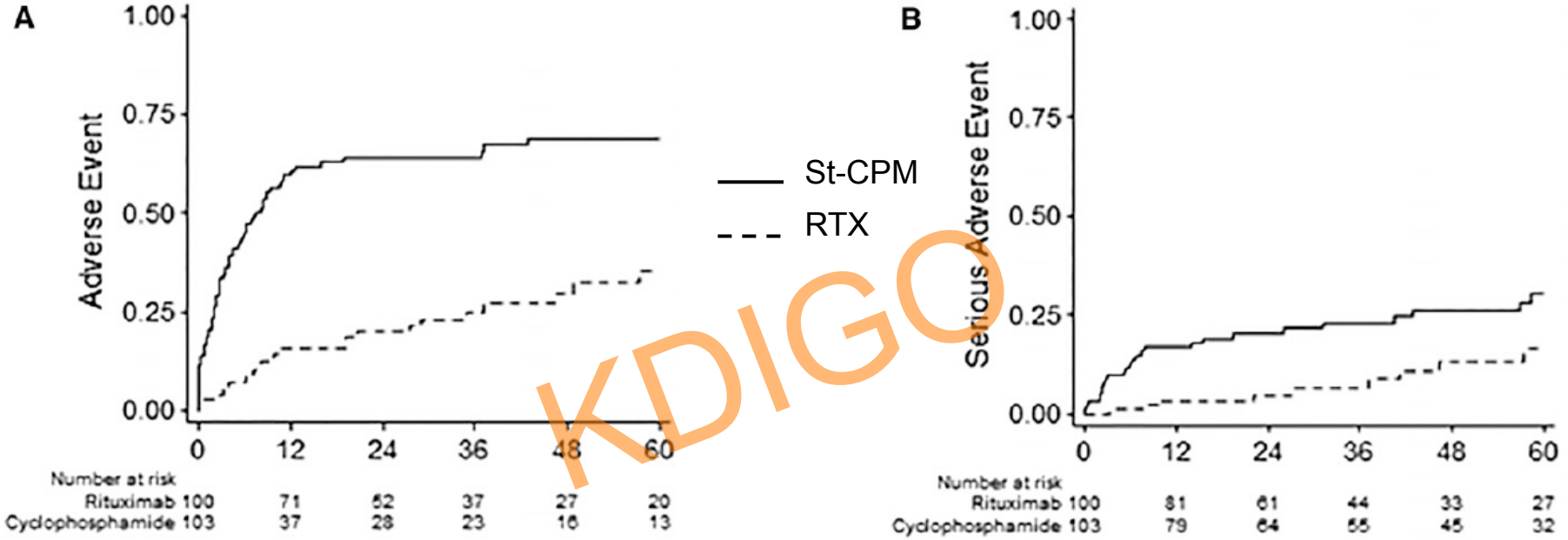
# Toxicity is an important issue

- CPM gives a 3-fold increase in cancer risk, annually from 0.3 to 1.0% for the average patient (van den Brand et al, CJASN 2014, 9:1066)
- In a comparison between CPM (n=103) and RTX (n=100) with a FU of 40 months, the RTX group had less adverse events (63 vs173), both serious (11vs46) and nonserious (52 vs127), (van den Brand……Remuzzi, JASN 2017, on line)
- However CPM protocols differ between:

  Claudio Ponticelli (6 months, alternative therapy, 2.5 mg/kg)

  Jack Wetzels (6 to12 months, continuous therapy,1.5 mg/kg)

# Comparison of safety and efficacy of RTX vs Steroids and Cyclophosphamide

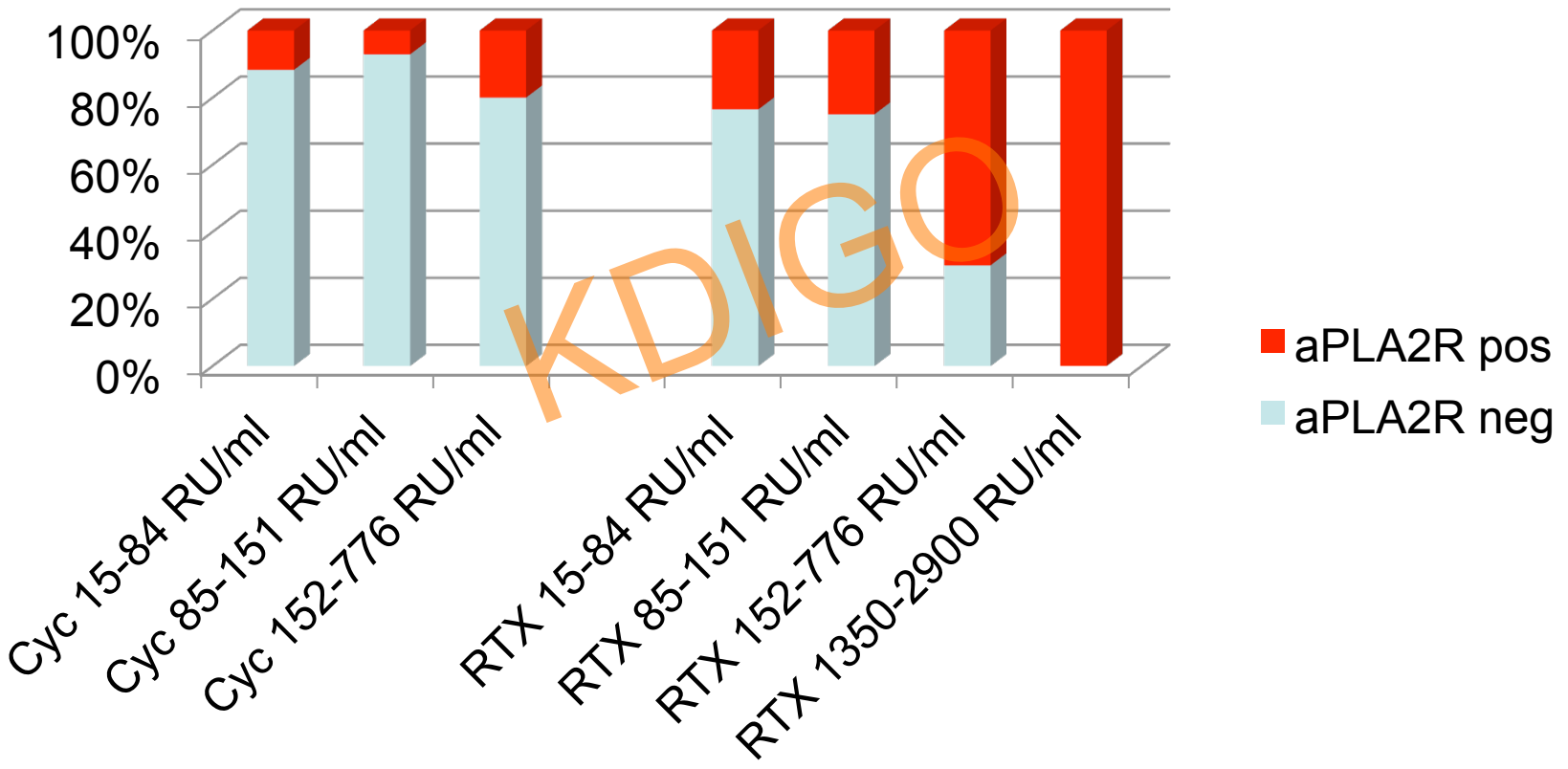





| Rates | RTX | St-CPM | P |
|---|---|---|---|
| PR | 70.6% | 94.8% | 0.01 |
| CR | 40.3% | 41.5% | 0.95 |

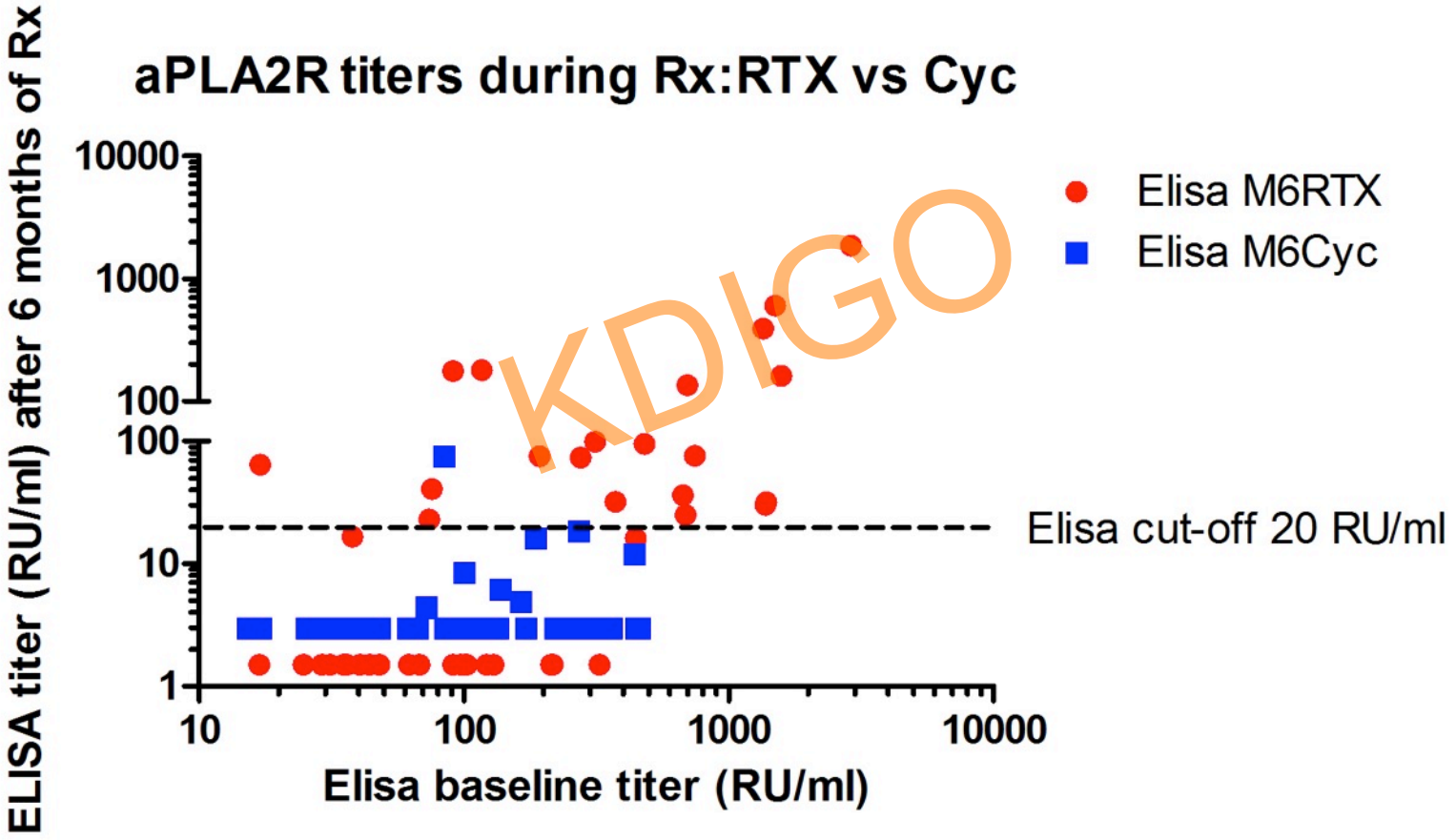
*van den Brand et al, JASN 2017, 28 : online*

