Zhi-Hong Liu, MD, PhD

- Zhi-Hong Liu, MD, PhD, is Professor of medicine; Academician of Chinese Academy of Engineering; Dean of Nanjing University School of Medicine; Director of National Clinical Research Center of Kidney Disease, Jinling Hospital, Nanjing University School of Medicine; Councilor of International Society of Nephrology (ISN).
- She has published 600 articles, edited 4 books on kidney disease, and contributed chapters to the textbooks on nephrology. She is the chief scientist of the National Basic Research Program of China (973 Program), and was honored with the National Science and Technology Progress Award of China.

Clinical Practice of IgA Nephropathy and Lupus Nephritis in China

Zhi-Hong Liu

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Primary Glomerulonephritis

(n=18813, 2000-2010 , Nanjing)

	n	%
IgAN	8580	45.61
FSGS	2400	12.87
MN	2422	12.76
IgMN	240	1.28
MPGN	242	1.29
EnPGN	213	1.13

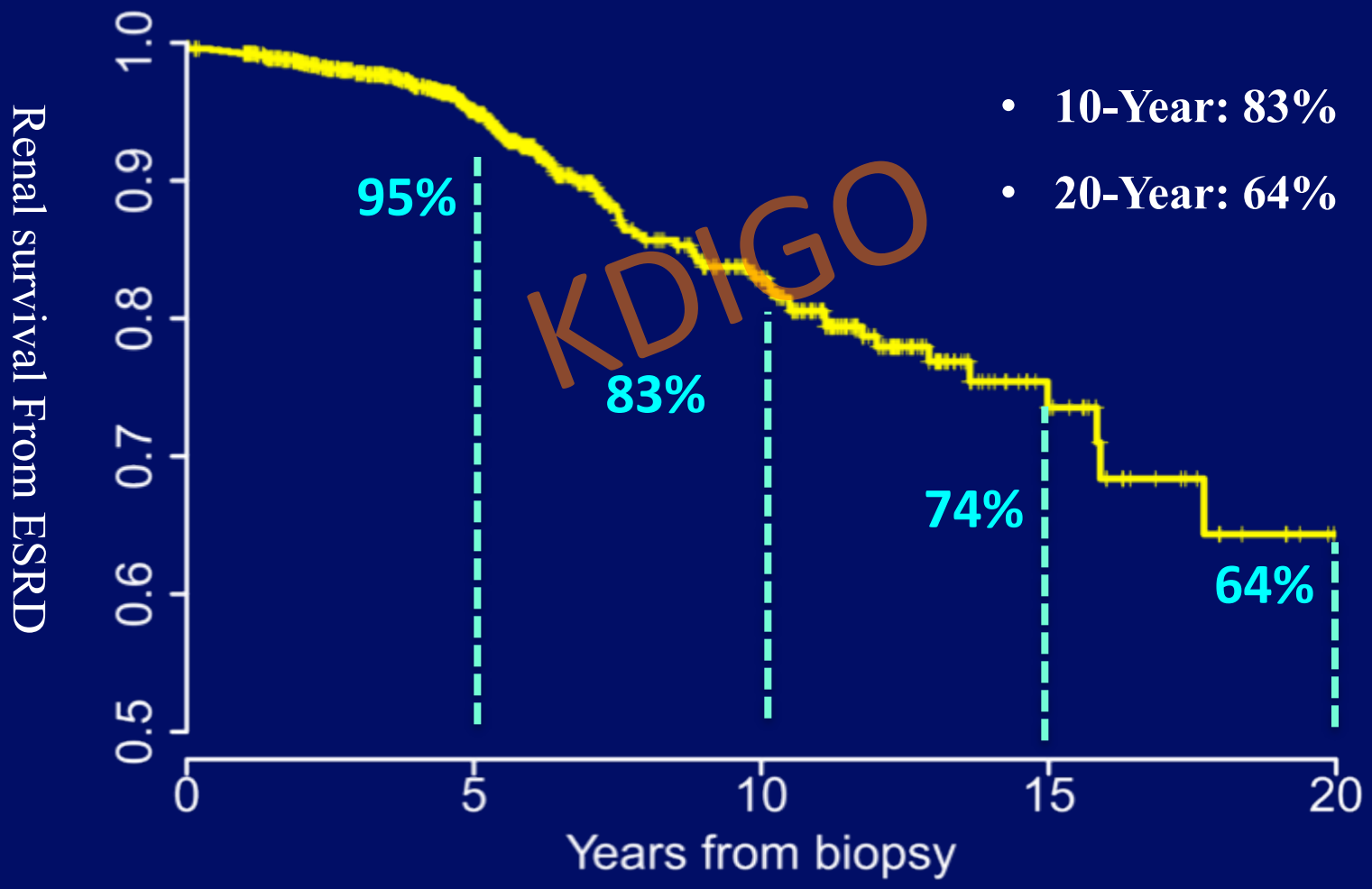
Secondary glomerular disease

(n= 5162 : 2000-2010)

	n	%
Lupus Nephritis	**2970**	**57.53**
Hernch-Schonlein purpura	1784	34.56
Systemic Vasculitis	228	4.42
HUS/TTP	69	1.34
Rheumatoid arthritis	31	0.6
Sjögren's syndrome	80	1.55

- A frequently progressive form of glomerular diseases, exhibiting diverse renal pathology and clinical expression
- Who develops persistent and progressive disease? How can they best be identified early in the course of disease? (Pathology/Clinical)
- Facilitate the identification of the features that may predict response to specific treatments, and refine recruitment to clinical trials by their risk of progression

Renal survival of Chinese Patients with IgAN (1155 Cases)



WeiBo Le, Zhihong Liu, et al Nephrol Dial Transplant (2012) 27: 1479–1485

Five key determinants of renal survival in IgAN

	Multivariate Cox regression	
	HR(95% CI)	P
Urinary protein>1.0g/d	3.3(2.2-4.9)	<0.001
Hypertension (>140/90mmHg)	1.9(1.3-2.7)	<0.001
eGFR<60ml/min per 1.73m^2	2.6(1.4-2.8)	<0.001
Hypoalbuminemia	2.0(1.4-2.8)	<0.001
Hyperuricemia	1.8(1.2-2.6)	0.002

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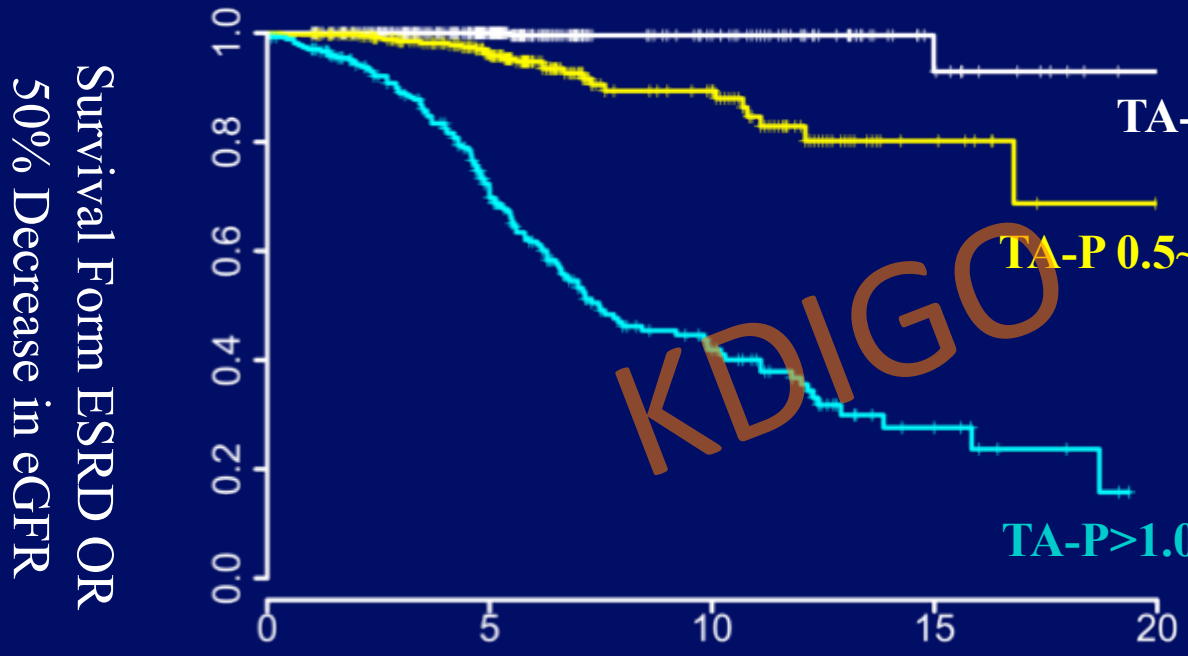
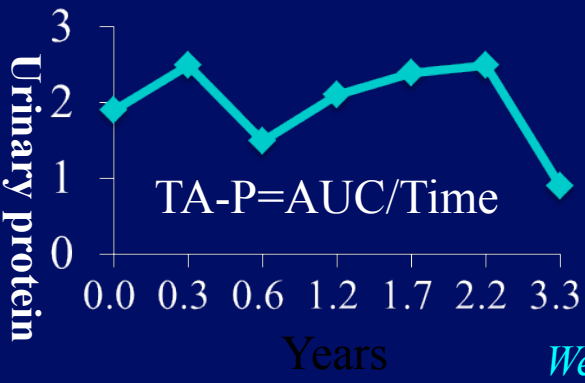
Time-average proteinuria (TA-P) and renal survival





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The predictors of renal survival from data during the Follow-up period

Predictors	Univariate Cox regression		MultivariateCox regression△	
	HR(95% CI)	P Value	HR(95% CI)	P Value
TA-P	1.8(1.7-1.9)	<0.001	1.8(1.6-1.9)	<0.001
TA-MAP	1.04(1.03-1.06)	<0.001	1.03(1.01-1.04)	<0.001
TA-RBC	1.3（1.1-1.7）	0.01	2.1（1.6-2.7）	<0.001

TA-P： Time-average proteinuria
TA-MAP： Time-average mean arterial blood pressure
TA-RBC： Time-average hematuria

