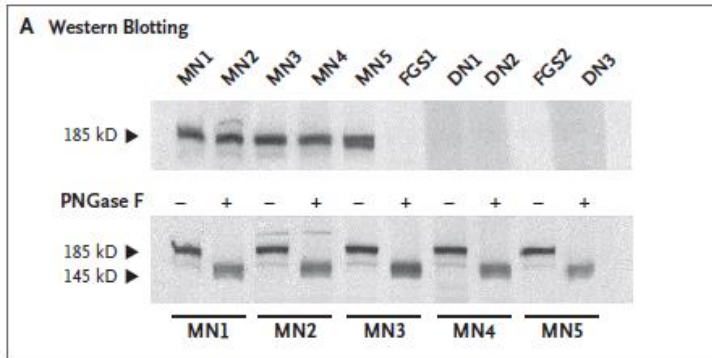


PLA2R antibodies: do we need epitope specific ELISA's?

Anne-Els van de Logt
Papendal 12-12-2018

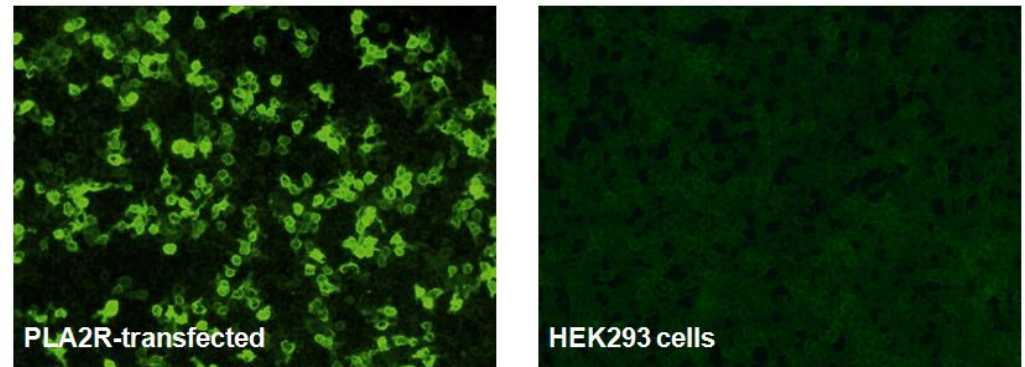
Anti-PLA2R-measurements

Western Blot



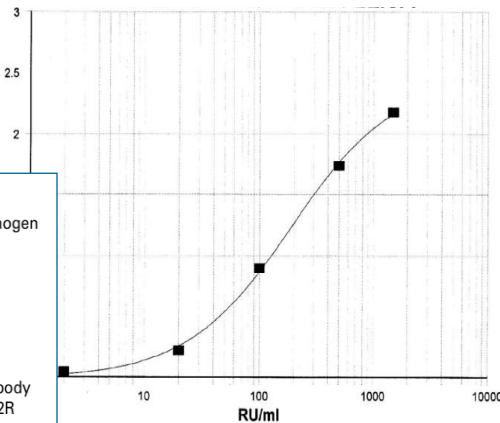
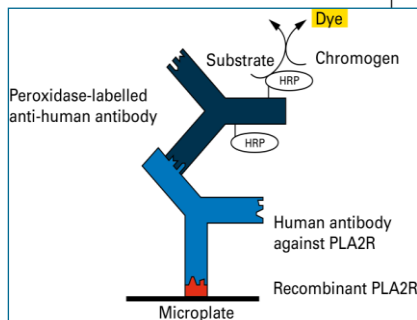
Beck et al. NEJM 2009

Immunofluorescence (IIFT)