# Immunological remission in PLA2R-Ab associated MN Steroids-CPM versus RTX (375 mg/m2, D1, D7)




*van de Logt et al, ASN Renal Week 2017*

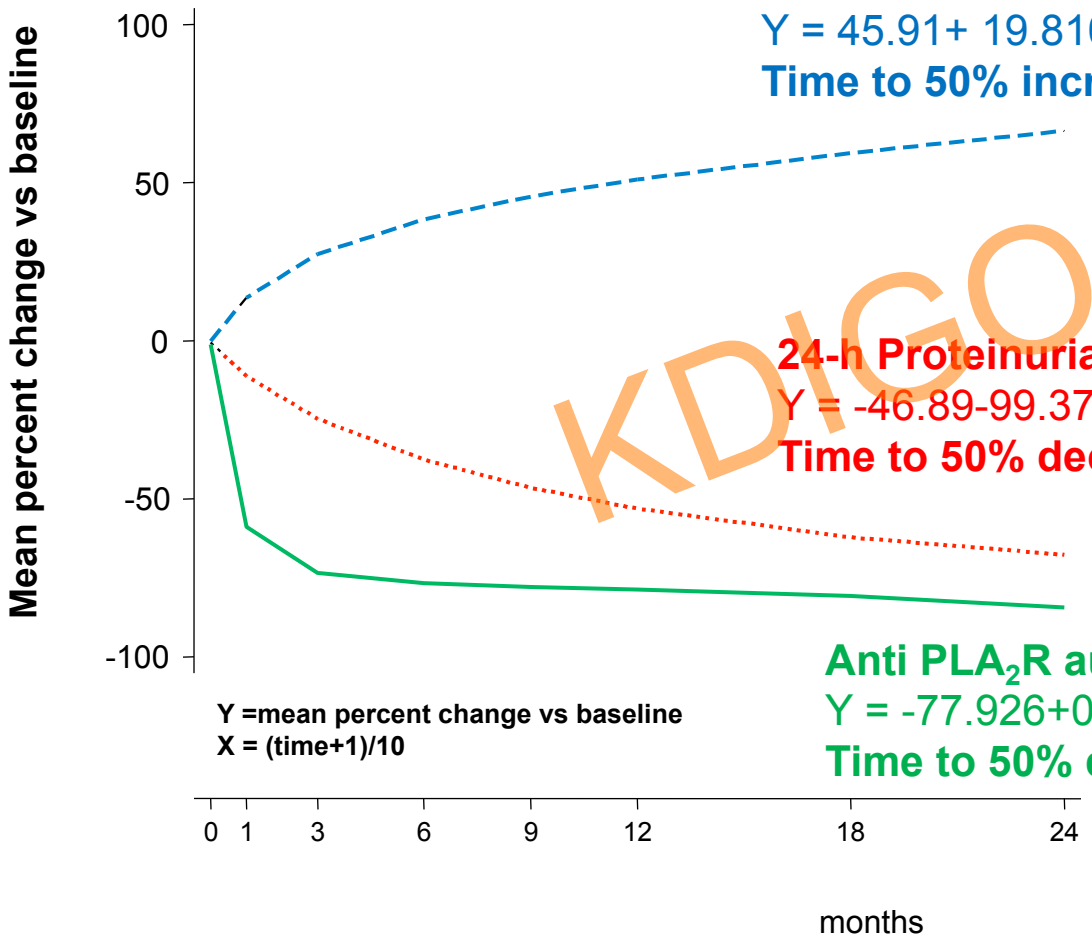
# Rituximab less effective at the used dose (375 mg/m2, D1, D7) in reducing aPLA2R after 6 months




*van de Logt et al, ASN Renal Week 2017*

# How to monitor and predict clinical response and relapse?

# PLA2R-Ab decrease precedes improvement of clinical parameters




**Serum Albumin**
Y = 45.91+ 19.810*(ln(X)-0.0124)+0.179*(X^3-1.038)
**Time to 50% increase = 11.4 months**

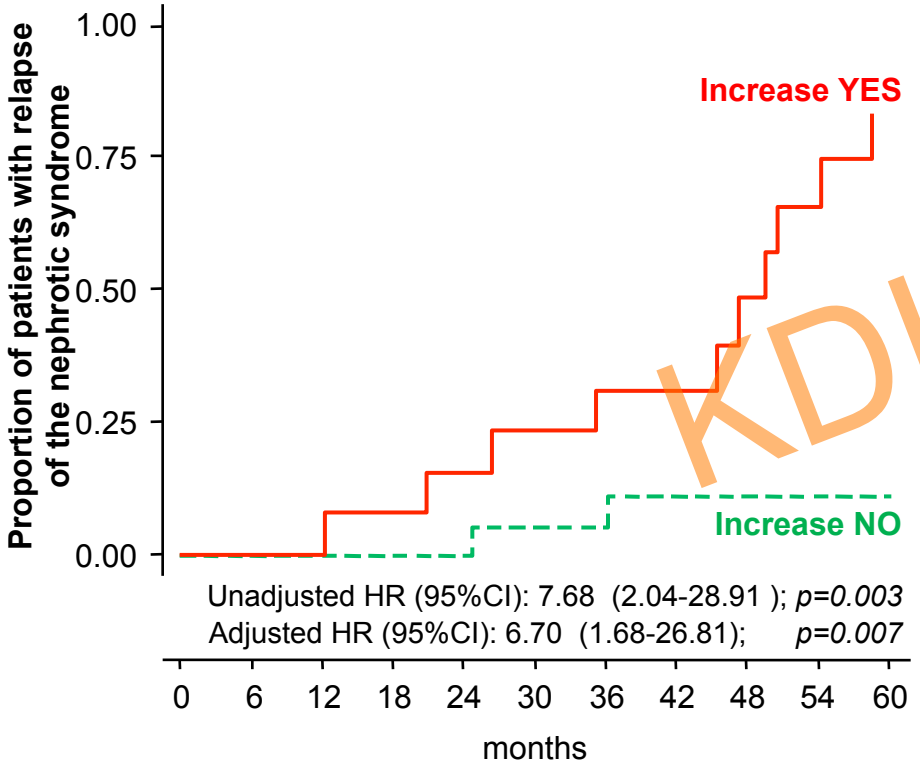
**24-h Proteinuria**
Y = -46.89-99.379*(X^0.5-1.006)+24.376*(X-1.0125)
**Time to 50% decrease = 10.5 months**

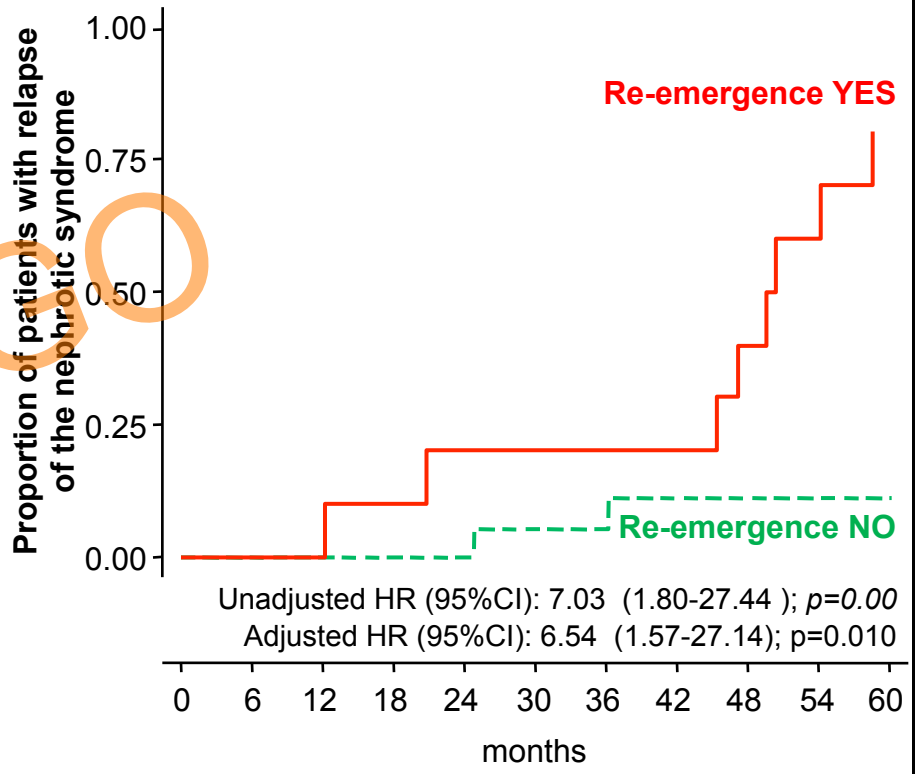
**Anti $PLA_2R$ autoantibody**
Y = -77.926+0.770*(X^-2-.975)-0.404*(X^3-1.038)
**Time to 50% decrease = 0.65 months**



*Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 26:2545*

# PLA2R Ab titer increase or antibody re-emergence is associated with a high risk of relapse






**Patients at risk**

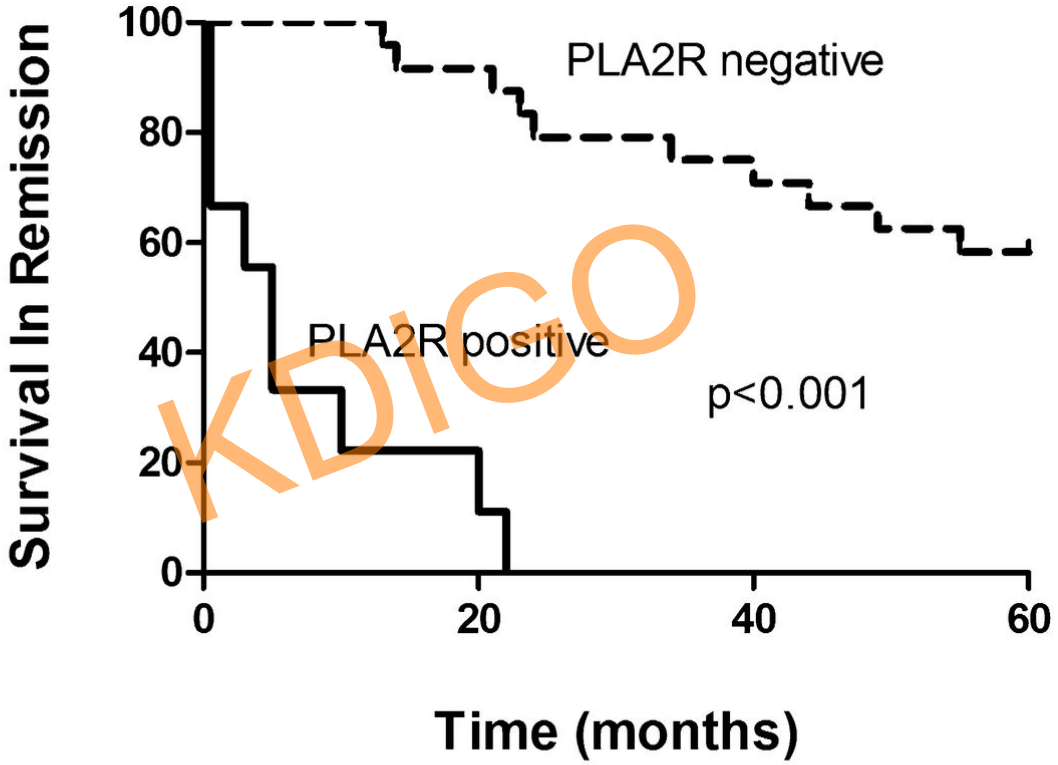
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Increase NO | 31 | 31 | 27 | 26 | 24 | 16 | 16 | 12 | 12 | 11 | 10 |
| Increase YES | 13 | 13 | 13 | 12 | 11 | 10 | 9 | 8 | 6 | 4 | 2 |

**Patients at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Emergence NO | 31 | 31 | 27 | 26 | 24 | 16 | 16 | 12 | 12 | 11 | 10 |
| Emergence YES | 10 | 10 | 10 | 9 | 8 | 8 | 8 | 8 | 6 | 4 | 2 |