The Oxford Classification of IgA Nephropathy

Present in ≤50% of the glomeruli	M0
Present in >50% of the glomeruli	M1
Segmental glomerulosclerosis	
Absent	S0
Present	S1
Endocapillary hypercellularity	
Absent	E0
Present	E1
Tubular atrophy/interstitial fibrosis	
0–25% of cortical area	T0
26–50% of cortical area	T1
>50% of cortical area	T2

nature reviews | nephrology2009,5:557-559

AJKD
Original Investigation

A Multicenter Application and Evaluation of the Oxford Classification of IgA Nephropathy in Adult Chinese Patients

Cai-Hong Zeng, PhD,[1] Weibo Le, MD,[1]* Zhaohui Ni, PhD,[2] Minfang Zhang, PhD,[2] Lining Miao, PhD,[3] Ping Luo, PhD,[3] Rong Wang, MD,[4] Zhimei Lv, PhD,[4] Jianghua Chen, MD,[5] Jiong Tian, PhD,[5] Nan Chen, PhD,[6] Xiaoxia Pan, MD,[6] Ping Fu, PhD,[7] Zhangxue Hu, MD,[7] Lining Wang, MD,[8] Qiuling Fan, PhD,[8] Hongguang Zheng, PhD,[9] Dewei Zhang, MD,[9] Yaping Wang, MD,[10] Yanhong Huo, MD,[10] Hongli Lin, MD,[11] Shuni Chen, MS,[11] Shiren Sun, PhD,[12] Yanxia Wang, MD,[12] Zhangsuo Liu, PhD,[13] Dong Liu, MD,[13] Lu Ma, MD,[14] Tao Pan, MD,[14] Aiping Zhang, MD,[15] Xiaoyu Jiang, MD,[15] Changying Xing, PhD,[16] Bing Sun, PhD,[16] Qiaoling Zhou, MD,[17] Wenbing Tang, MD,[17] Fuyou Liu, MS,[18] Yinghong Liu, PhD,[18] Shaoshan Liang, MD,[1] Feng Xu, MD,[1] Qian Huang, MD,[1] Hongbing Shen, PhD,[19] Jianming Wang, PhD,[19] Yu Shyr, PhD,[20] Sharon Phillips, MS,[20] Stéphan Trojanov, MD,[21] Agnes Fogo, MD,[22] and Zhi-Hong Liu, MD[1]*

Background: The Oxford classification of immunoglobulin A (IgA) nephropathy (IgAN) provides a histopathologic grading system that is associated with kidney disease outcomes independent of clinical features. We evaluated the Oxford IgAN classification in a large cohort of patients from China.

Study Design: Retrospective study.

Setting & Participants: 1,026 adults with IgAN from 18 referral centers in China. Inclusion criteria and

Caihong Zeng, Zhihong Liu et al :Am J Kidney Dis. 2012;60(5):812-820

A Multi-center Validation of the Oxford Classification of IgAN in Chinese patients

- We confirmed the associations of mesangial hypercellularity **(M)** and tubular atrophy/interstitial fibrosis **(T)** with kidney disease outcomes.

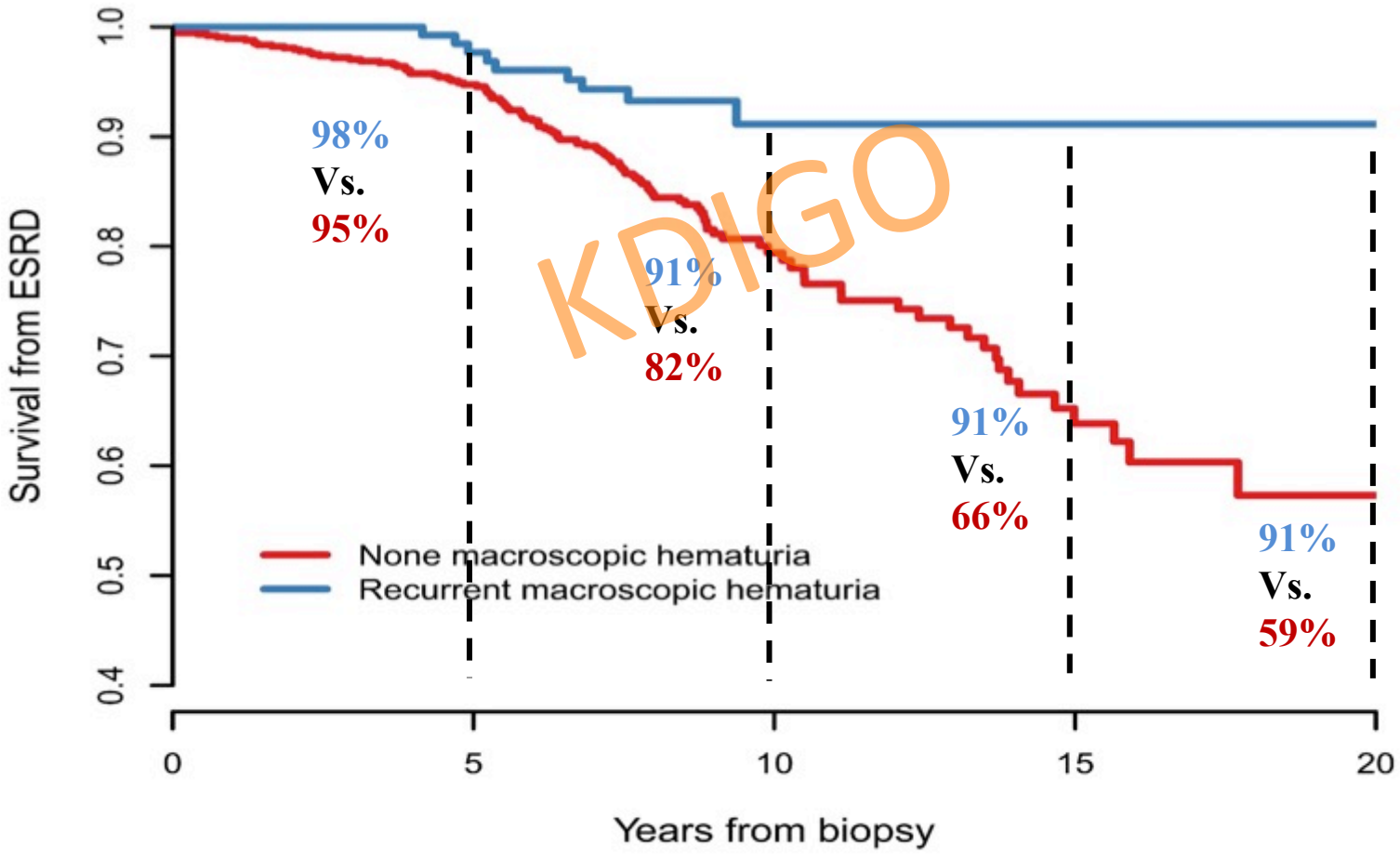
- We did not find the associations between the lesion of S,E, C, and N and disease outcomes.

Caihong Zeng, Zhihong Liu et al :Am J Kidney Dis. 2012;60(5):812-820

IgA Nephropathy

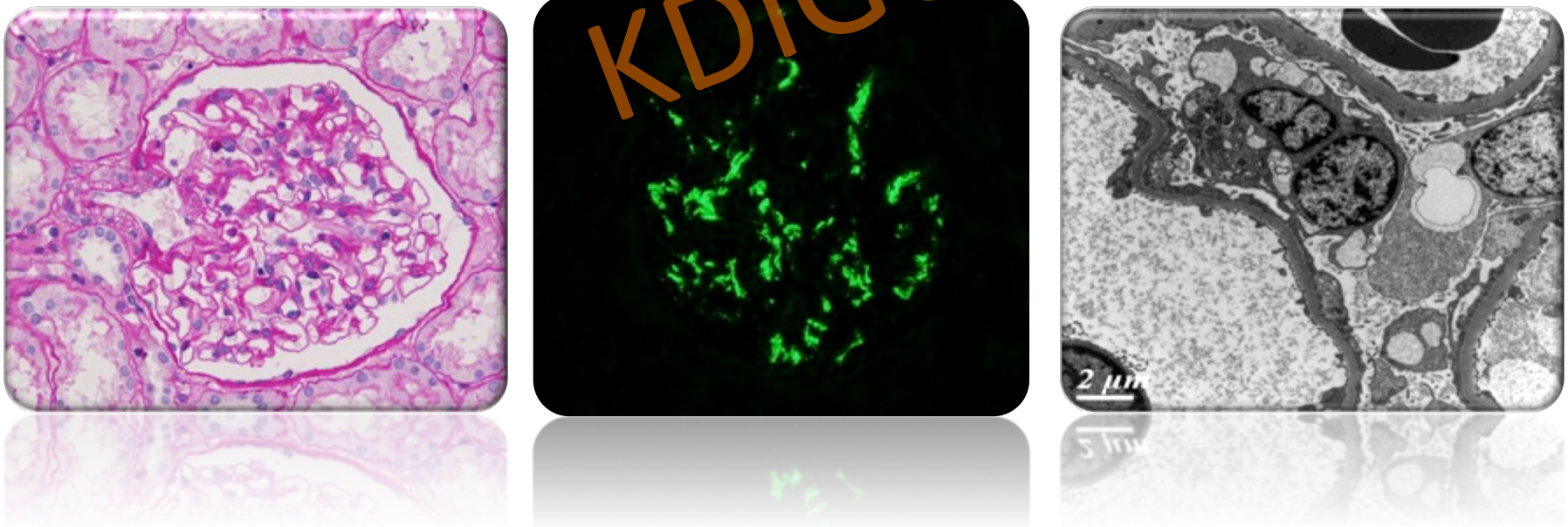
- IgAN with recurrent macroscopic hematuria
- IgAN with minimal change disease
- IgAN in elderly patients