©Euroimmun AG

Elisa



©Euroimmun AG

Kanigicherla in house ELISA

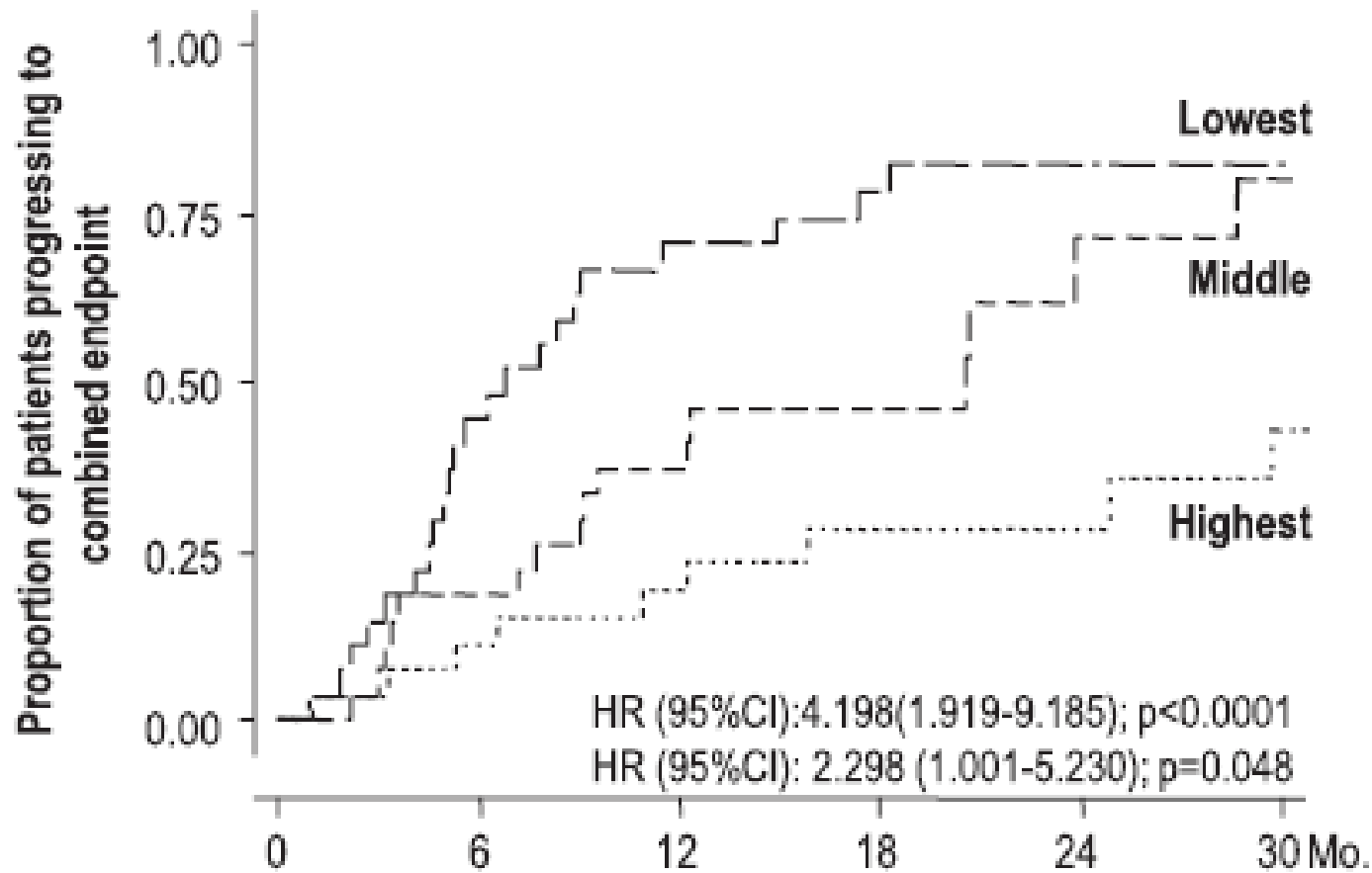
(73% positives)

High antibody titers: low likelihood of spontaneous remission

Outcome	low (n=26)	medium (n= 26)	high (n=27)	p-value