*Ruggenenti, Debiec,…, Ronco, Remuzzi, J Am Soc Nephrol 2015 26:2545*

# Anti-PLA2R antibodies predict relapse rate after IS therapy

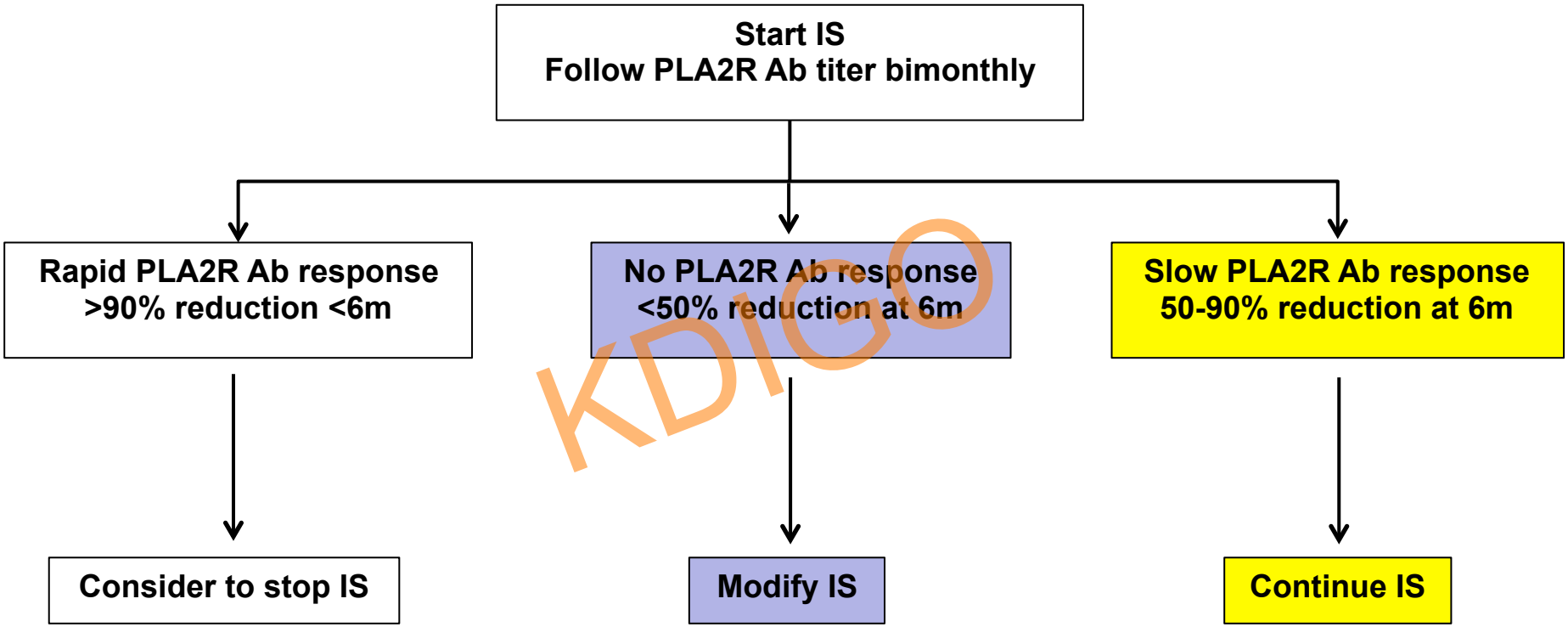





| | | | | |
|---|---|---|---|---|
| PLA2R positive | 9 | 2 | 0 | 0 |
| PLA2R negative | 24 | 22 | 18 | 14 |

*Bech et al, Clin JASN 2014, 9:1386*

# Therapeutic algorithm of membranous nephropathy : Look at kinetics of PLA2R-Ab!

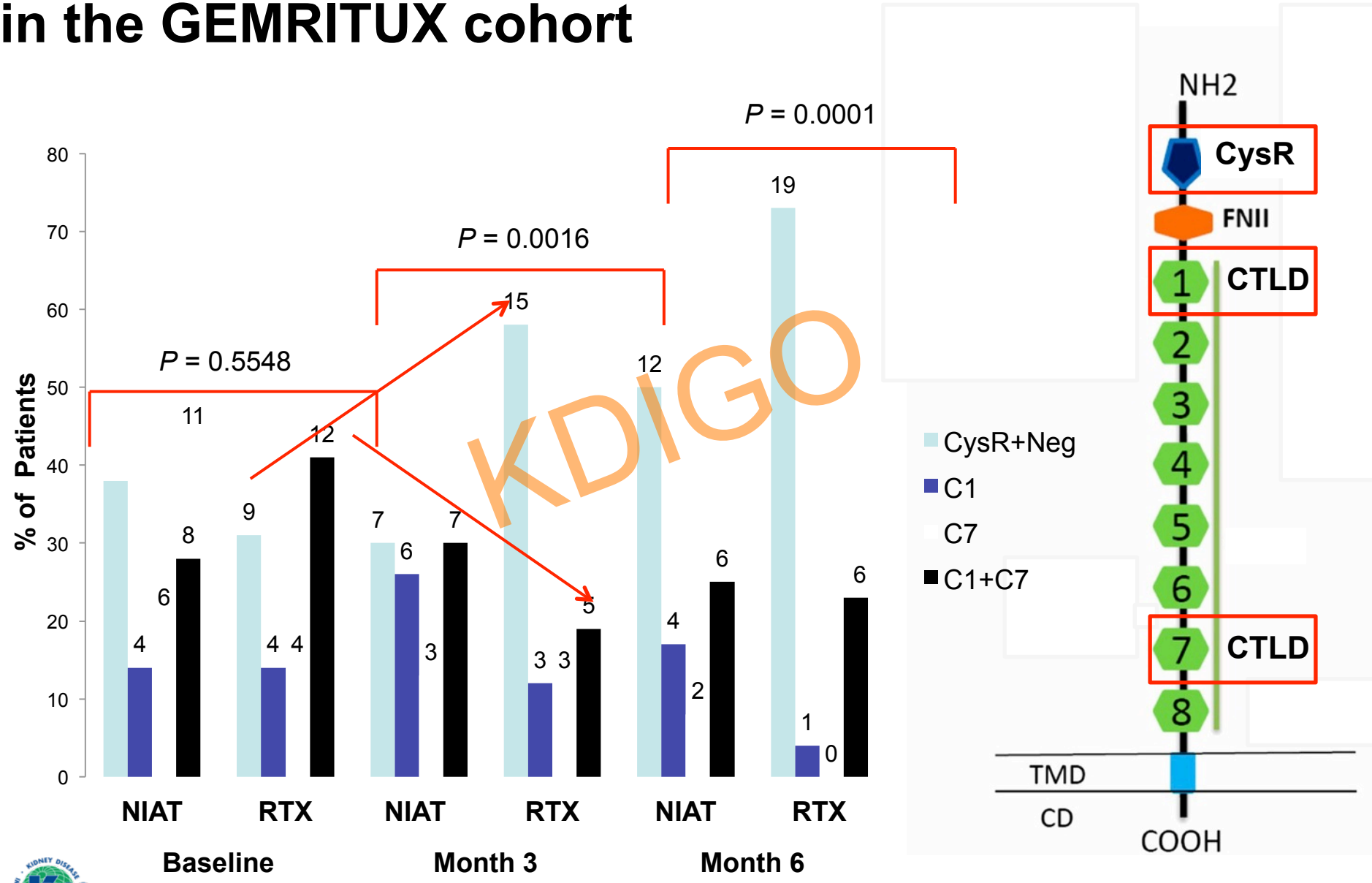





*De Vriese et al, JASN 2017, 28:421 (Mayo Clinic, California)*

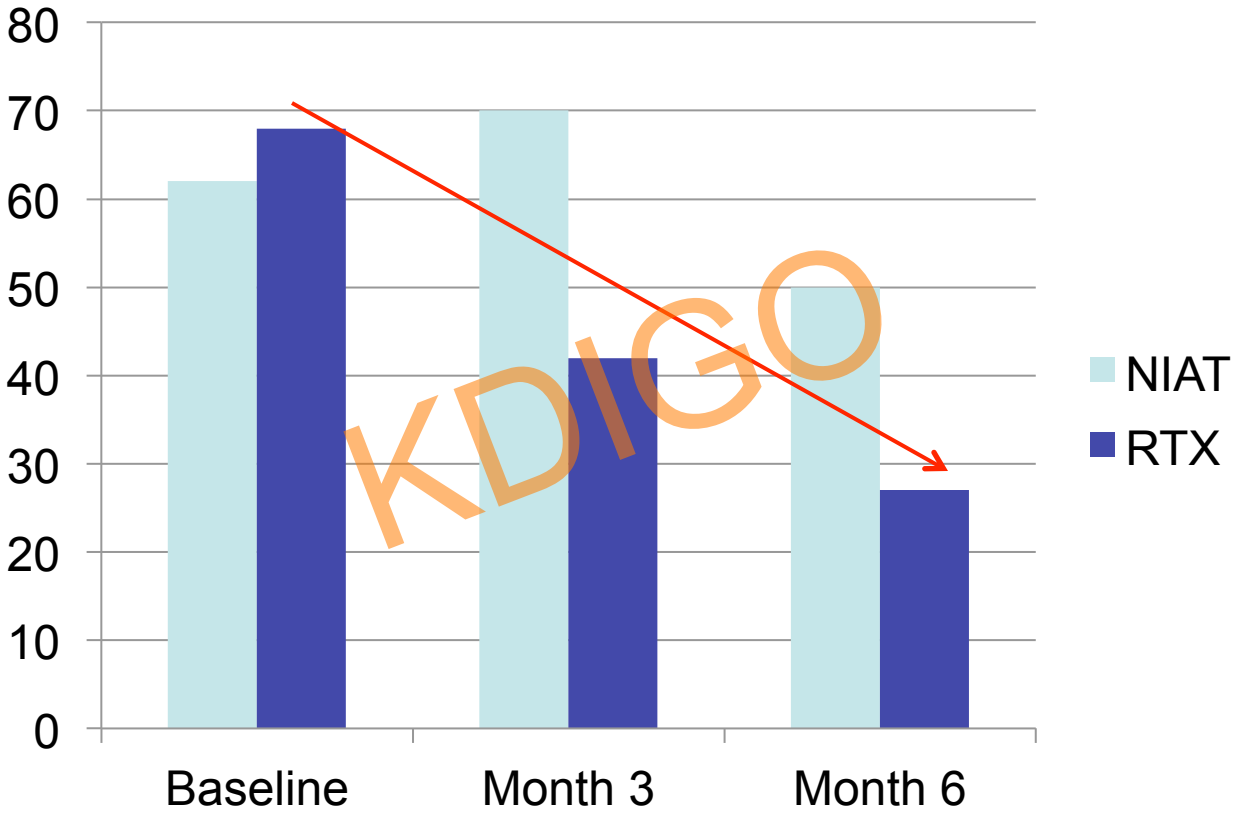
Should we wait for 6 months in pts with persisting high titers of PLA2R-Ab (and Ab spreading) until reinforcing/changing/combining therapy? Or consider 3 months as the turning point (GEMRITUX)?