Long-term outcome of IgAN with recurrent macroscopic hematuria

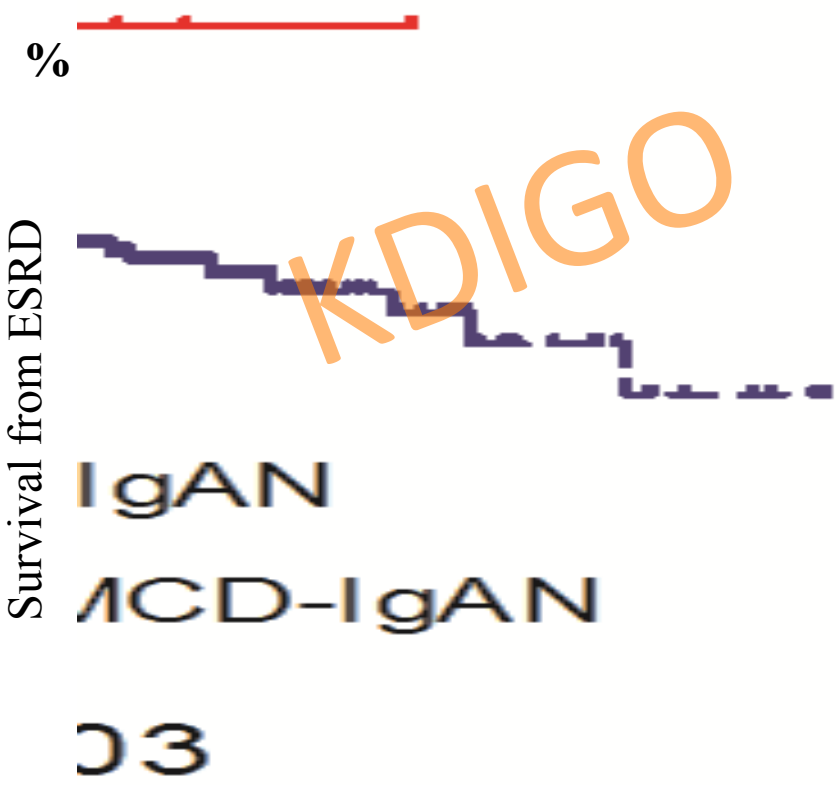


WB Le, ZH Liu et al. Am J Nephrol 2014

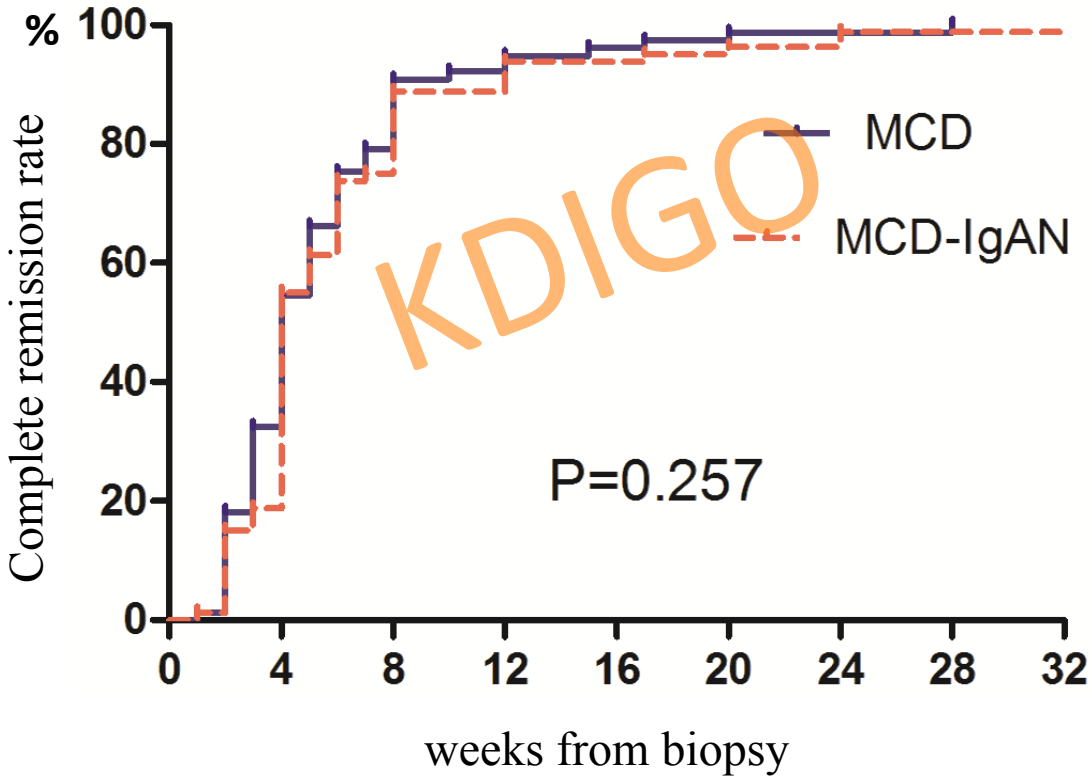
IgAN with minimal change disease



Long-term outcome of IgAN with minimal change disease

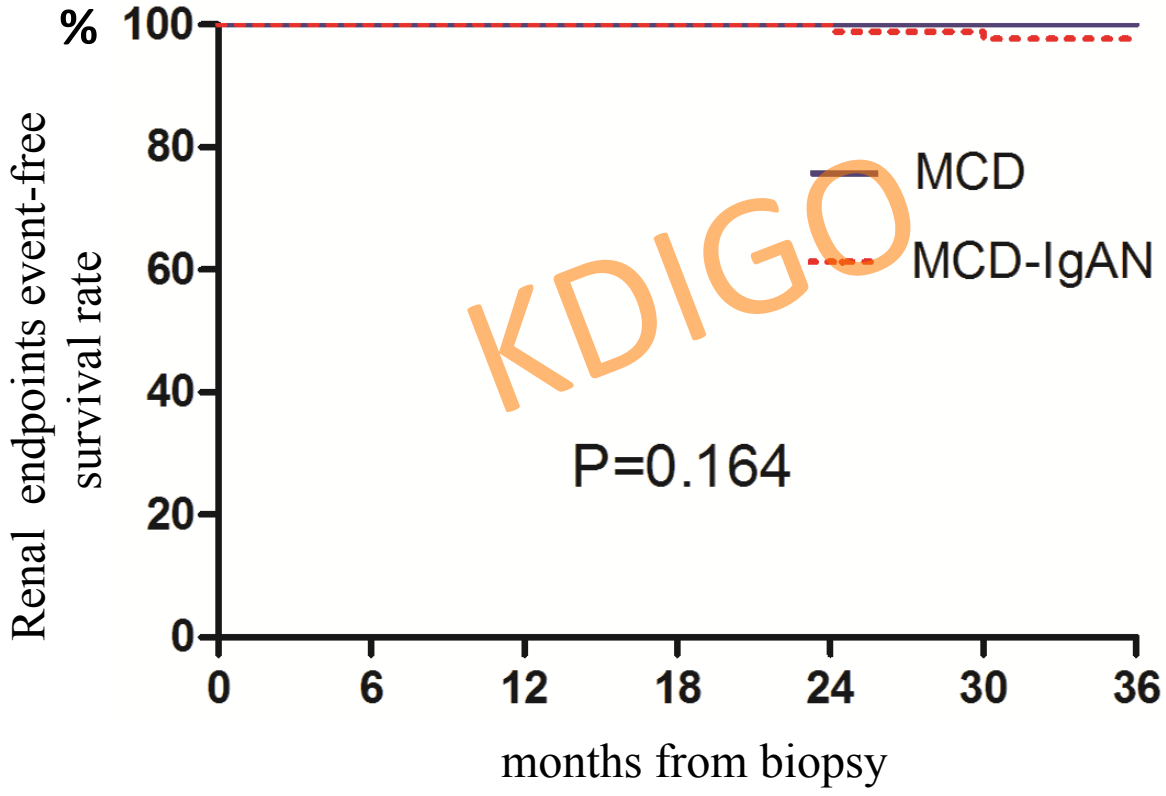


Response to steroid treatment of IgAN patients with minimal change disease



MCD: Minimal change disease （n=77)
MCD-IgAN: IgAN with minimal change disease (n=80)

Comparison of long-term outcome between patients with MCD-IgAN and MCD



MCD: Minimal change disease (n=77)
MCD-IgAN: IgAN with minimal change disease (n=80)

The spectrum of biopsy-proven kidney diseases in elderly Chinese patients

Bo Jin*, Caihong Zeng*, Yongchun Ge, Weibo Le, Honglang Xie, Hao Chen, Shaoshan Liang, Feng Xu, Song Jiang and Zhihong Liu