Part.remission	11	8	11	ns
Compl.remission	7	9	8	ns
Renal failure	1	3	5	ns
Spont. remission	10	8	1	<0.01

Hofstra, JASN 2012; in house ELISA

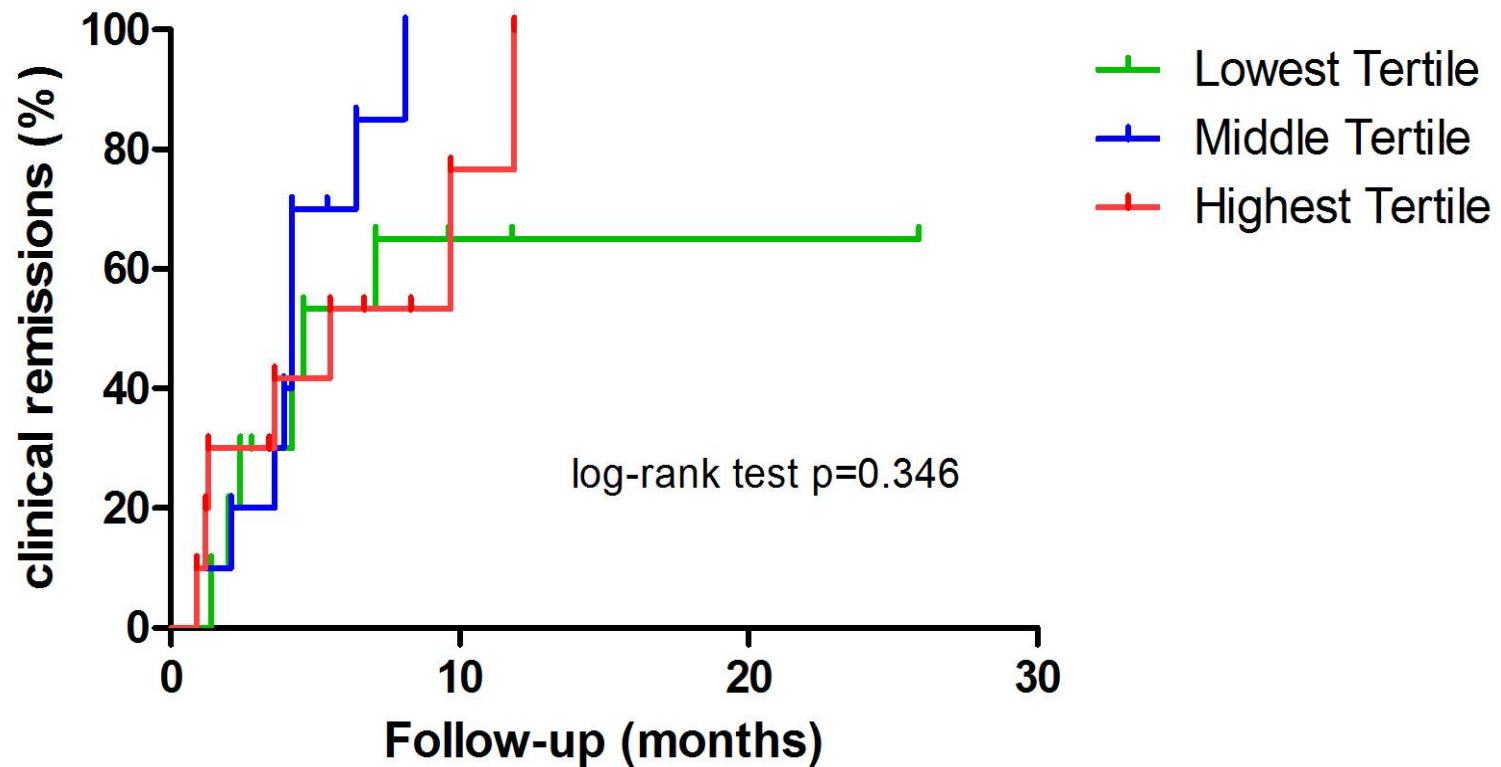
Rituximab is not effective in patients with high aPLA2R levels