# Effect of rituximab on epitope reactivity in the GEMRITUX cohort




*Seitz-Polski B, Debiec H…, Lambeau G, Ronco P, Nov. 7th 2017*

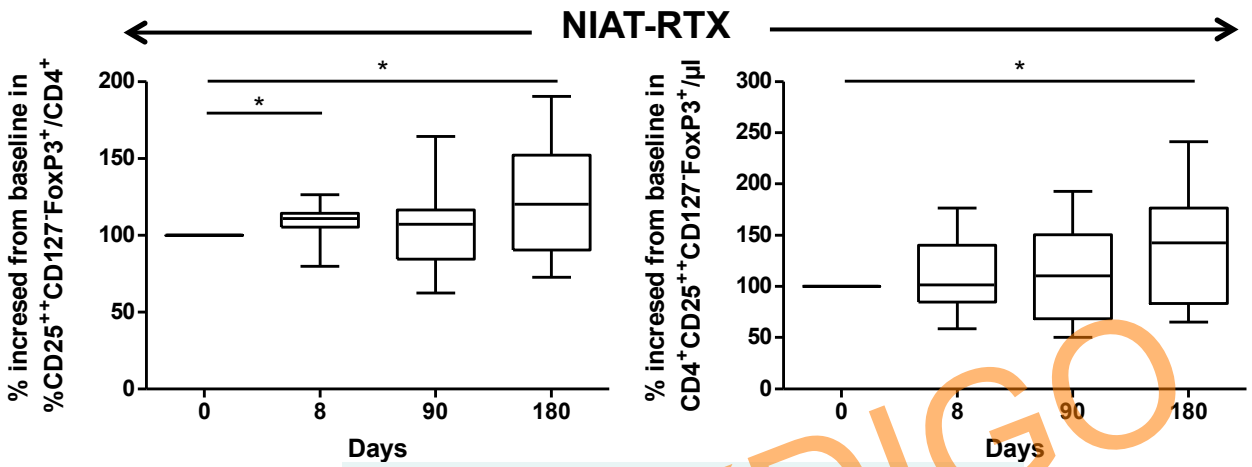
# Outcome of spreading (CysR C1/C7) in the GEMRITUX cohort



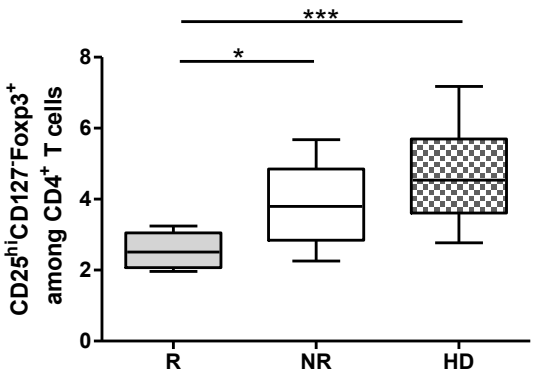

**Spreading at baseline is associated with a decreased rate of remission at 6 months (OR 0.16 , P= 0.02) and last follow-up (OR 0.14, P=0.01), irrespective of PLA2R-Ab titer at baseline**

*Seitz-Polski B, Debiec H…, Lambeau G, Ronco P , Nov. 7th 2017*

# Changes in Treg in iMN patients treated with NIAT-Rituximab

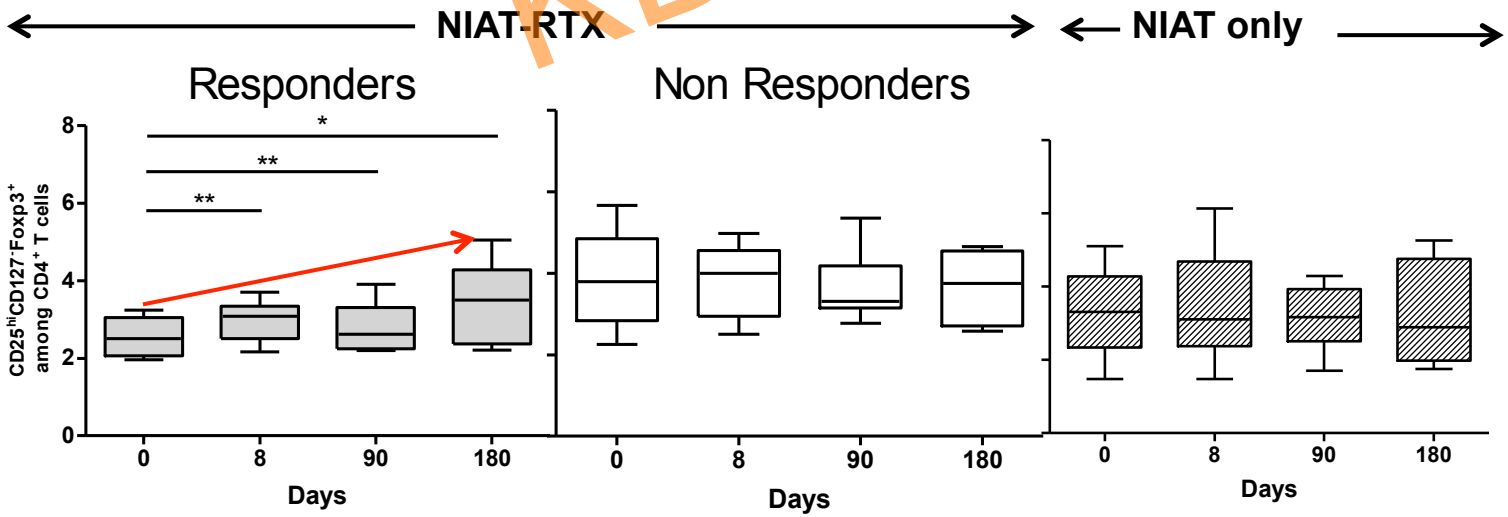



Changes in the total population




Comparison of Treg at baseline






*Rosenzwajg et al, Kidney Int. 2017 Mar 15*

# Our today practice at Tenon Hospital

- Shorten the « wait and see » period to 3 months in patients with high-level PLA2R-Ab persisting at 3 months
- Start with rituximab (RTX) as first-line therapy
- Retreat patients (re-infuse RTX) on the basis of PLA2R-Ab level, not CD19 depletion
- Use combined therapy (Prograf-RTX) in « refractory » patients
- Consider epitope spreading (epitope-specific ELISAs soon available)

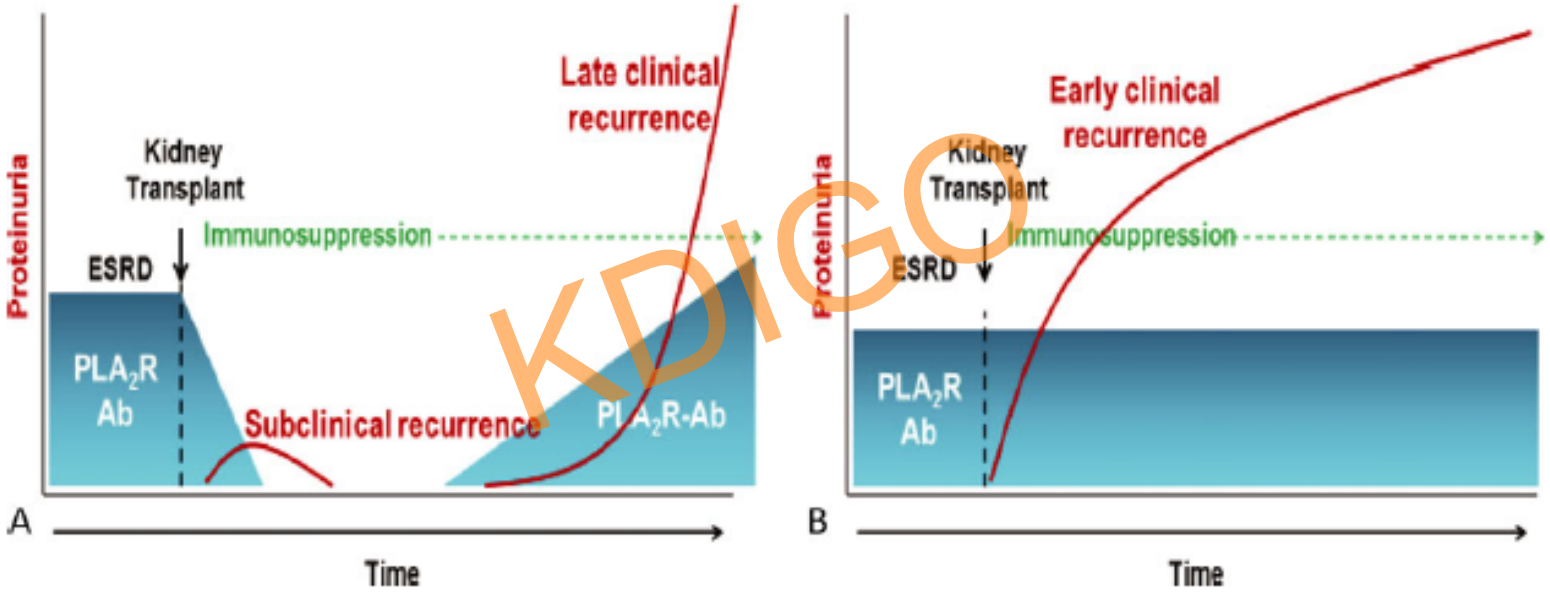
# Revisit definitions of remissions and relapse to better define therapeutic endpoints?

- Immunological remission should be defined by disappearance of PLA2R-Ab by IFT (remains positive longer than ELISA)
- Complete clinical remission is easy to define
- Partial remission (and relapse) relies on proteinuria which is highly variable
- PLA2R-Ab should be considered in the definition of disease remission
- Long-term complete remission without relapse remains the ultimate goal
- But treatment should first/also aim at immunological remission (complete) which usually precedes clinical remission by several weeks or months despite outliers (epitopes to be identified)

# Unsolved questions and future challenges

- Understand remission/ progression/recurrence
- Revisit MN classification based on antigens (causes are shared)
- Refine epitope analysis and replicate predictive value of spreading: delay treatment in patients with CysR-Ab only?
- Search for additional antigens
- Identify T-cell epitopes and replicate Treg data
- Develop anti-C5b-9 compounds
- Develop new treatment strategies (immunoadsorption, anti-B/plasma cell drugs) and combined therapies to fill the gap of the 30 to 40% failure
- Set large international trials with adaptive strategies

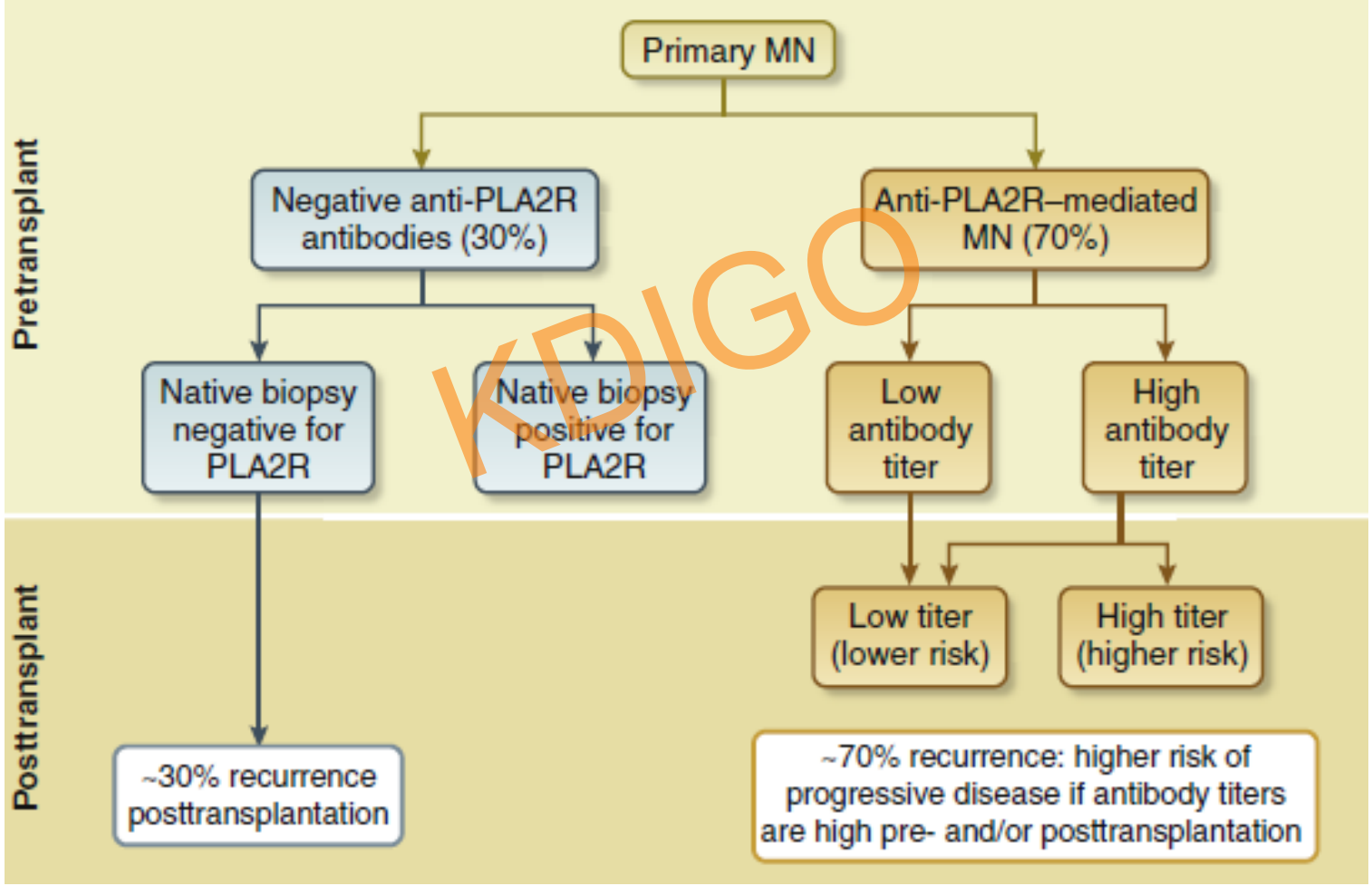
# Proposed patterns of recurrence of membranous nephropathy according to PLA2R-Ab outcome