National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, P.R. China

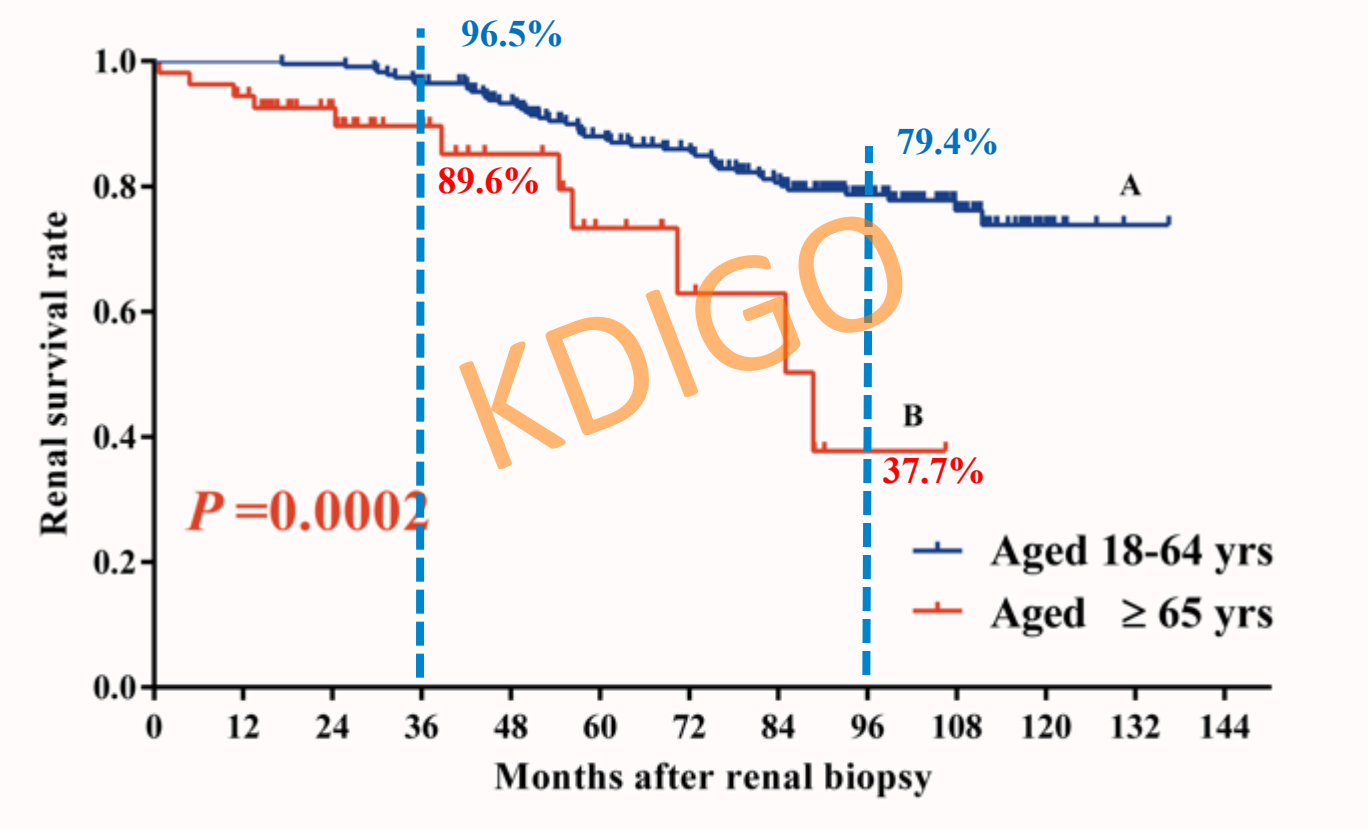
Nephrol Dial Transplant (2014) 0: 1–9

Table 1. Classification of renal diseases based on renal biopsies in elderly patients

	Number of cases	%
Primary glomerular disease	459	53.94
MN	245	28.79
IgAN	82	9.64
MCD	41	4.82
FSGS	40	4.70
MsPGN	24	2.82
IgMN	9	1.06
MPGN	7	0.82

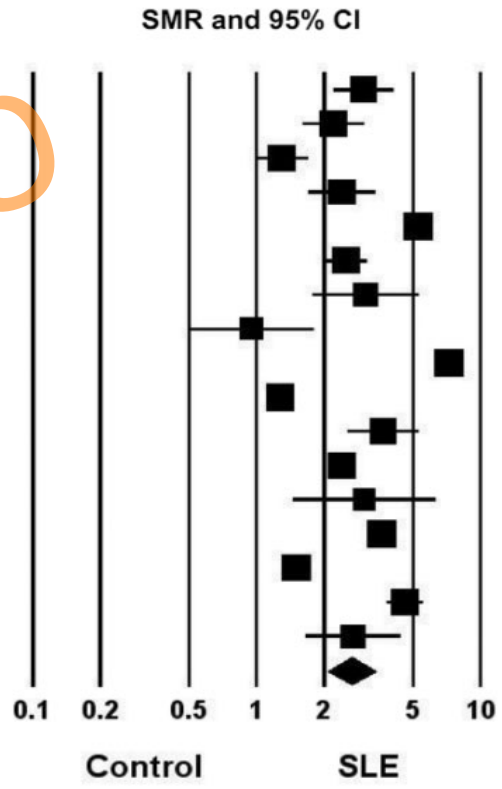
Nephrol Dial Transplant (2014) 0: 1–9

Renal survive in IgA nephropathy between elderly and non-elderly patients



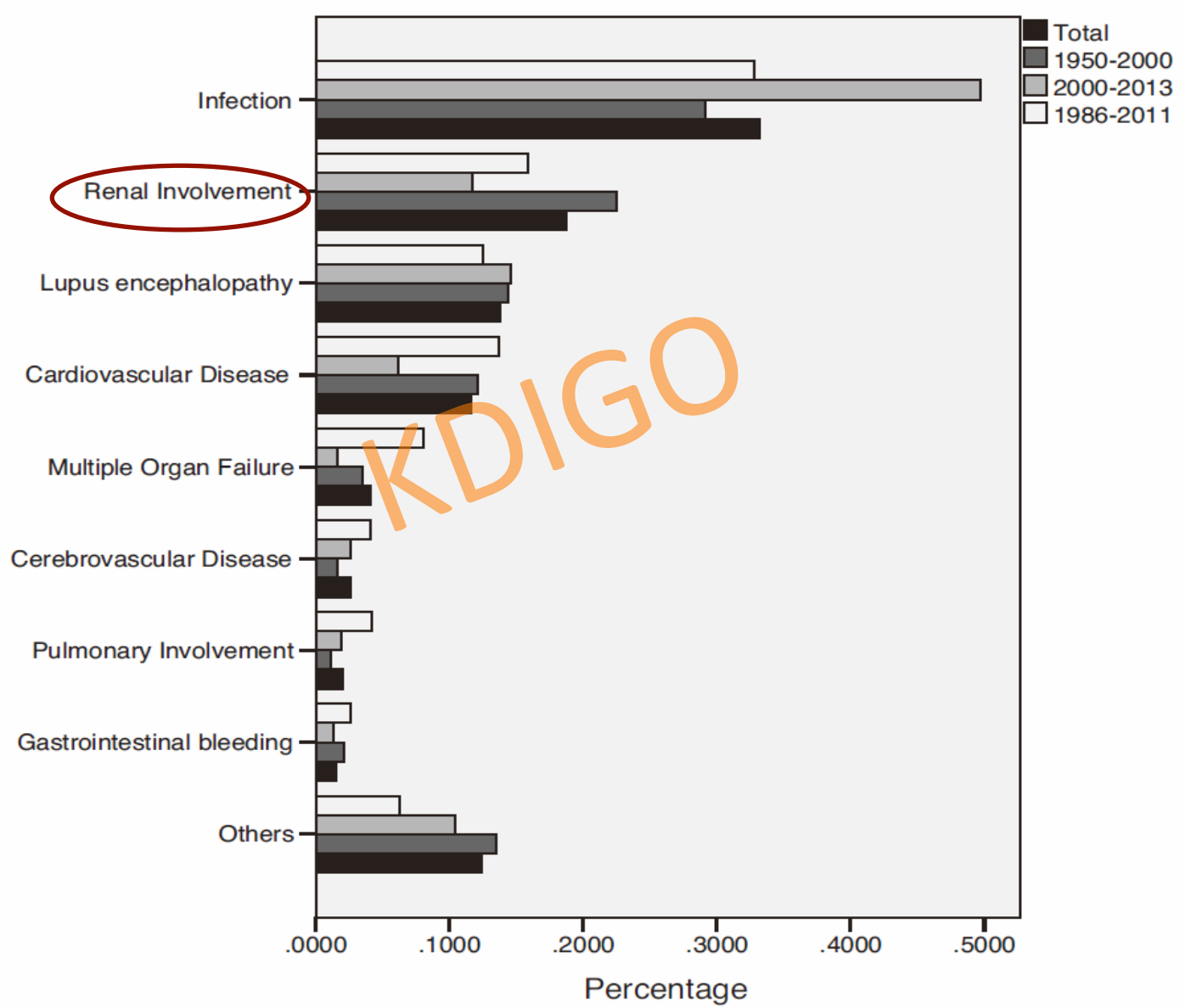
All-cause SMR was significantly increased 2.6-fold in patients with SLE

Study name	SMR	Lower limit	Upper limit	p-Value
Lerang, 2014	3.000	2.200	4.091	0.000000000
Voss, 2013	2.200	1.600	3.025	0.000001218
Yu, 2013	1.300	0.997	1.695	0.052602196
Gustafsson, 2012	2.400	1.700	3.388	0.000000649
Mok, 2011	5.250	4.775	5.772	0.000000000
Hersh, 2010	2.500	2.000	3.125	0.000000000
Hashkes, 2010	3.060	1.780	5.260	0.000052131
To-1, 2009	0.950	0.500	1.805	0.875537151
To-2, 2009	7.230	6.700	7.802	0.000000000
To-3, 2009	1.270	1.100	1.466	0.001114652
Mok, 2008	3.670	2.528	5.327	0.000000000
Bernatsky,2006	2.400	2.302	2.502	0.000000000
Chun, 2005	3.020	1.450	6.290	0.003151645
Bjornadal, 2004	3.630	3.488	3.778	0.000000000
Alamanos, 2003	1.500	1.300	1.731	0.000000028
Jacobsen, 1999	4.600	3.824	5.534	0.000000000
Uramoto, 1999	2.700	1.650	4.418	0.000077192
	2.663	2.090	3.393	0.000000000