Ruggenti, JASN 2015

Cyclophosphamide is effective independent of aPLA2R levels

FIGURE 1: Cumulative incidence of remission

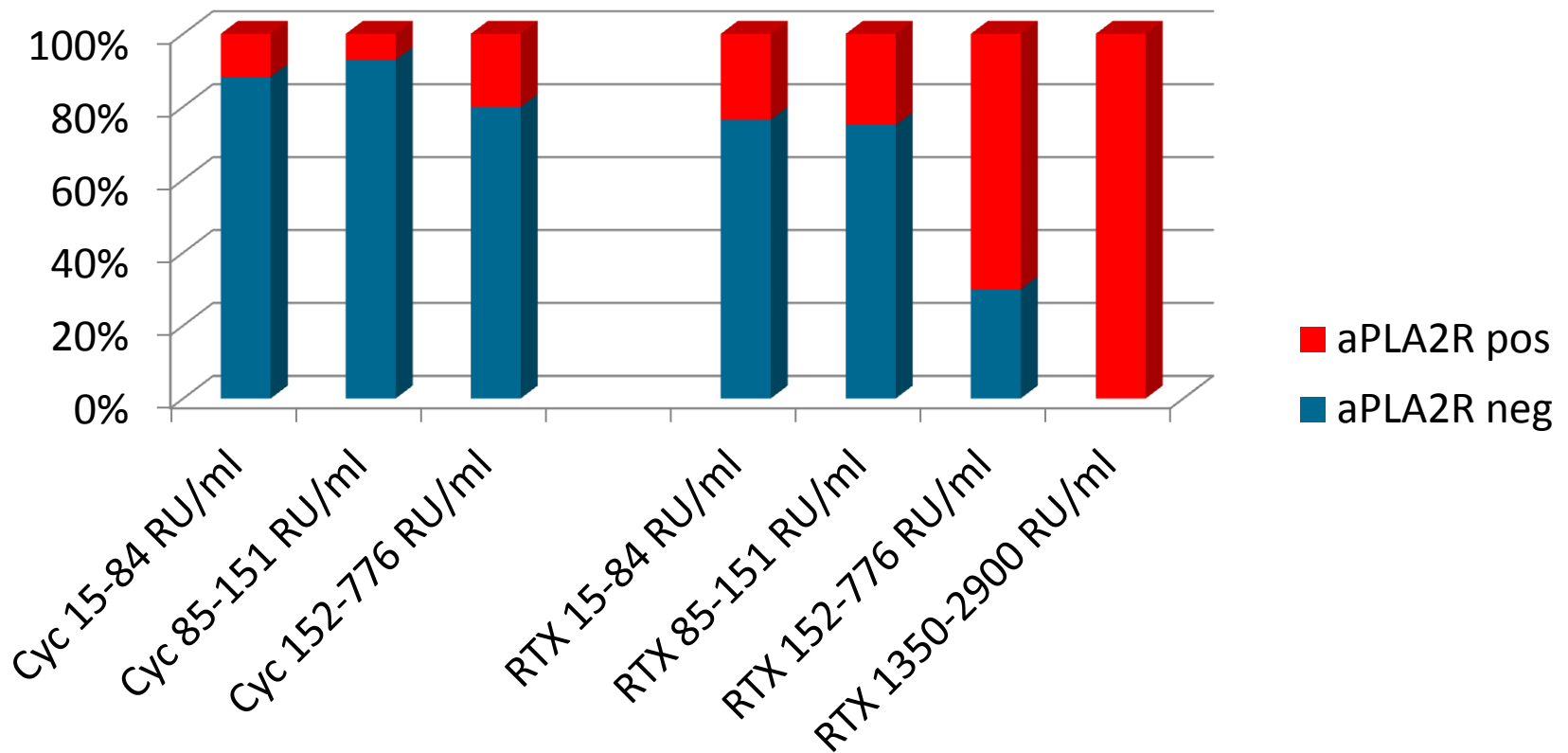


van de Logt SA-PO 631, kidney week 2016

Research question

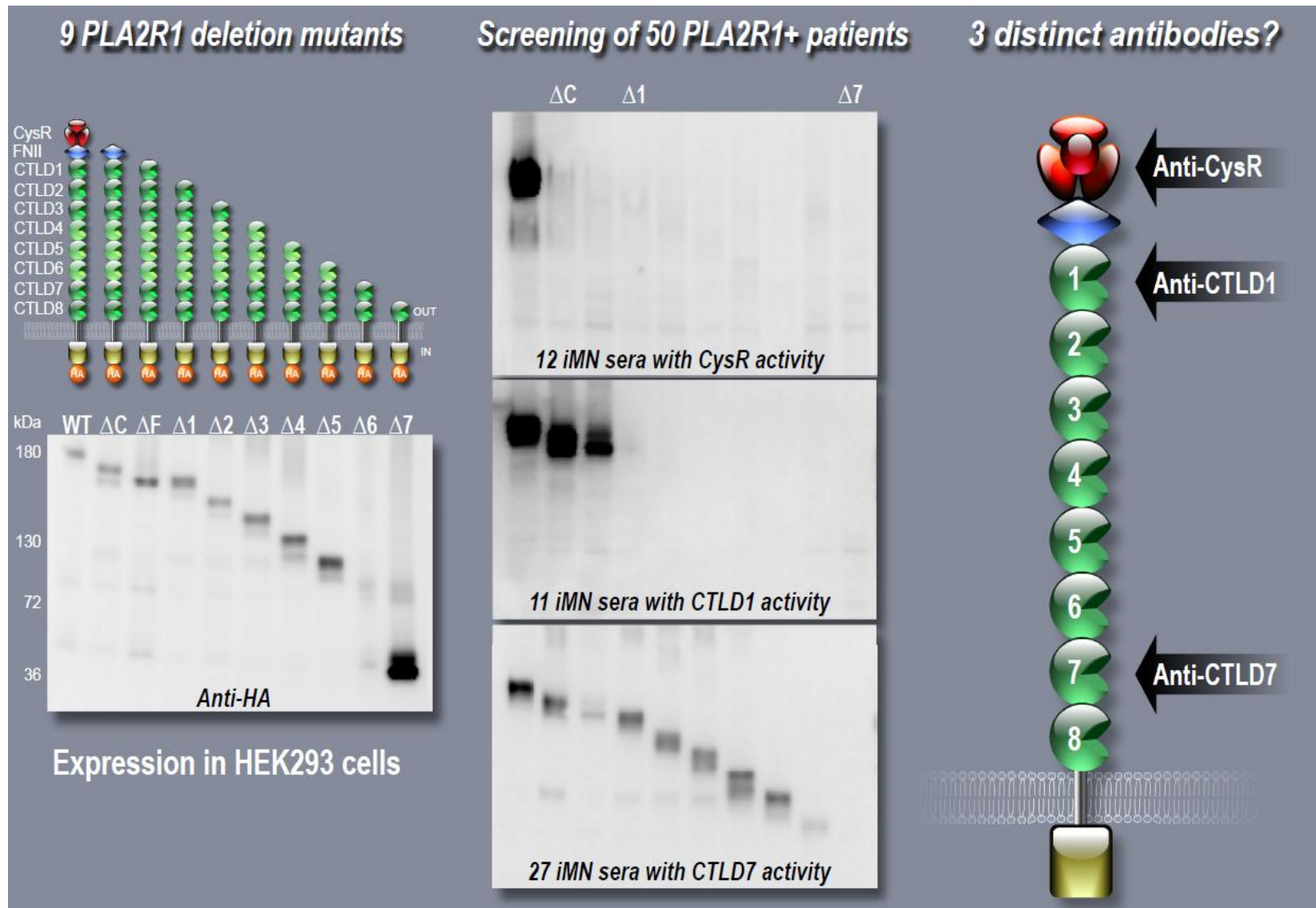
Is rituximab less effective than cyclophosphamide in inducing an immunological and clinical remission in patients with membranous nephropathy and a high aPLA2R titer?