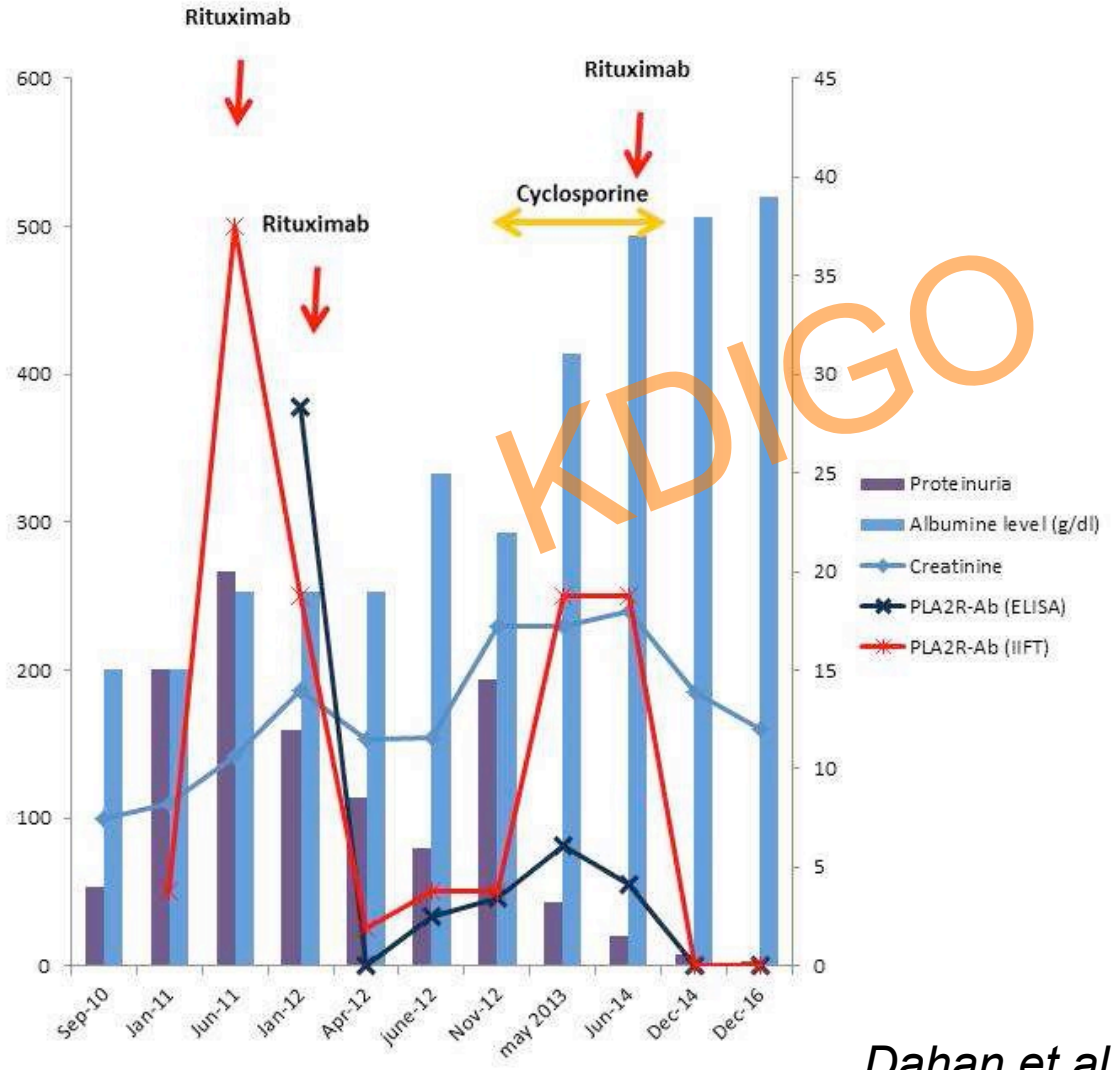

*Gupta et al, Clin Transplant 2016, 30:461 ;*
*Debiec et al, Am J Transplant 2011, 11:2144*

# Assessment of risks of MN recurrence and progression post transplantation based on laboratory parameters obtained before and after transplantation




*Cosio et al, Kidney Int 2017, 91:304*

# Complete clinical remission required complete disappearance of PLA2R-Ab by IFT






*Dahan et al Kidney Int Reports in press*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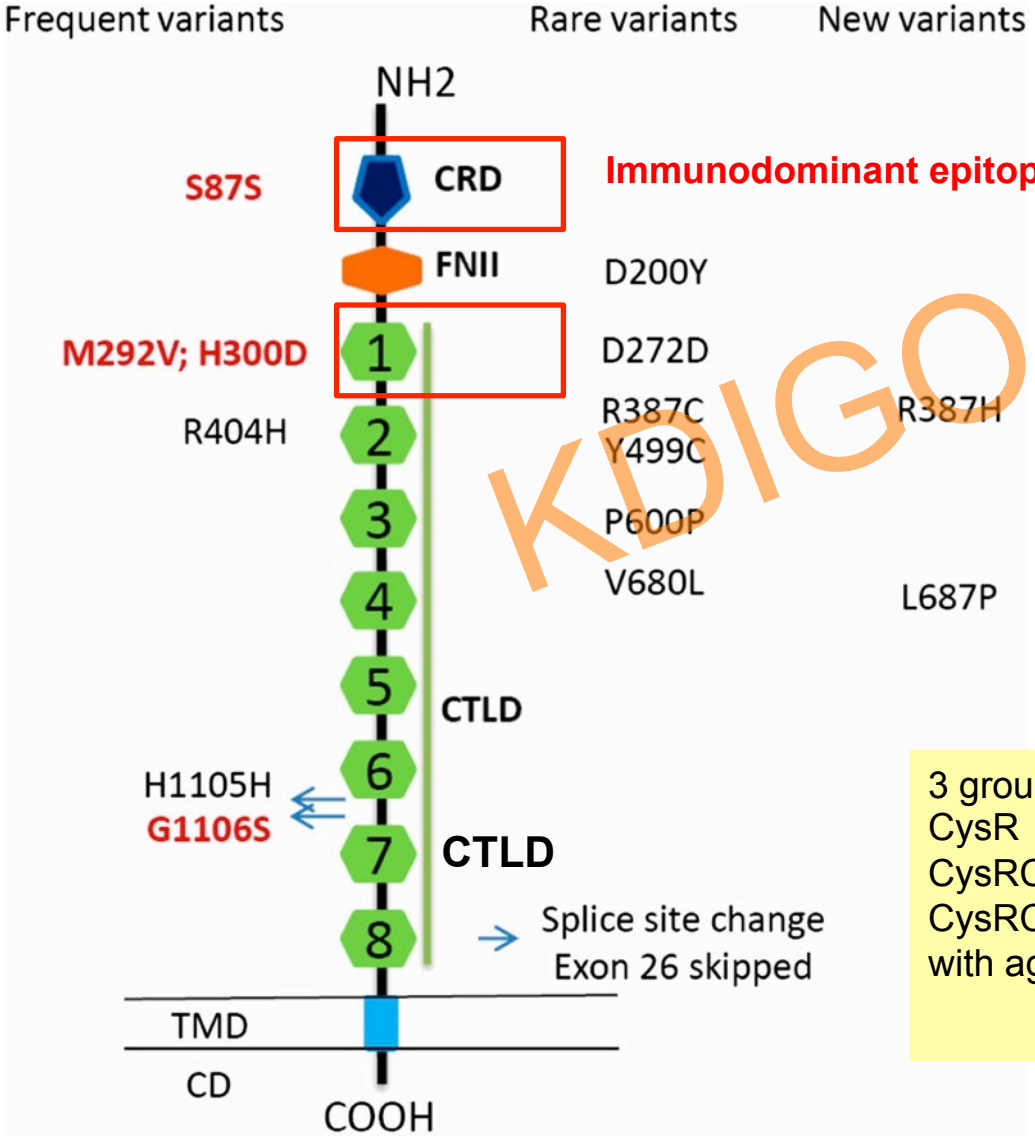
# An indirect immunofluorescence assay for anti-THSD7A antibody (Euroimmun AG)

- 92% sensitivity and 100% specificity compared to Western blot
- Prevalence of THSD7A associated MN : 2.6% (prospective cohort of 345 patients)
- 40 patients with THSD7A-associated MN identified among 1276 patients with MN (retrospective and prospective, Hamburg and Boston cohorts)
- Eight patients developed a malignancy within 3 months
- Most patients were women



*Hoxha et al JASN 2017, 28: 520*

# Epitope spreading as a new predictor

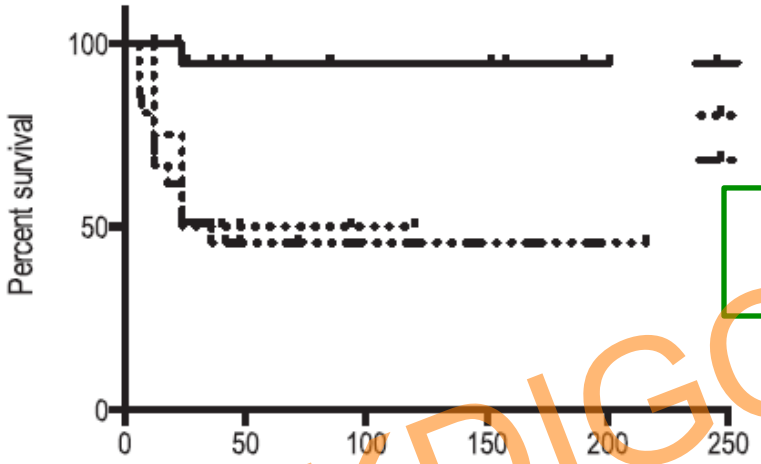





*Coenen et al, JASN, 2013 24:677 ; Seitz-Polski et al, JASN 2016 27:1517*

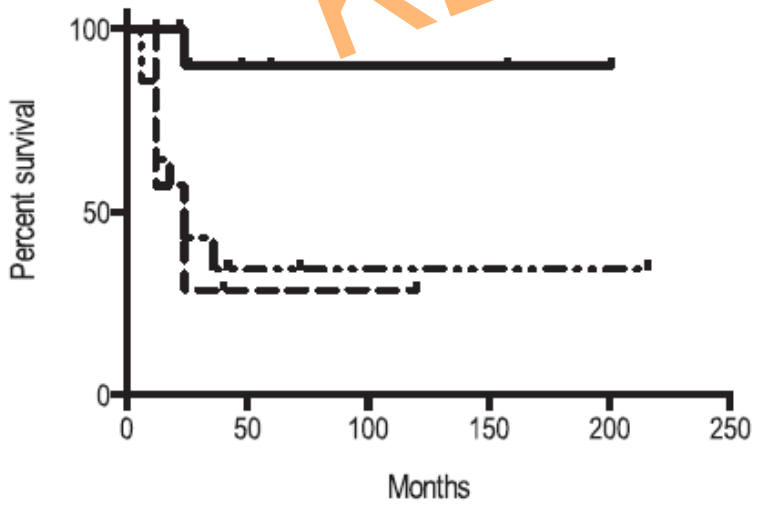
3 groups :
CysR
CysRC1
CysRC1 C7 spreading increasing with age and proteinuria levels