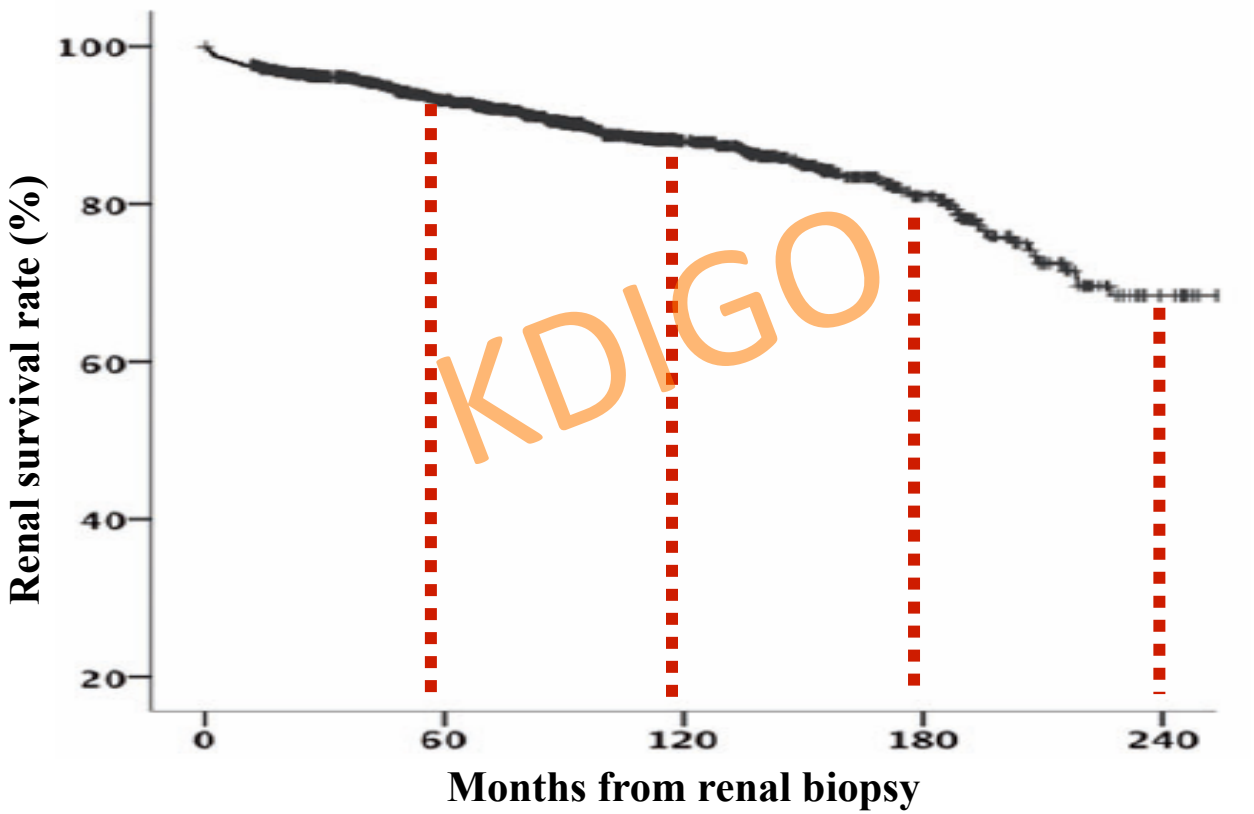
Lee YH et al, Lupus. 2016

Death Causes of SLE in China



Wang Z et al, Medicine (Baltimore). 2015

Cumulative renal survival rates in patients with LN（n=1814)



Cumulative renal survival rates	5y	10y	15y	20y
	93.1%	87.9%	81.0%	68.3%

J Yang, ZH Liu et al. Lupus; 2015

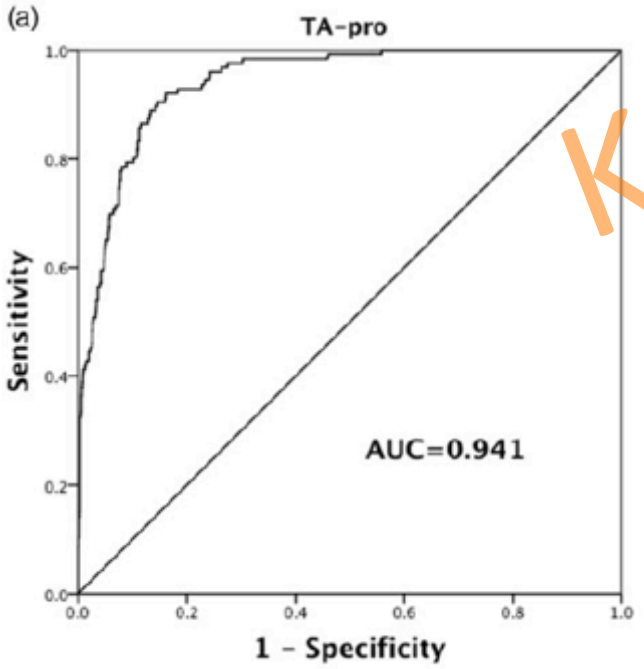
Independent risk factors for ESRD in LN（n=1814)

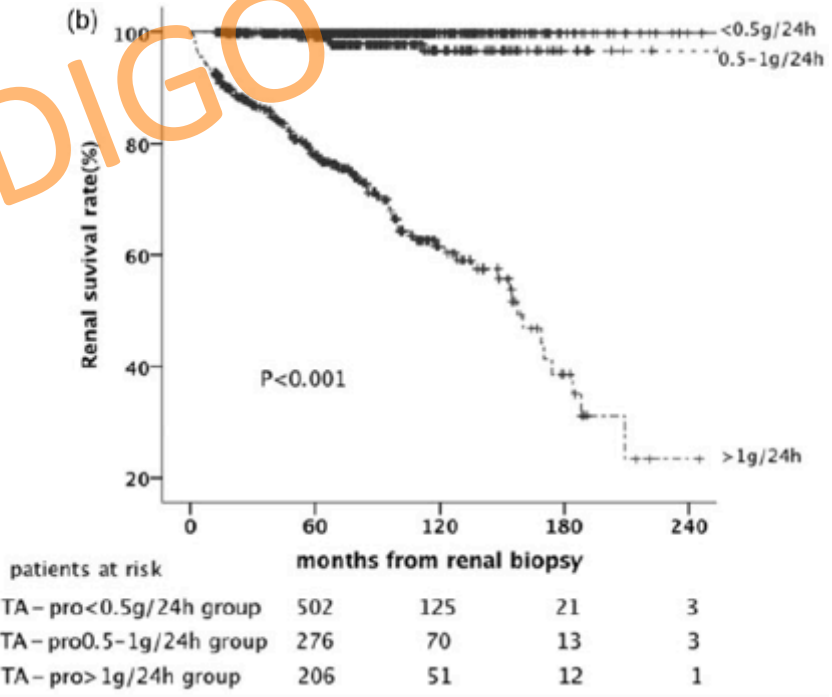
	Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P
Gender [a]	2.181 (1.580-3.011)	<0.001	2.166 (1.530-3.066)	<0.001
LN duration (months)	1.005 (1.002-1.009)	0.002	1.006 (1.002-1.009)	0.002
Mean arterial pressure (mmHg)	1.027 (1.018-1.037)	<0.001	1.016 (1.006-1.026)	0.002
24-h urinary protein (g/24 h)	1.084 (1.045-1.124)	<0.001	1.042 (1.002-1.084)	0.039
Serum creatinine (mg/dl) [b]	1.622 (1.540-1.709)	<0.001	1.509 (1.409-1.617)	<0.001
Haemoglobin (g/dl) [b]	0.788 (0.741-0.837)	<0.001	0.898 (0.840-0.961)	0.002
Serum complement C4 (g/l)	3.044 (1.278-7.250)	0.012	2.962 (1.268-6.922)	0.012

J Yang, ZH Liu et al. Lupus; 2015

The time-average proteinuria（TA-Pro）

The patients with TA-Pro 0.5–1g/24 h and TA-Pro >1 g/24 h were associated with a **12.567-fold and 237.698-fold** higher risk for ESRD than those with TA-Pro<0.5 g/24 h, respectively



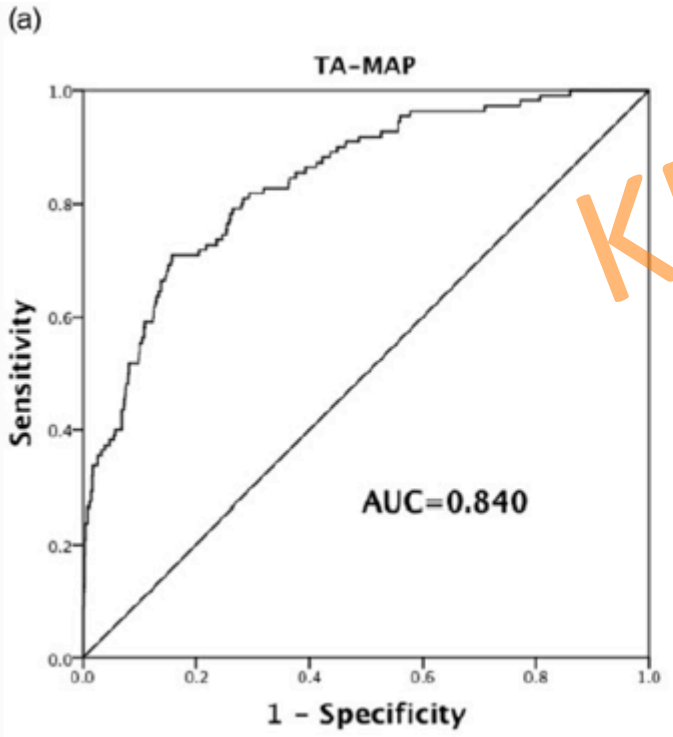


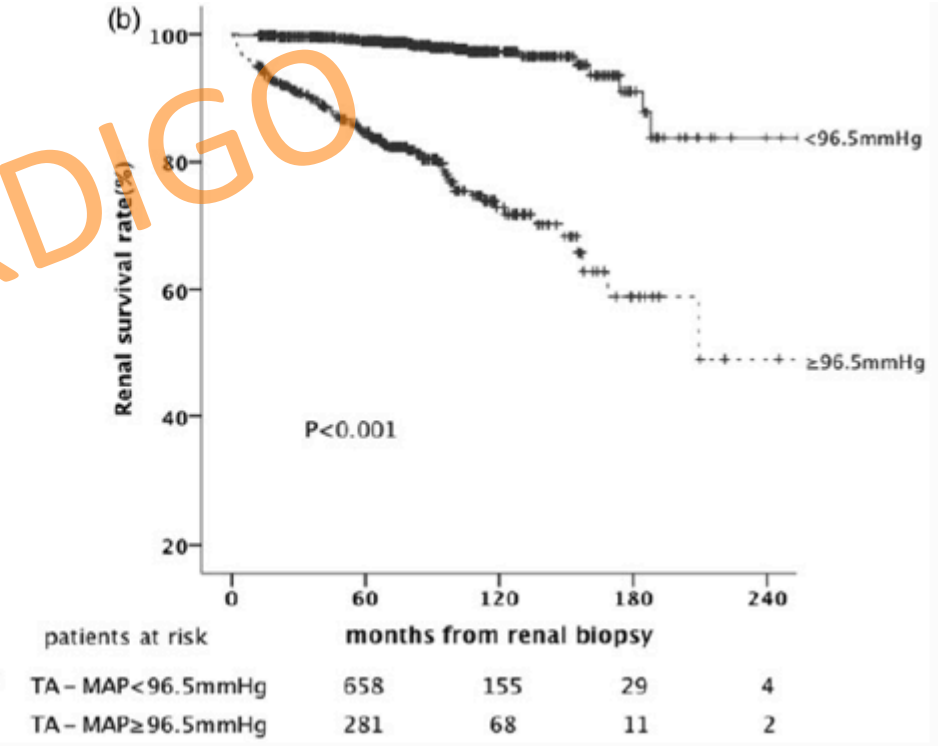
Evaluation of TA-Pro values for discriminating the patients with ESRD from the patients without ESRD