Results: disappearance of aPLA2R after 6 months



van de Logt et al, KI 2018

Epitope-specific antibodies



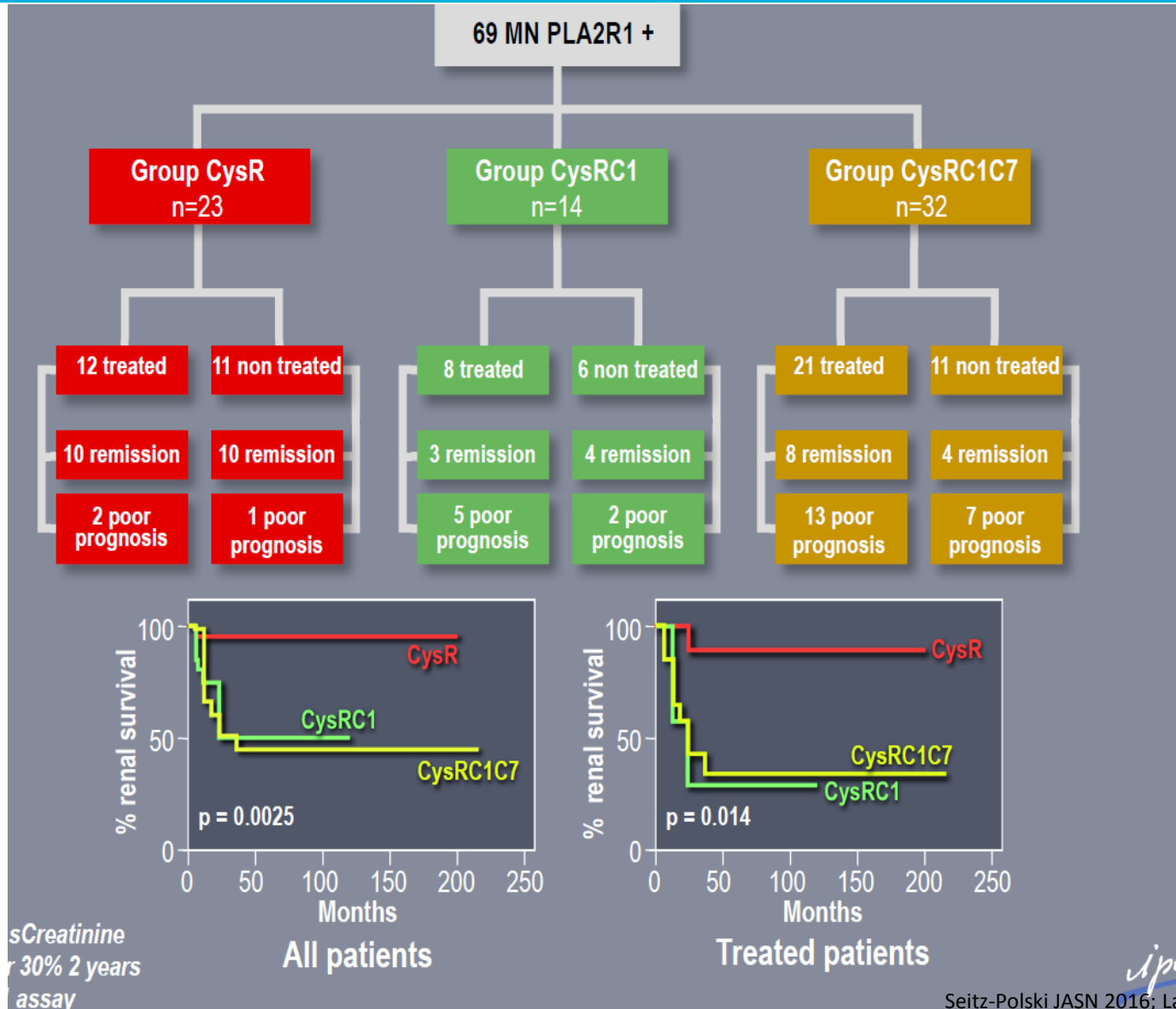
Seitz-Polski JASN 2016; Lambeau ASN 2016

Epitope-specific antibodies

Comparison between the 3 groups

	CysR	CysRC1	CysRC1C7	p value
Age	48±12	54±16	61±15	0.008
Sex	19M/4F	10M/4F	25M/7F	ns
Anti-PLA2R1 titer (EIV)	3175 (394-8043)	1625 (367-5947)	4288 (210-50,817)	ns
Proteinuria (g/g)	3.0 (0.3-5.1)	3.0 (0.8-10.6)	5.0 (0.3-24.0)	0.02
sCreatinine (μmol/L)	92 (45-149)	96 (43-280)	100 (59-926)	ns
Follow-up (months)	36 (12-201)	44 (12-133)	33 (12-216)	ns
Spontaneous remission	10/23 (43%)	4/14 (29%)	4/32 (12%)	0.03
Hemodialysis	0/23	2/14	10/32	0.01

Epitope-specific antibodies



Seitz-Polski JASN 2016; Lambeau ASN 2016

Natural history of iMN and epitope spreading associated with severity: a working hypothesis