# Impact of spreading on renal function outcome




**Whole population**
**n= 55, p=0.0025**





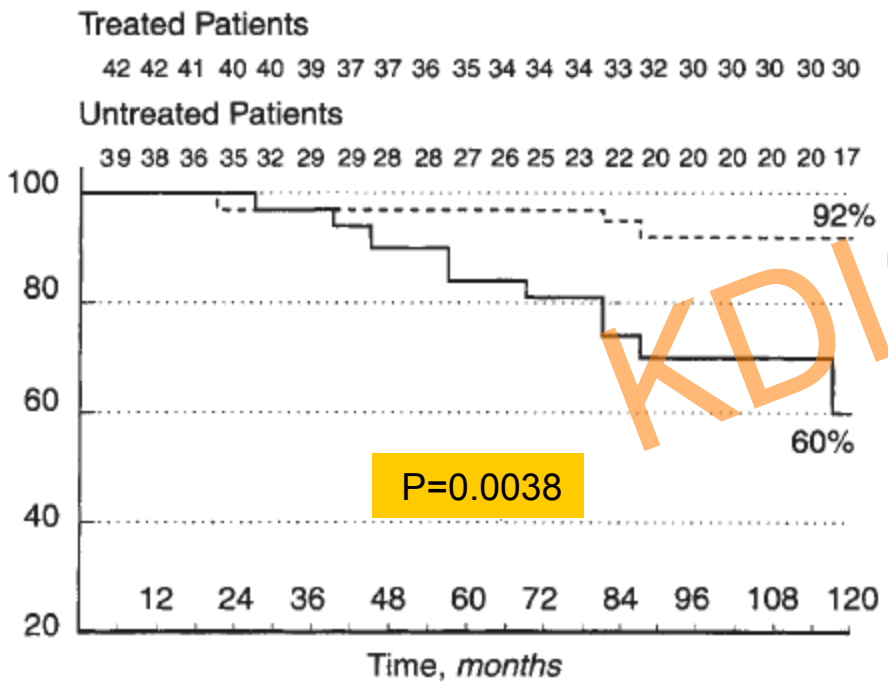

**IS treated group**
**n=33, p=0.014**

Endpoint =30% increase of creatinine

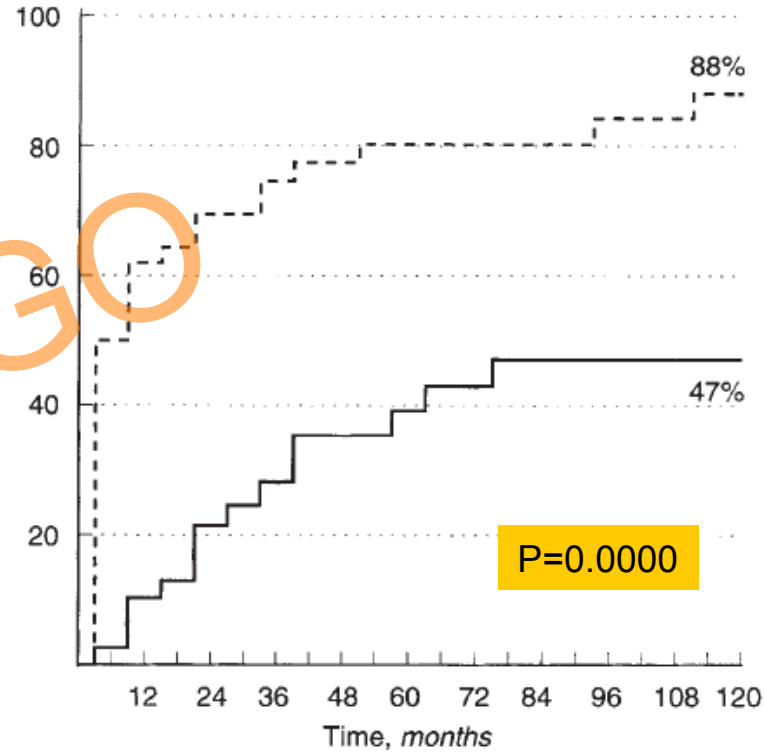
*Seitz-Polski et al, JASN 2016 27:1517*

# A ten-year follow-up of the Ponticelli protocol (methylprednisone and chlorambucil)

Cumulative probability of survival without dialysis




Probability of complete or partial remission





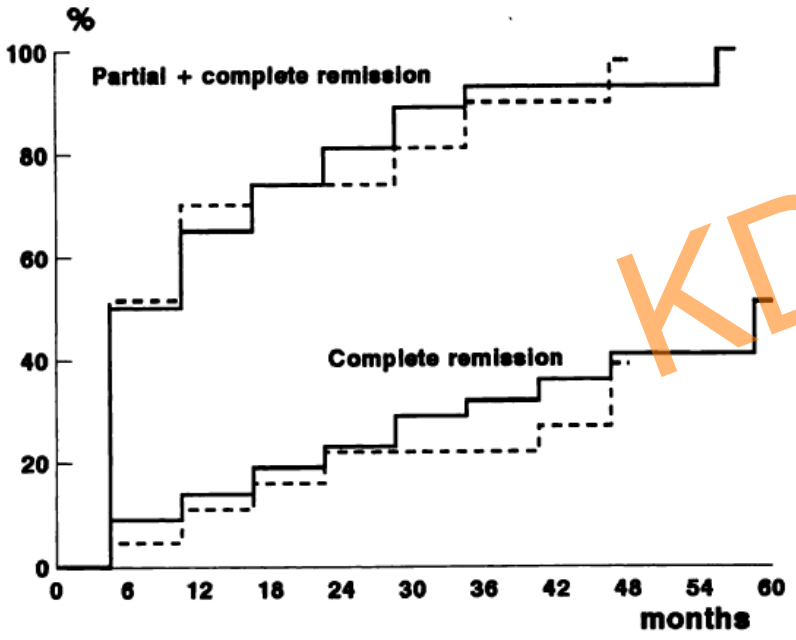

untreated controls

treated patients

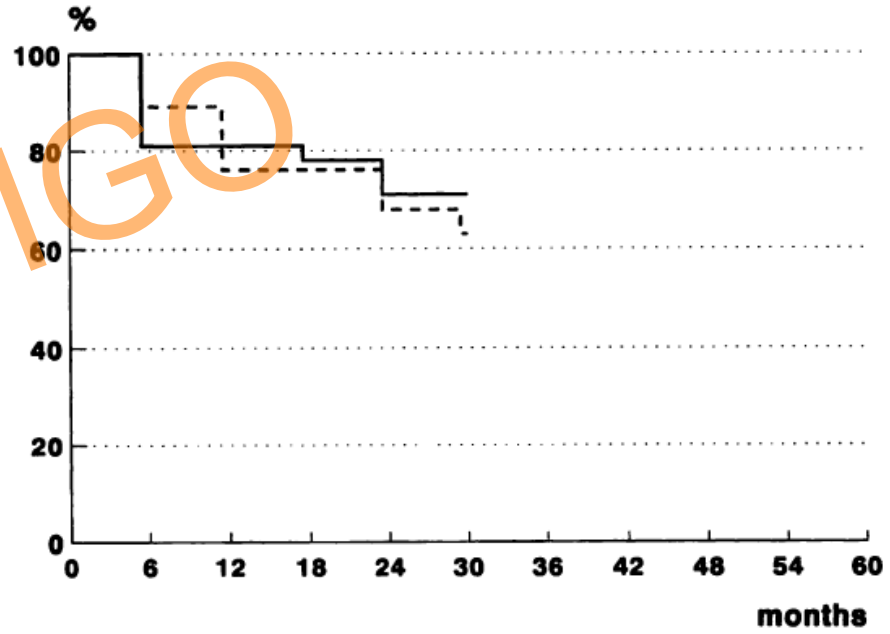
*Ponticelli et al, Kidney Int 1995, 48:1600*

# Cumulative probability of remission and relapse-free survival in patients given MP + Chlor. Vs MP + CPM

Cumulative probability of partial or complete remission




Cumulative probability of relapse-free survival






——— Methylprednisolone + cyclophosphamide

- - - - Methylprednisolone + chlorambucil

*Ponticelli et al, JASN 1998, 9:444*

# Severe adverse events

| Severe Adverse Events | Rituximab Group (N=37) | NIAT group (N=38) |
|---|---|---|
| | *no. of events* | |
| Acute renal failure | 0 | 2 |
| Infection | | |
| Prostatitis | 1 | 0 |
| Pleural effusion | 0 | 1 |
| Cardiac and vascular disorders | | |
| Myocardial infarction | 1 | 1 |
| Critical limb ischemia | 0 | 1 |
| Mesenteric Ischemia | 1 | 0 |
| Carotid endarteriectomy | 1 | 0 |
| Cancer | 0 | 1 |
| Acute hepatitis | 0 | 1 |
| Others | | |
| Oedema | 1 | 1 |
| Pain | 1 | 0 |
| Total | 6 | 8 |

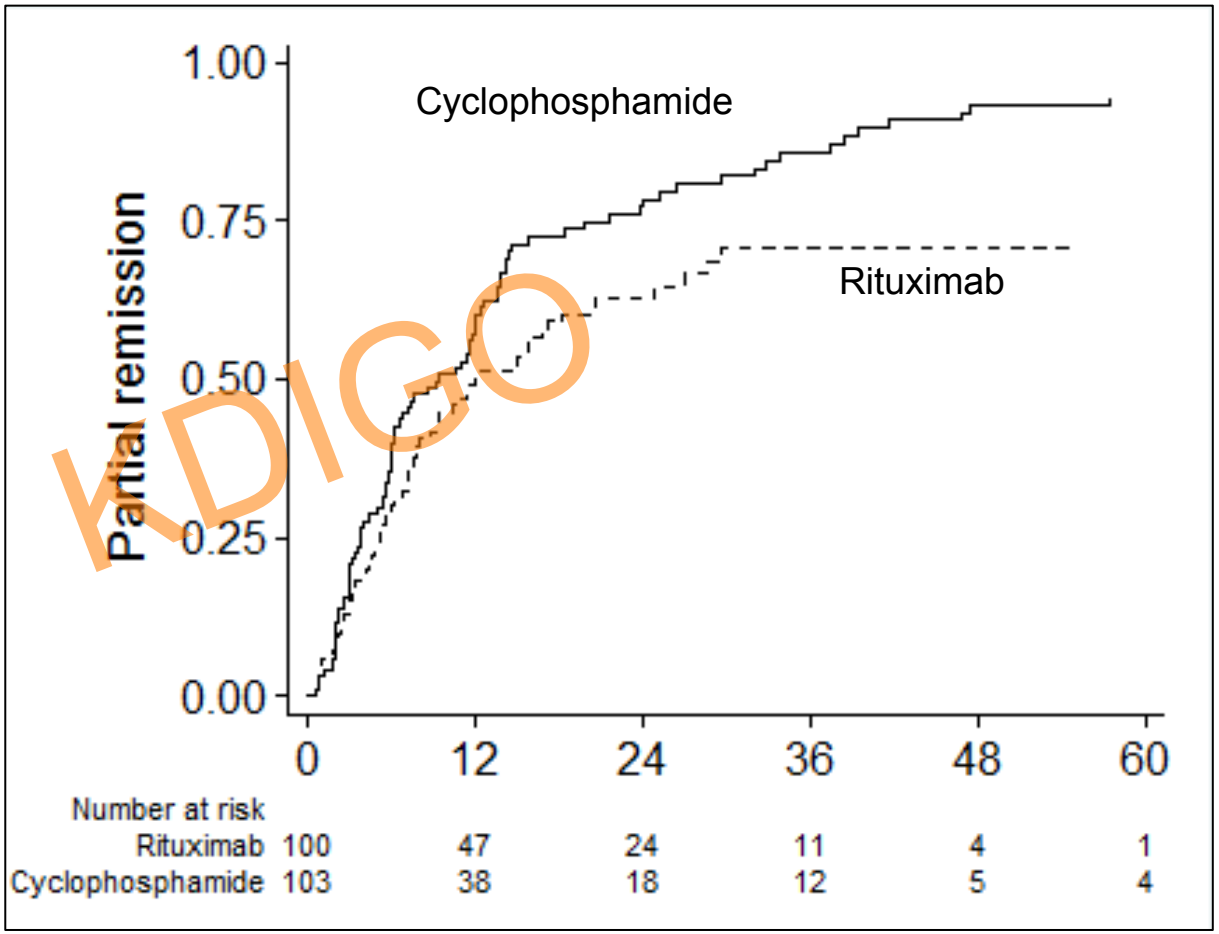
# Incidence of partial remissions is higher with cyclophosphamide