Renal survival rates in various groups

The time average mean arterial pressure (TA-MAP)

The patients with TA-MAP ≥96.5mmHg were associated with a **10.045-fold** higher risk for ESRD than those with TA-MAP<96.5 mmHg

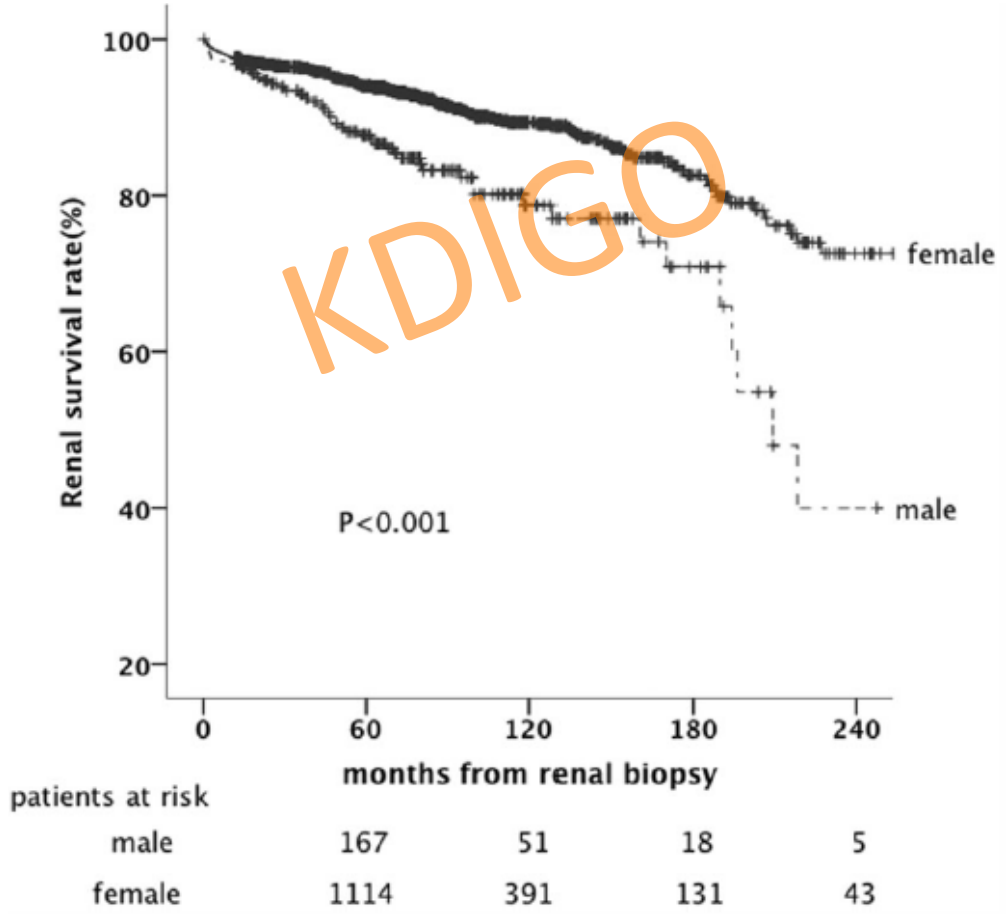




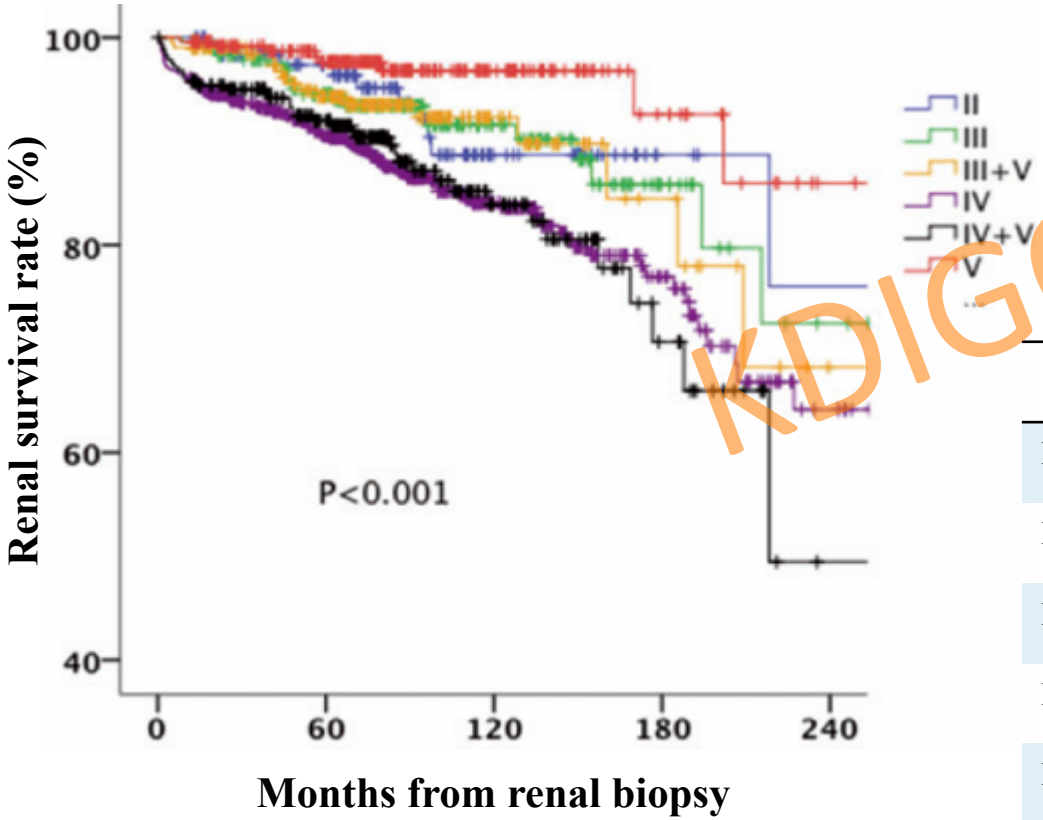
Evaluation of the TA-MAP values for discriminating the patients with ESRD from the patients without ESRD

Renal survival rates in various groups

The male patients were associated with a 2.181-fold higher risk for ESRD than the female patients



Cumulative renal survival rates in different histological classes (n=1814)



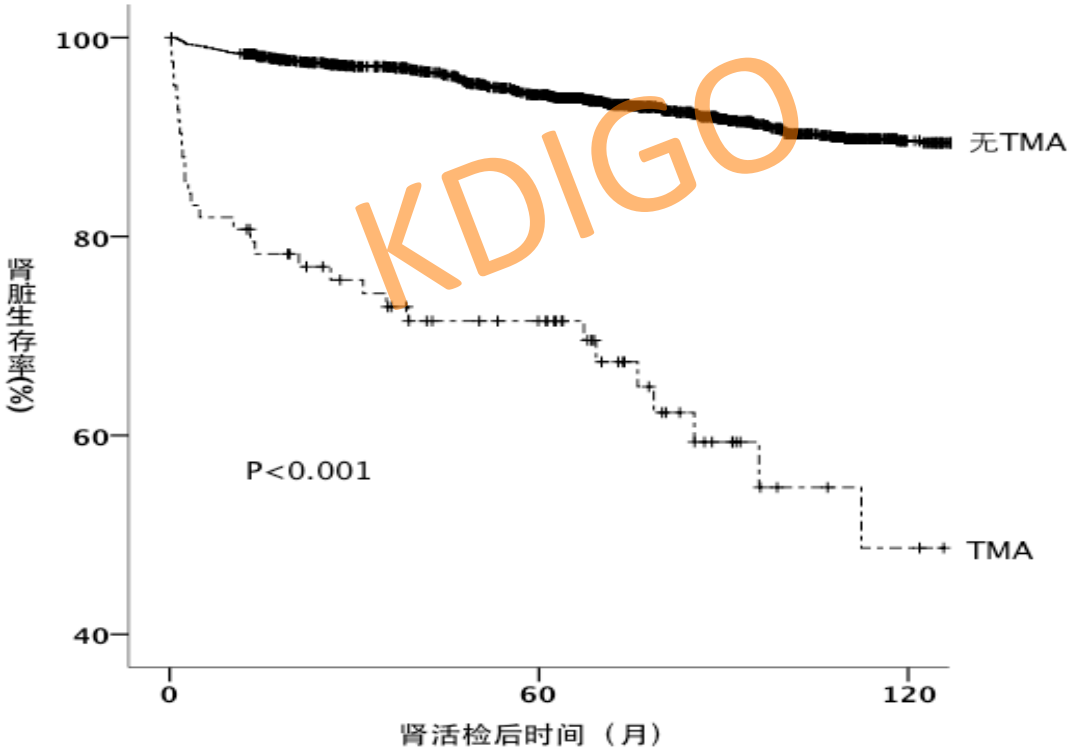
	5-yr	10-yr	15-yr	20-yr
II	97.4%	88.7%	88.7%	76.0%
III	94.5%	91.6%	85.8%	72.5%
III+V	94.3%	92.3%	84.5%	68.2%
IV	90.5%	84.1%	77.0%	64.2%
IV+V	92.0%	83.9%	70.7%	49.5%
V	97.6%	96.8%	92.6%	86.0%