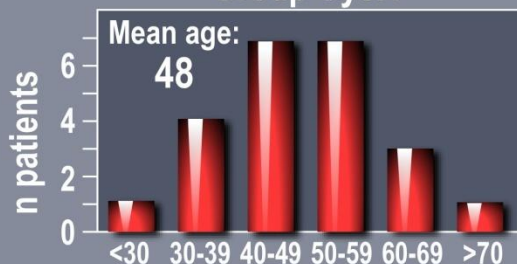
First event

No evolution

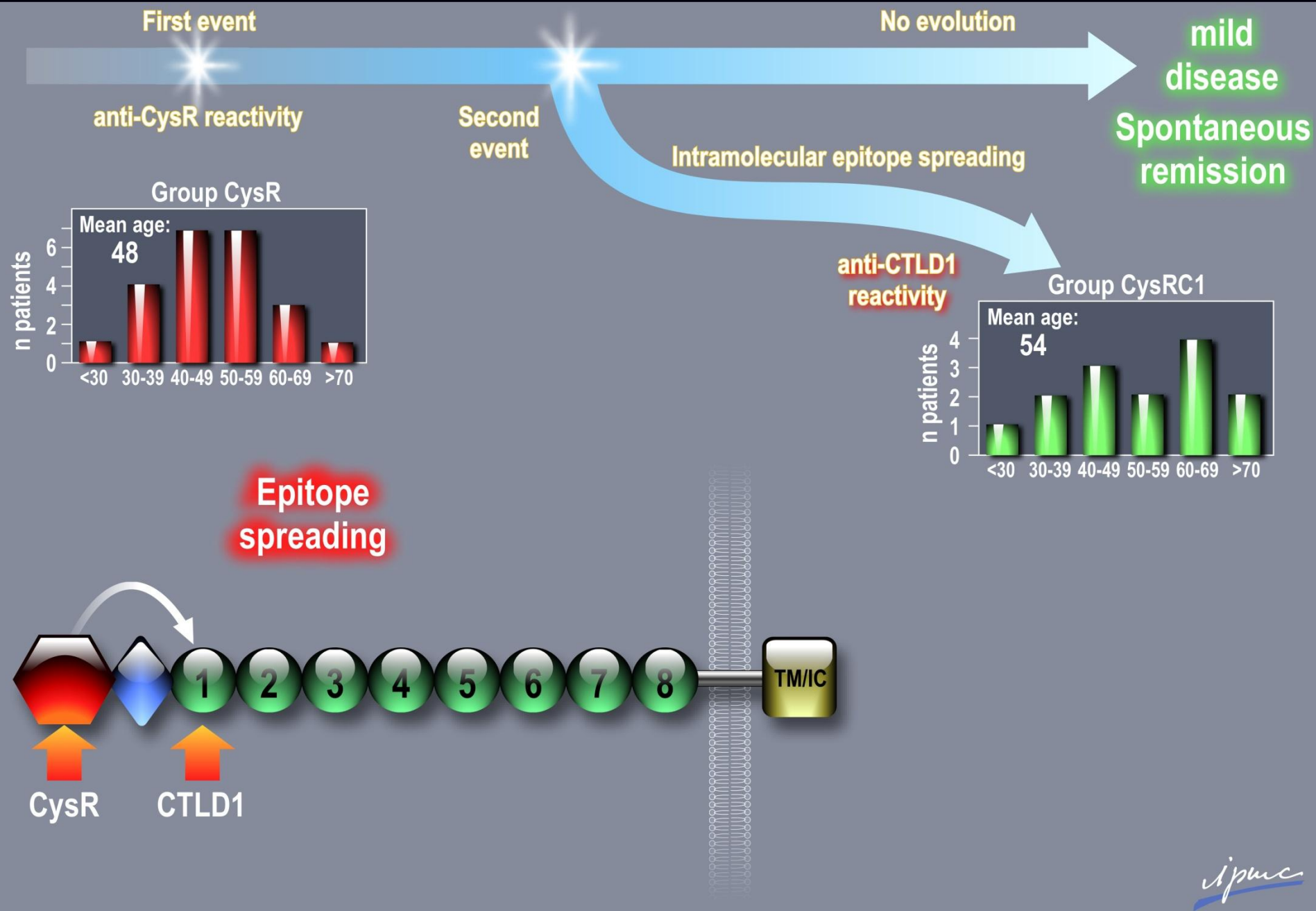
anti-CysR reactivity

mild
disease
Spontaneous
remission

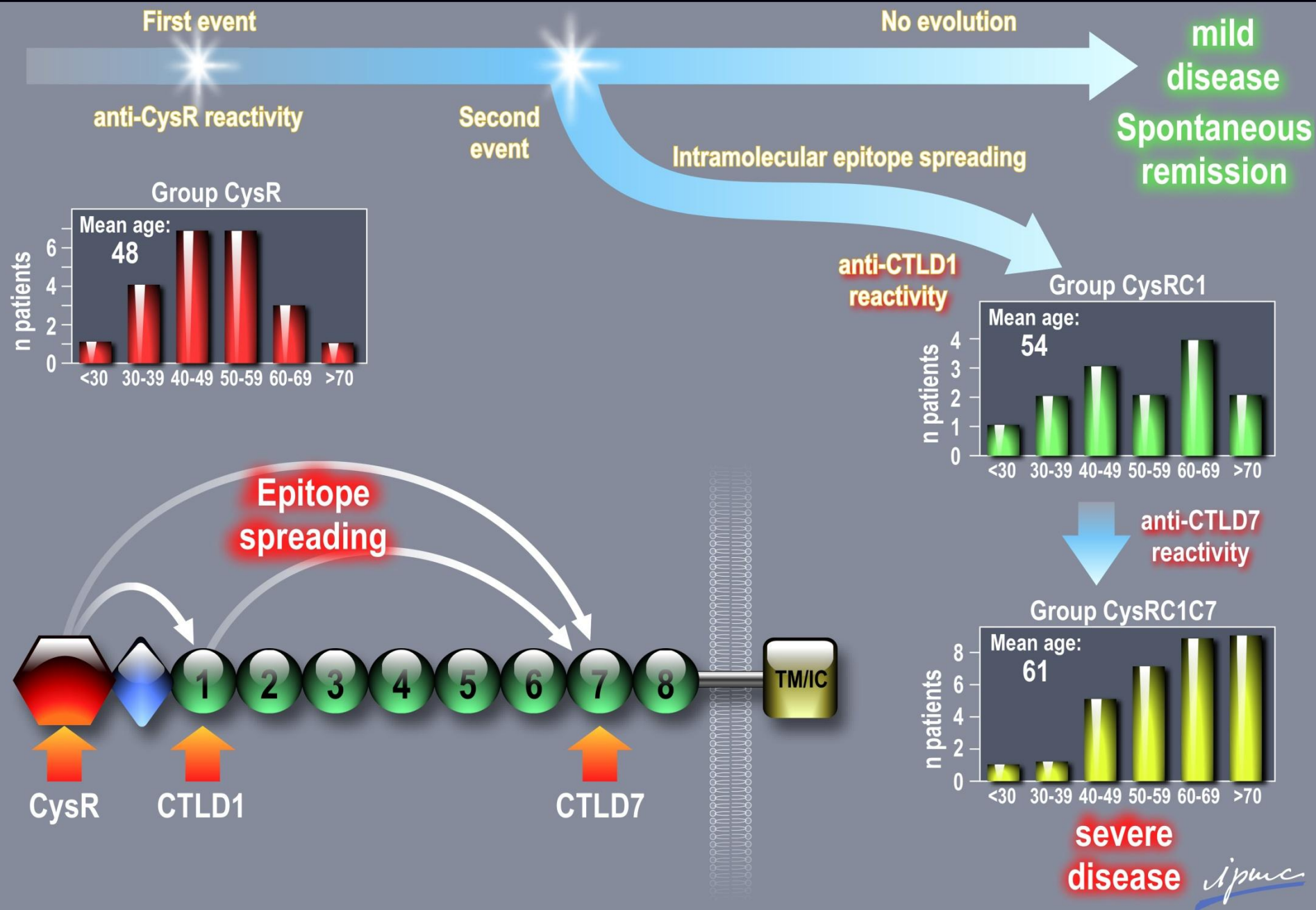
Group CysR



Natural history of iMN and epitope spreading associated with severity: a working hypothesis