Rituximab:

Fewer (S)AE's

Complete remissions ~
Renal failure ~

Partial remissions: ↓






*van de Brand, JASN 2017*

# Remission Status over time

| 6 Months | CSA (n=63) | RTX (n=64) |
|---|---|---|
| Complete Remission | 1 | 0 |
| Partial Remission | 31 | 23 |
| ≥25% Proteinuria reduction but not CR/PR | 13 | 27 |
| Treatment failure | 18 | 14 |

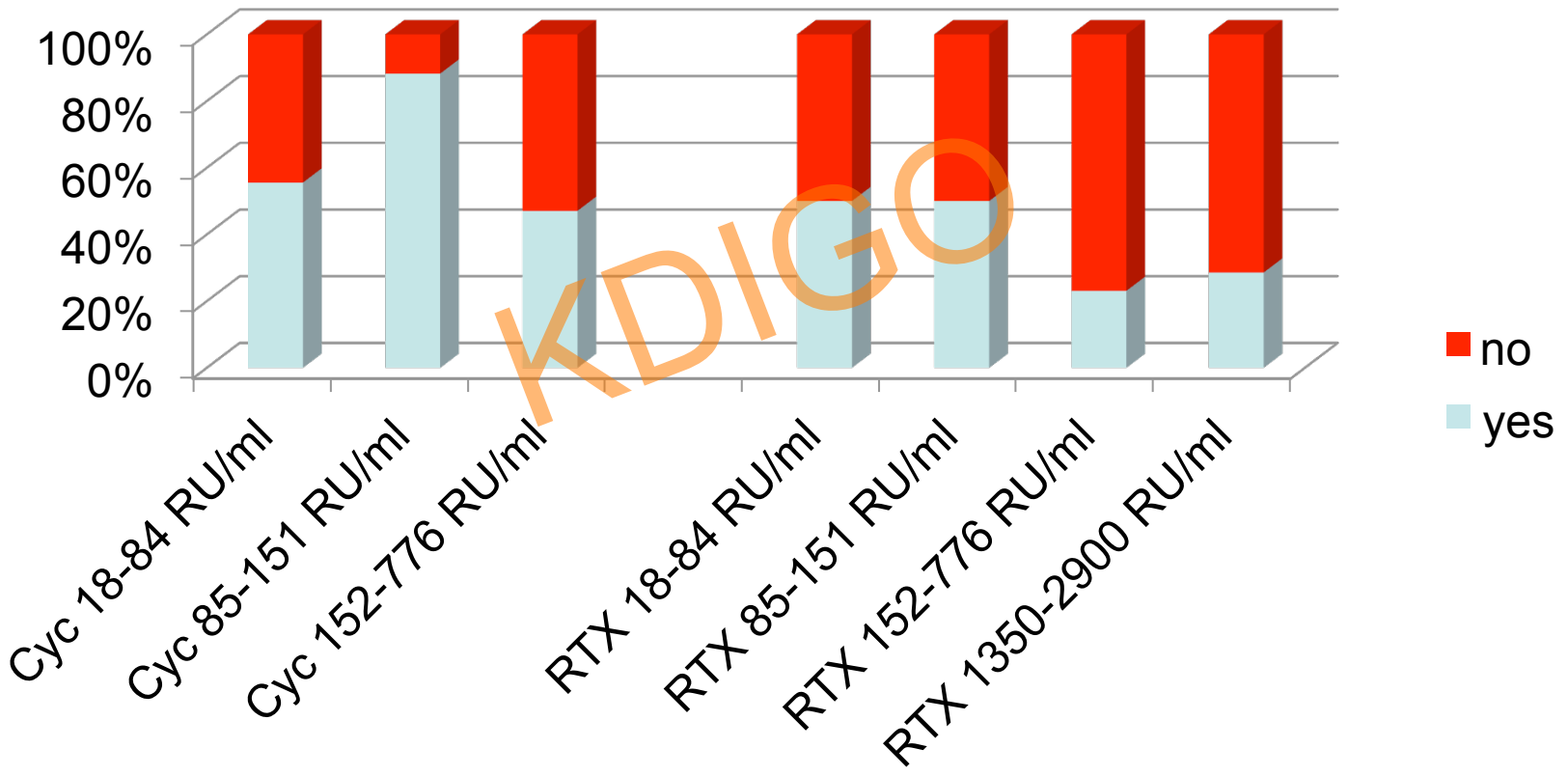
| 12 Months | CSA (n=63) | RTX (n=64) |
|---|---|---|
| Complete Remission | 3 | 9 |
| Partial Remission | 30 | 30 |
| Treatment failure | 30 | 25 |

| 24 Months | CSA (n=63) | RTX (n=64) |
|---|---|---|
| Complete Remission | 0 | 23 |
| Partial Remission | 13 | 17 |
| Treatment failure | 50 | 24 |

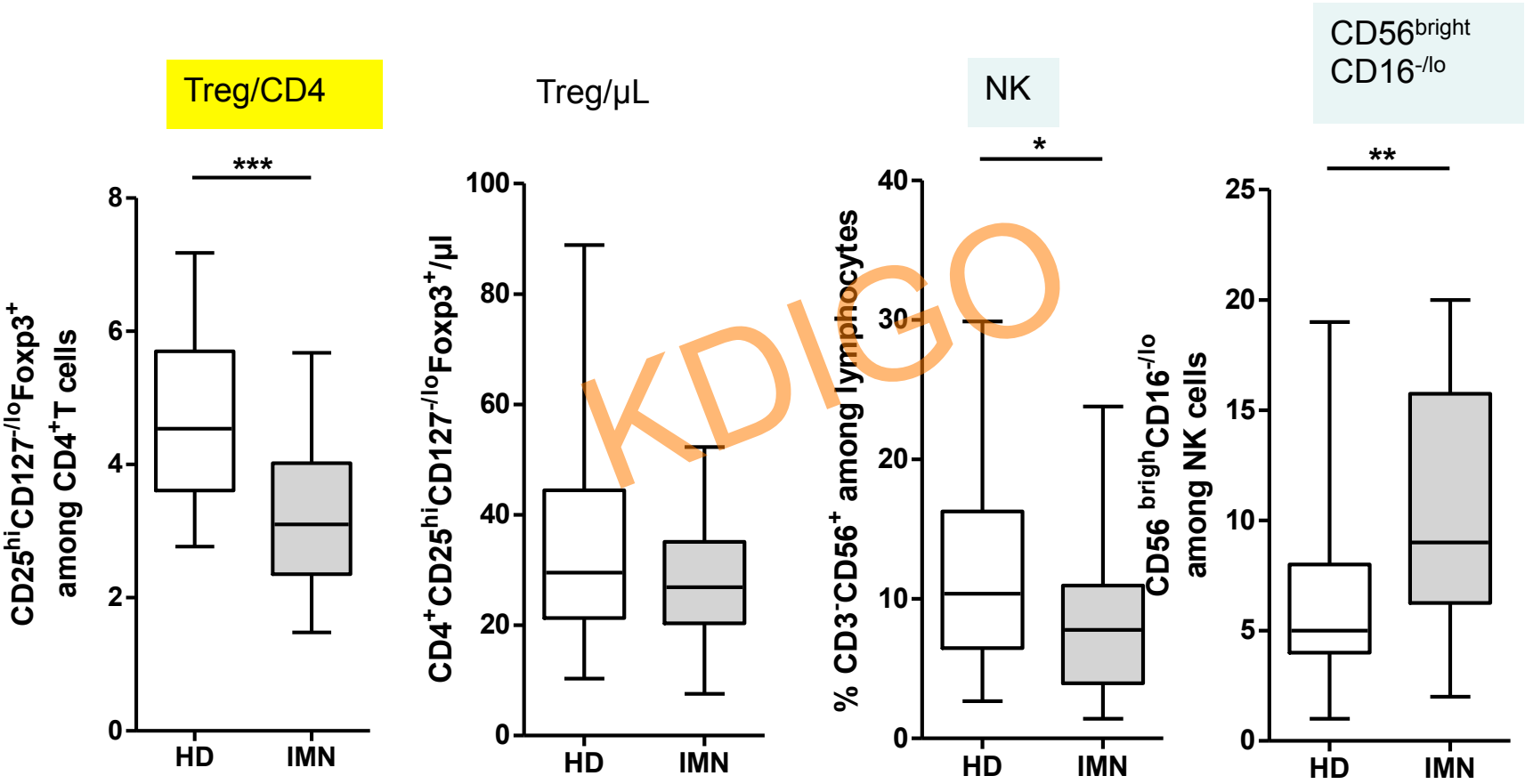
# Serious Adverse Events by SOC

| | CSA (n=65) | RTX (n=65) |
|---|---|---|
| Cardiac disorders | 2 | 0 |
| Endocrine disorders | 0 | 1 |
| Gastrointestinal disorders | 1 | 1 |
| General disorders and administration site conditions | 1 | 1 |
| Hepatobiliary disorders | 1 | 0 |
| Infections and infestations | 5 | 3 |
| Investigations | 1 | 1 |
| Metabolism and nutrition disorders | 1 | 1 |
| Musculoskeletal and connective tissue disorders | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | 1 |
| Nervous system disorders | 1 | 1 |
| Renal and urinary disorders | 3 | 0 |
| Respiratory, thoracic and mediastinal disorders | 1 | 1 |
| Surgical and medical procedures | 0 | 1 |
| Vascular disorders | 5 | 1 |
| **Total SAEs:** | **23** | **13** |

# Results 3: clinical remission rate after 6 months



# Comparison of Treg and NK cells in iMN patients and healthy donors



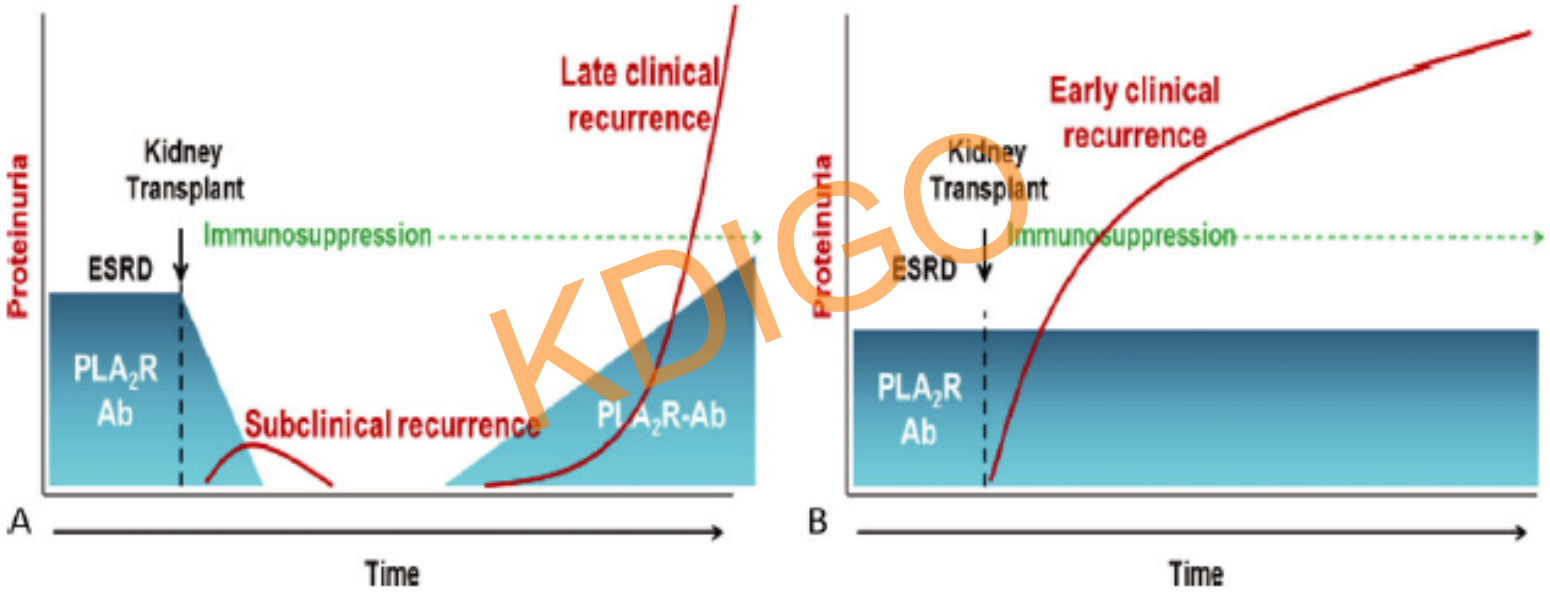



HD : Healthy blood donors (n=27)