The 2003 ISN/RPS classification

J Yang, ZH Liu et al. Lupus; 2015

The incidence of TMA in LN: 4.6%

LN with TMA were associated with a 5.7-fold higher risk for ESRD than those without TMA



J Yang, ZH Liu et al. Lupus; 2015

Patients with podocytopathy showed a good response to steroid therapy and good outcomes

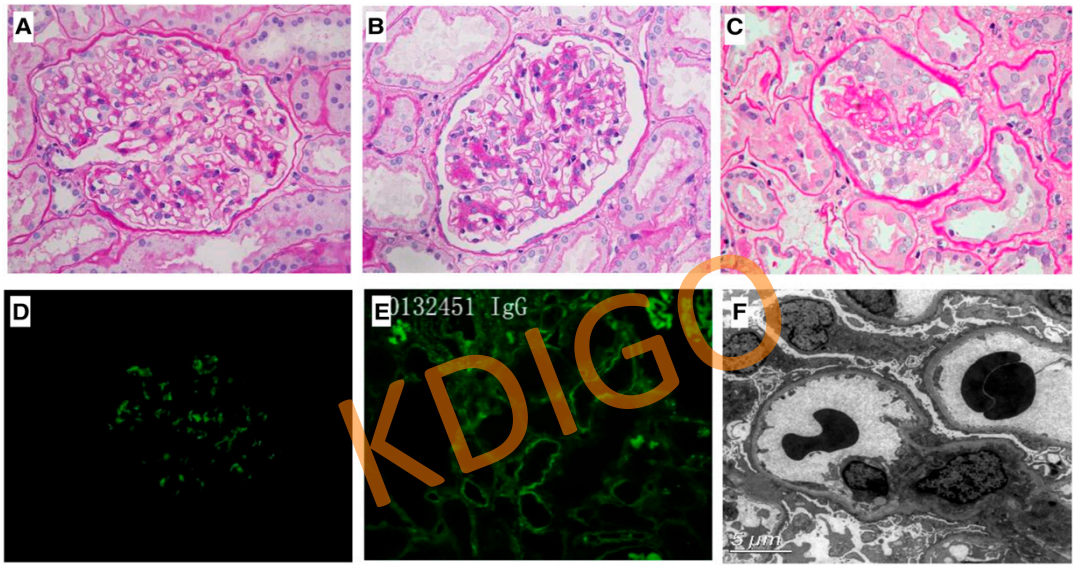


Table 4. Treatment response among different groups of lupus podocytopathy

Treatment Response and Outcomes	Total (*n*=50)	MCD (*n*=13)	MsP (*n*=28)	FSGS (*n*=9)	*P* values
Treatment response					0.001
Complete remission	38 (76.0)	12 (92.3)	24 (85.7)	2 (22.2)	
Partial remission	9 (18.0)	1 (7.7)	3 (10.7)	5 (55.6)	
No response	3 (6.0)	0	1 (3.6)	2 (22.2)	
Time to remission (weeks)	4 (2, 8)	4 (2, 8)	4 (2, 7)	8 (5, 10)	0.25
Relapse	28 (56.0)	7 (53.8)	15 (53.6)	6 (66.7)	0.86
Histologic transition	6/13 (46.2)	1/5 (20.0)	3/5 (60.0)	2/3 (66.7)	0.48

Data are expressed as *N* (%) or median (interquartile range). MCD, minimal change disease; MsP, mesangial proliferation.

WX Hu, ZH Liu, et al. CJASN, 2016

Considerable interethnic variation is evident in the efficacy and tolerability of the various immunosuppressive regimens, which necessitates individualized treatment and comparison of the efficacy and side effects across different ethnic groups.

Evidence origin from Chine in KDIGO GN Guideline(2012)

	n	RCT	Retrospective
IgAN	3	1	2
SRNS	1	1	0
MCD	0	0	0
MN	2	1	1
FSGS	0	0	0
LN	2	2	0
MPGN	0	0	0
HSPN		0	0
anti-GBM disease	1	0	1
ANCA vasculitis	1	1	0
Total	10	6	4

Published Randomized Controlled Trial from China during 2012 to 2016

Diseases	RCT
IgAN	5
MN	4
FSGS/MCD	4
LN	5
AAV	1
HSPN	2
Total	**21**

ORIGINAL RESEARCH

Annals of Internal Medicine

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized Trial

Zhihong Liu, MD; Haitao Zhang, MD; Zhangsuo Liu, MD; Changying Xing, PhD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Hongli Lin, MD; Fuyou Liu, MD; Yongcheng He, MD; Yani He, MD; Lining Miao, MD; Nan Chen, MD; Ying Li, MD; Yong Gu, MD; Wei Shi, MD; Weixin Hu, MD; Zhengzhao Liu, MD; Hao Bao, MD; Caihong Zeng, PhD; and Minlin Zhou, MD

Background: Treatment of lupus nephritis (LN) remains challenging.

Objective: To assess the efficacy and safety of a multitarget therapy consisting of tacrolimus, mycophenolate mofetil, and steroid compared with intravenous cyclophosphamide and steroid as induction therapy for LN.

Design: 24-week randomized, open-label, multicenter study. (ClinicalTrials.gov: NCT00876616)

Setting: 26 renal centers in China.

group (25.6%) showed complete remission (difference, 20.3 percentage points [95% CI, 10.0 to 30.6 percentage points]; $P < 0.001$). The overall response incidence was higher in the multitarget group than in the intravenous cyclophosphamide group (83.5% vs. 63.0%; difference, 20.4 percentage points [CI, 10.3 to 30.6 percentage points]; $P < 0.001$), and the median time to overall response was shorter in the multitarget group (difference, −4.1 weeks [CI, −7.9 to −2.1 weeks]). Incidence of adverse events did not differ between the multitarget and intravenous cyclophosphamide groups (50.3% [91 of 181] vs. 52.5% [95 of 181]).

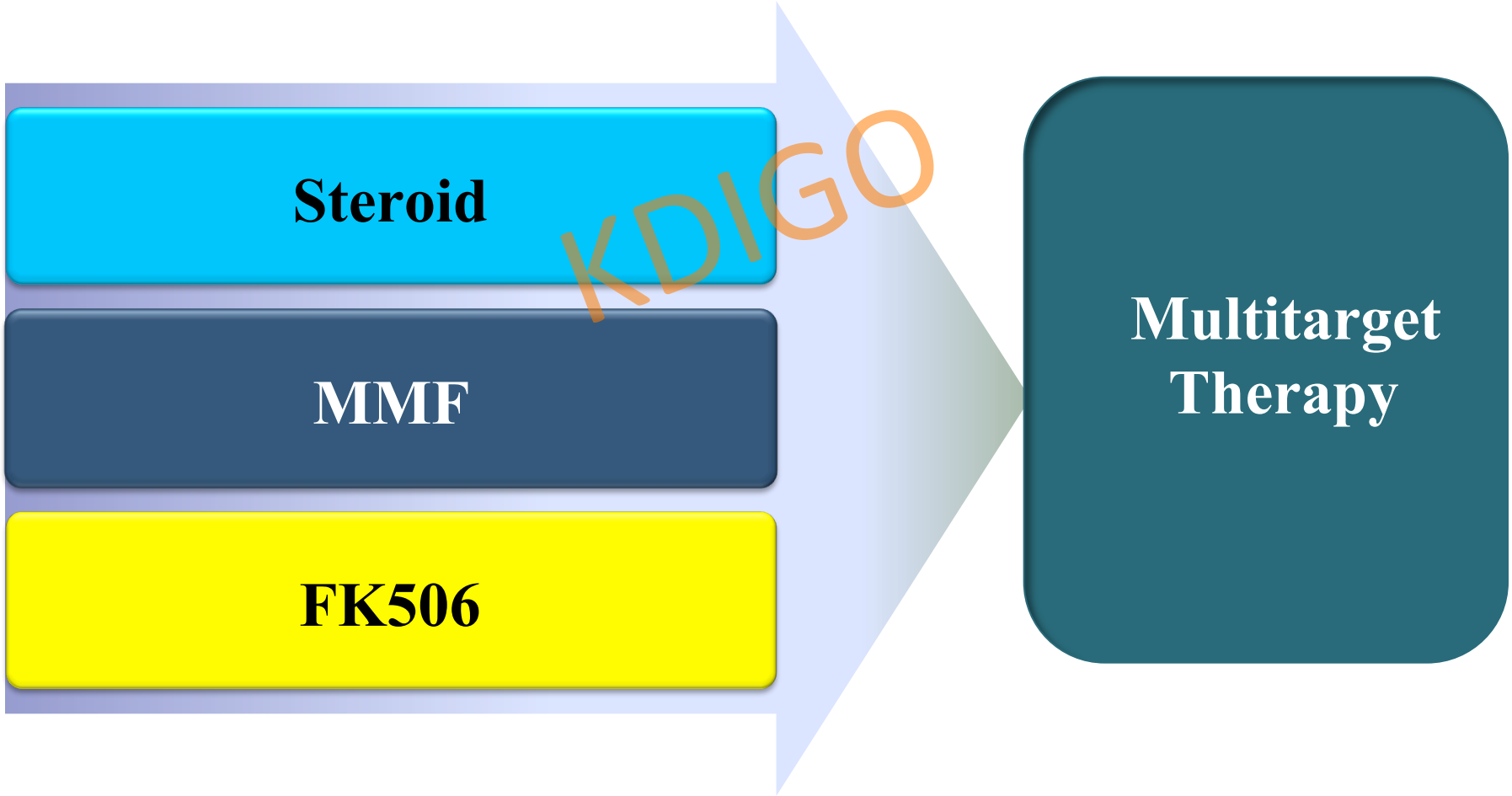
.Ann Intern Med. 2015 Jan 6;162(1):18-26