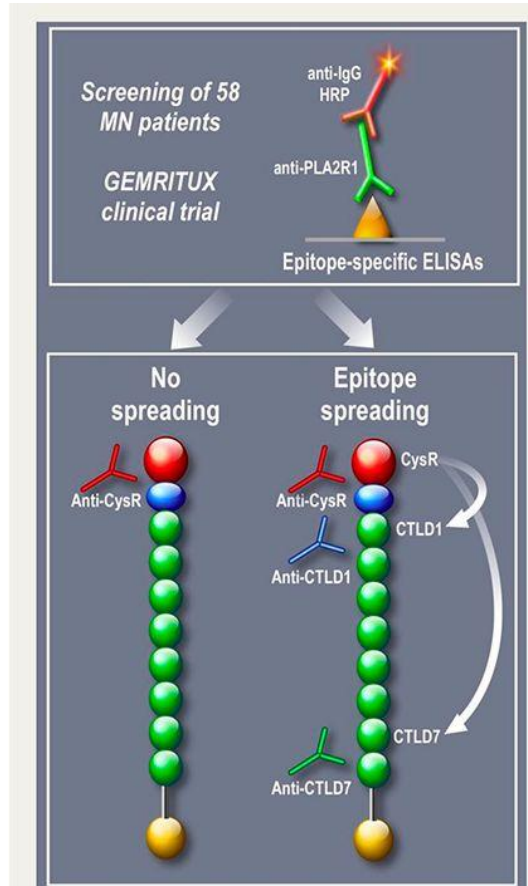


Natural history of iMN and epitope spreading associated with severity: a working hypothesis



Anti-PLA2R antibodies: epitope-specificity as predictors?

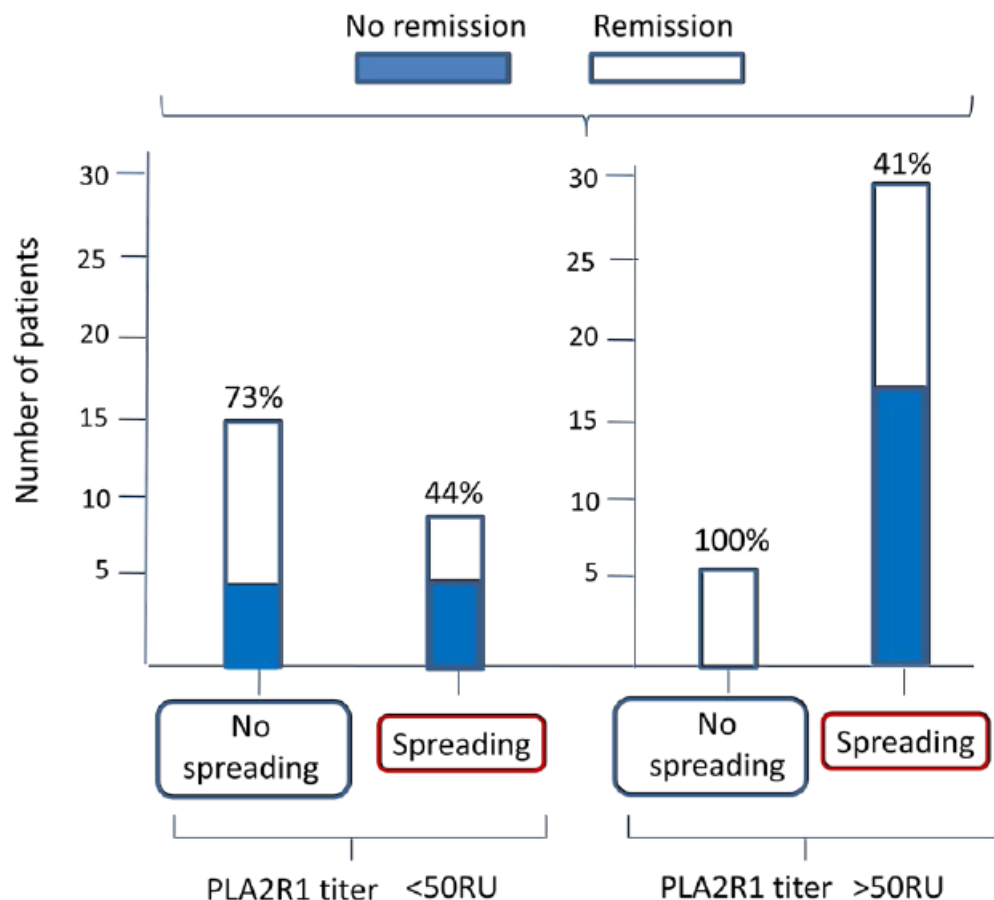
Anti-CysR = non spreading
 Anti-CysR + anti CTLD1/7 = spreading