IMN : Patients (n=25)

*Rosenzwajg et al, Kidney Int. 2017 Mar 15*

# Proposed patterns of recurrence of membranous nephropathy according to PLA2R-Ab outcome






*Gupta et al, Clin Transplant 2016, 30:461 ;*
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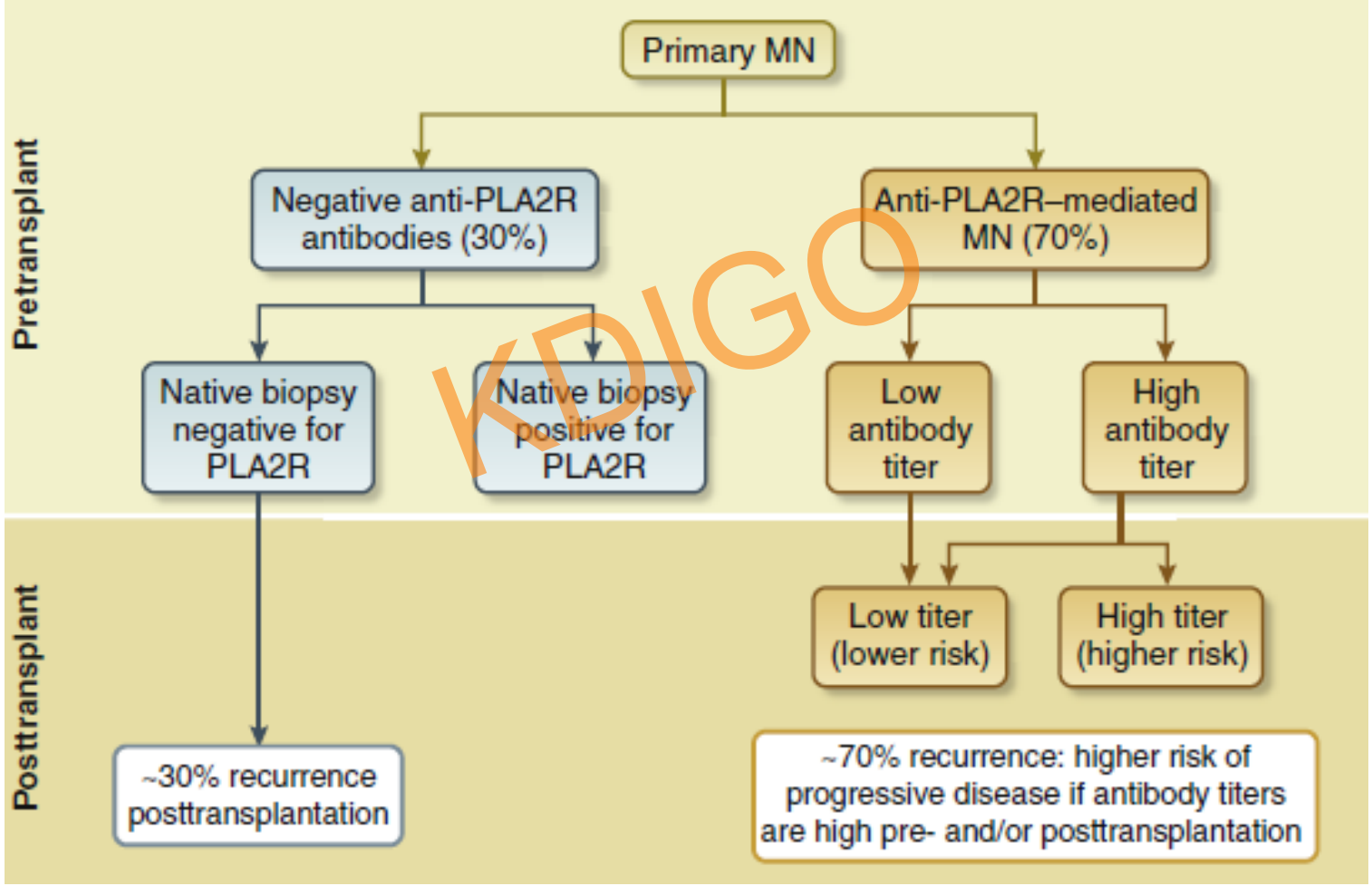
# Assessment of risks of MN recurrence and progression post transplantation based on laboratory parameters obtained before and after transplantation



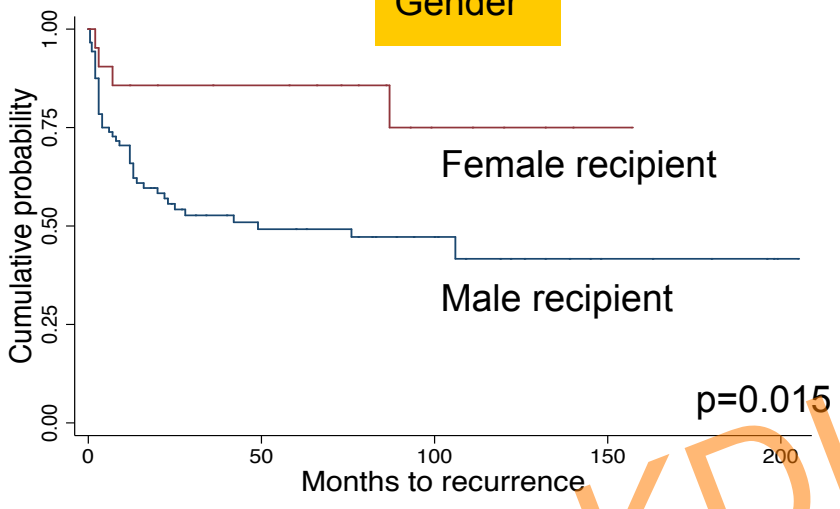

*Cosio et al, Kidney Int 2017, 91:304*

# Predictors of recurrence in a retrospective cohort of grafted patients with MN

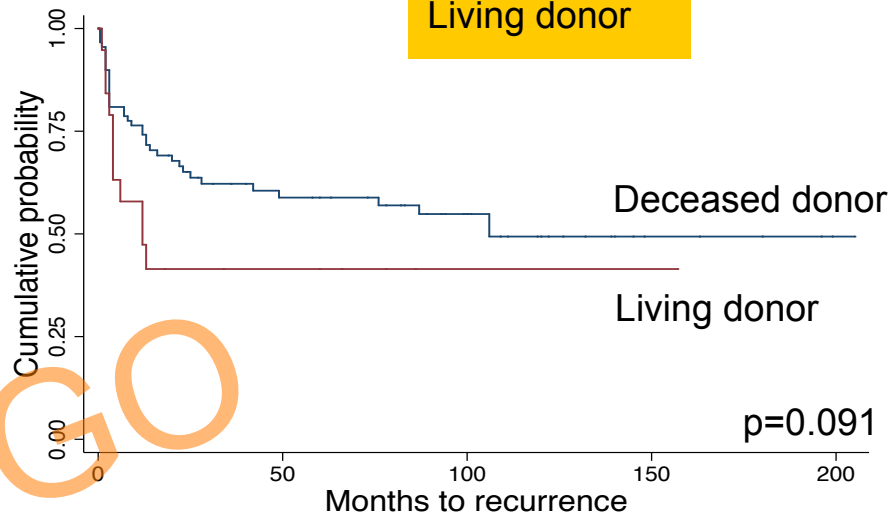
- 113 pairs of donors/recipients :
  - 51 R : recurrence (kidney biopsy)
  - 62 WR : without recurrence (39 biopsy proven ; 22 most likely with proteinuria < 0.5 g/day)
- Median time to R = 6 months ; to last FU = 80 months
- Early (24 < 6 months) vs late recurrence (25 ≥ 6 months) and log-rank test for follow-up
- Determination of PLA2R status (serum or biopsy)
- Genetic studies (risk SNPs, allelotypes)

# Clinical predictors of recurrence: cumulative probability of recurrence-free outcome

## Gender

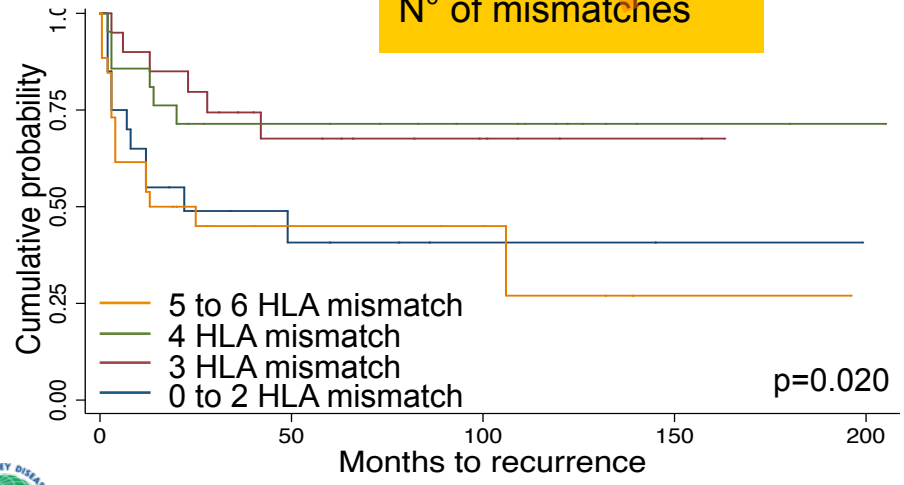



## Living donor

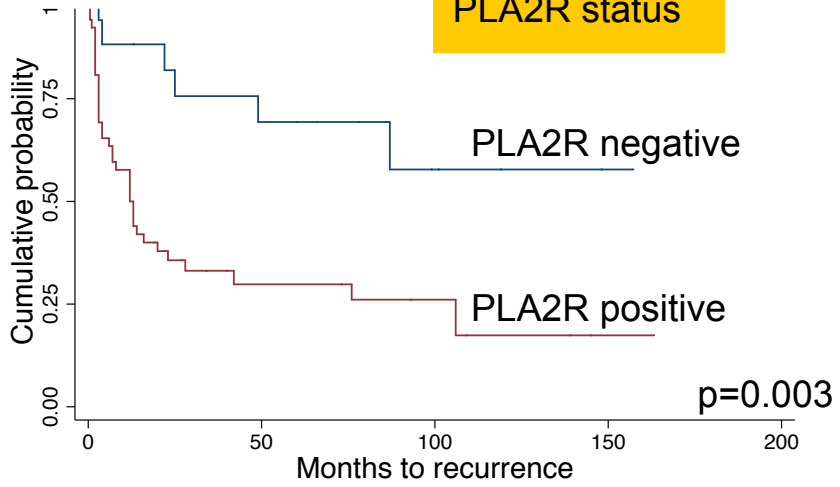





## N° of mismatches




## PLA2R status




*Berchtold et al. unpublished*