	No spreading (n=20)	Spreading (n=38)
Age (yrs)	59 (44-62)	52(41-64)
Male/Female	15/5	27/11
PLA2Rab titer (RU/ml)	32 (18-54)	377 (76-747)
sCreatinine (μmol/l)	NA	NA
sAlbumin (g/l)	22 (20-26)	21 (18-25)
uPCR (g/g)	7.9 (3.5-8.5)	8.3 (6.2-10.4)

Seitz-Polski, JASN 2018

Remission rate (%) at last FU according to aPLA2R titer and epitope spreading



Seitz-Polski et al, JASN 2018

Spreading vs (no) Remission

Control group	No spreading	Spreading
Remission	8	5
No Remission	3	13

Spreading predicts progression:
specificity 72 %

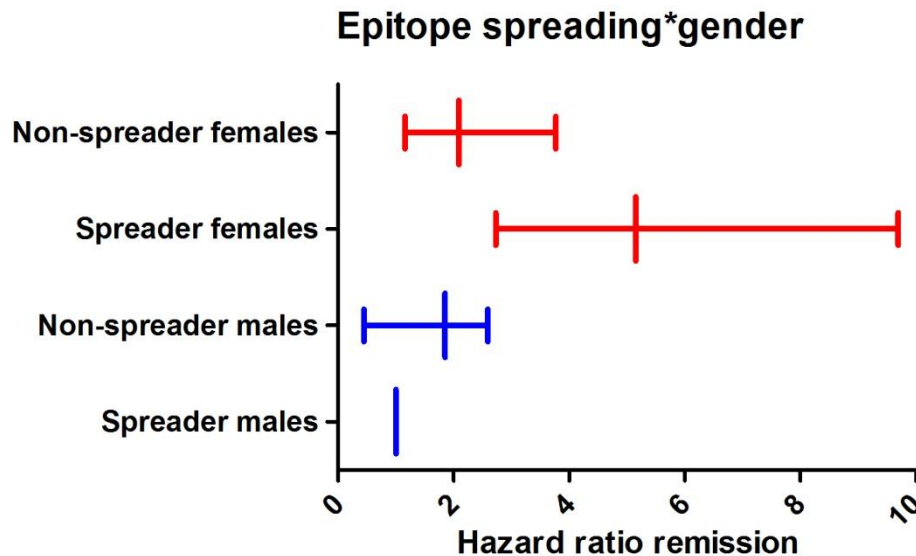
Rituximab	No spreading	Spreading
Remission	8	11
No Remission	1	9

Rituximab is not very effective in spreaders:
55 % remission rate

Seitz-Polski et al, JASN 2018

Predictive role of epitope spreading in rituximab treated patients?

- 117 Italian rituximab-treated patients with nephrotic syndrome and PLA2R-related MN.
- Higher aPLA2R titer > higher proportion of spreaders. Titer > 400 RU/l: all spreaders. They suggest an additional role beyond and over aPLA2R titer.



Brglez et al, ASN Kidney week 2018 FR-OR080

Conclusions

- Anti-PLA2R antibodies: more than one epitope.
- The added value of antibody titer and epitope spreading over and beyond traditional biomarkers for **predicting spontaneous remission** is negligible.
- Baseline aPLA2R titer **predicts response to treatment** in MN.
- Epitope spreading may **predict response to treatment**. The added value of epitope spreading over aPLA2Rab titer, and the accuracy of PLA2Rab titer needs to be investigated in larger cohorts.

Spreading vs (no) Remission

Control group	No spreading	Spreading
Remission	8	5
No Remission	3	13

Spreading predicts progression:
specificity 72 %

Seitz-Polski et al, JASN 2018



ANY
QUESTIONS
?

Baseline characteristics

	Cyclophosphamide (n=52)	Rituximab (n=39)	Rituximab* (n=7)
Elisa titer RU/ml (range)	102 (15-776)	91 (17-747)	1498 (1350-2900)
Male/Female	38/14	27/12	4/3
Age (years)	58 (42-66)	56 (42-65)	63 (36-69)
sCreatinine (μmol/l)	132 (99-154)	108 (87-146)	87 (77-127)
sAlbumin (g/l)	20 (16-25)	22 (18-27)	20 (15-24)
uPCR (g/10 mmol creat)	9.1 (6.2-13.2)	9.4 (5.2-12.3)	9.6 (4.8-10.2)
Previous IS therapy	6	4	0

van de Logt et al, KI 2018