Therapeutic goals for patients with lupus nephritis

- To achieve prompt complete remission
- To avoid renal flare, and chronic renal impairment
- To fulfill these objectives with minimal toxicity

Multiple drugs in lower dose

maximal the efficacy，minimal the side effects



Inclusion criteria

- Age 18-65 years old with either gender
- Fullfilled the criteria of the ACR for SLE
- Biopsy proved Class III/IV/V/III+V/IV +V LN
- SLE-DAI>10
- Chronicity index(CI)≤ 3
- Proteinuria ≥1.5g/24h, with or without activity urinary sediment
- Serum creatinine ≤3.0mg/dl (265.2umol/L)
- Provided written informed consent

Interventions

Multi-target Group

FK506: 4mg/d

MMF: 1.0g/d

Methylprednisolone : IV. 0.5g/d×3;

Pred. 0.6mg/kg/d ×4wks;

gradually tapered to 10mg/d

IVCY Group (control)

IVCY: 0.75g/m2/BSA/mo×6

Methylprednisolone : IV. 0.5g/d×3;

Pred. 0.6mg/kg/d ×4wks;

gradually tapered to 10mg/d

Zhi-Hong Liu, et al. Ann Intern Med. 2015 Jan 6;162(1):18-26

Outcomes (The primary end point)

Complete remission rate after 24 weeks

Complete remission(CR) :

- Proteinuria <0.4 g/24 h
- Without active urinary sediment
- Serum albumin ≥35 g/L
- Serum creatinine normal or increase < 15% above baseline values

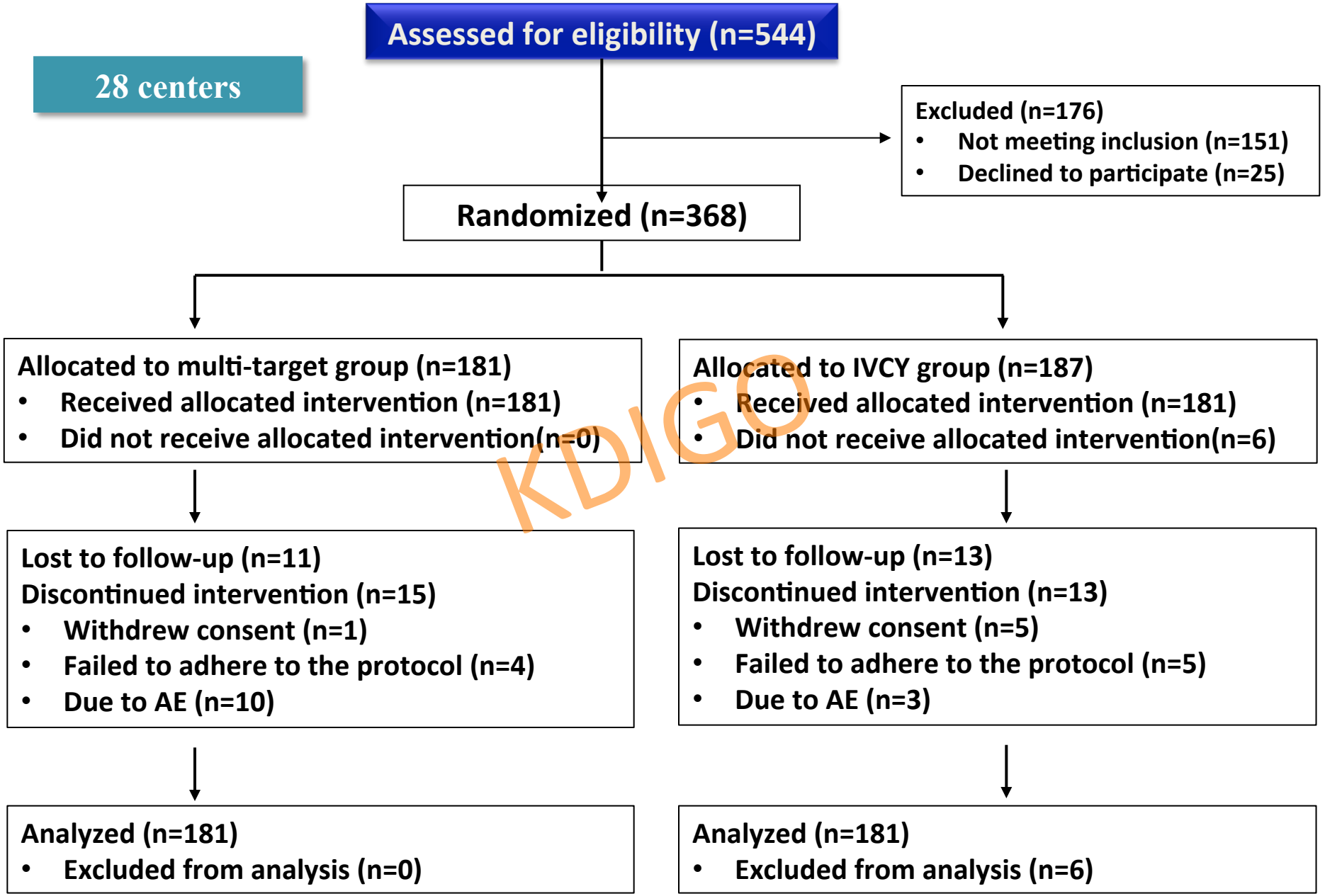
The partial remission rate (PR)

- 50% improvement in proteinuria
- urine protein <3.5g/24h,
- serum albumin ≥30 g/L,
- SCr normal or < 30% above baseline Scr

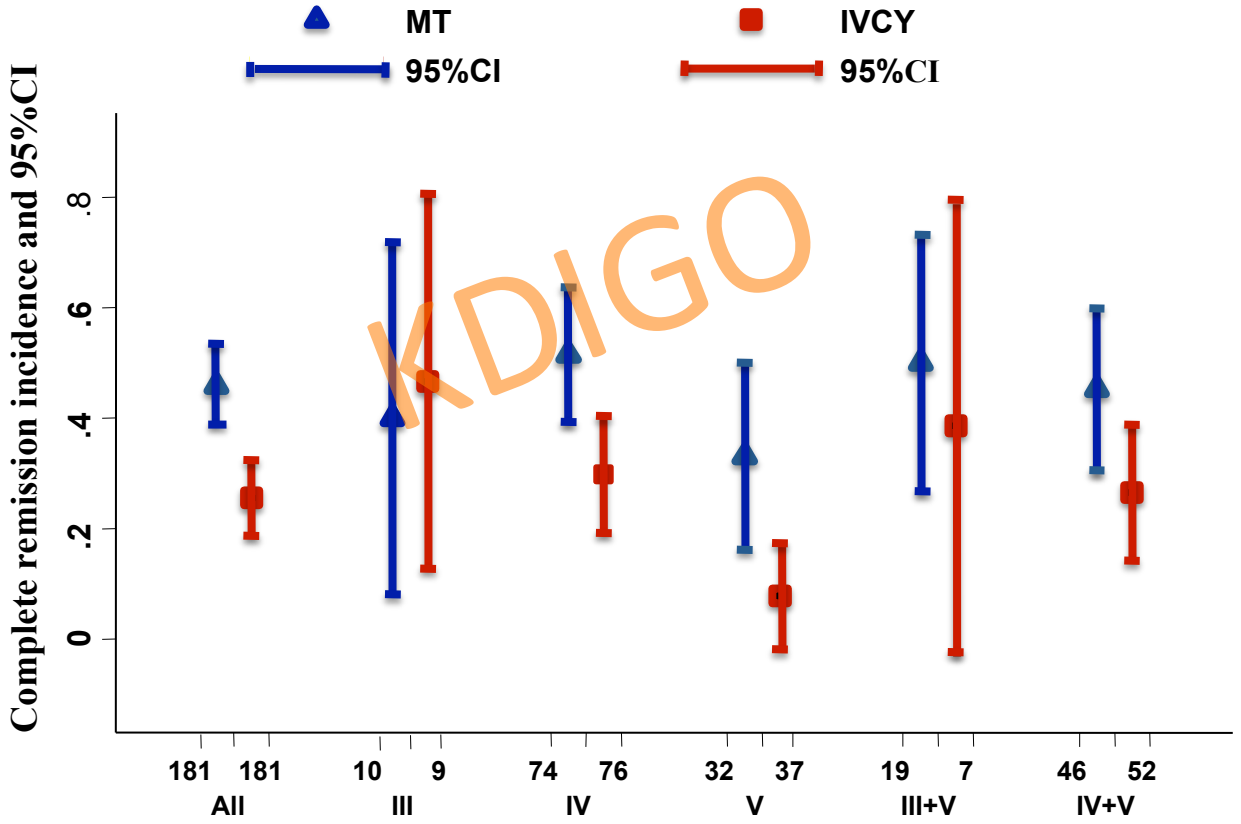
Overall remission： CR+PR

Outcomes (The secondary endpoint ）

- Overall response rate and the time to response
- Response rates in pathologic subgroups of patients
- 24 hour urinary protein excretion rate
- Changes of serum albumin and creatinine
- Disease activity
- The adverse events


28 centers
Assessed for eligibility (n=544)
Excluded (n=176)
• Not meeting inclusion (n=151)
• Declined to participate (n=25)
Randomized (n=368)
Allocated to multi-target group (n=181)
• Received allocated intervention (n=181)
• Did not receive allocated intervention(n=0)
Allocated to IVCY group (n=187)
• Received allocated intervention (n=181)
• Did not receive allocated intervention(n=6)
Lost to follow-up (n=11)
Discontinued intervention (n=15)
• Withdrew consent (n=1)
• Failed to adhere to the protocol (n=4)
• Due to AE (n=10)
Lost to follow-up (n=13)
Discontinued intervention (n=13)
• Withdrew consent (n=5)
• Failed to adhere to the protocol (n=5)
• Due to AE (n=3)
Analyzed (n=181)
• Excluded from analysis (n=0)
Analyzed (n=181)
• Excluded from analysis (n=6)

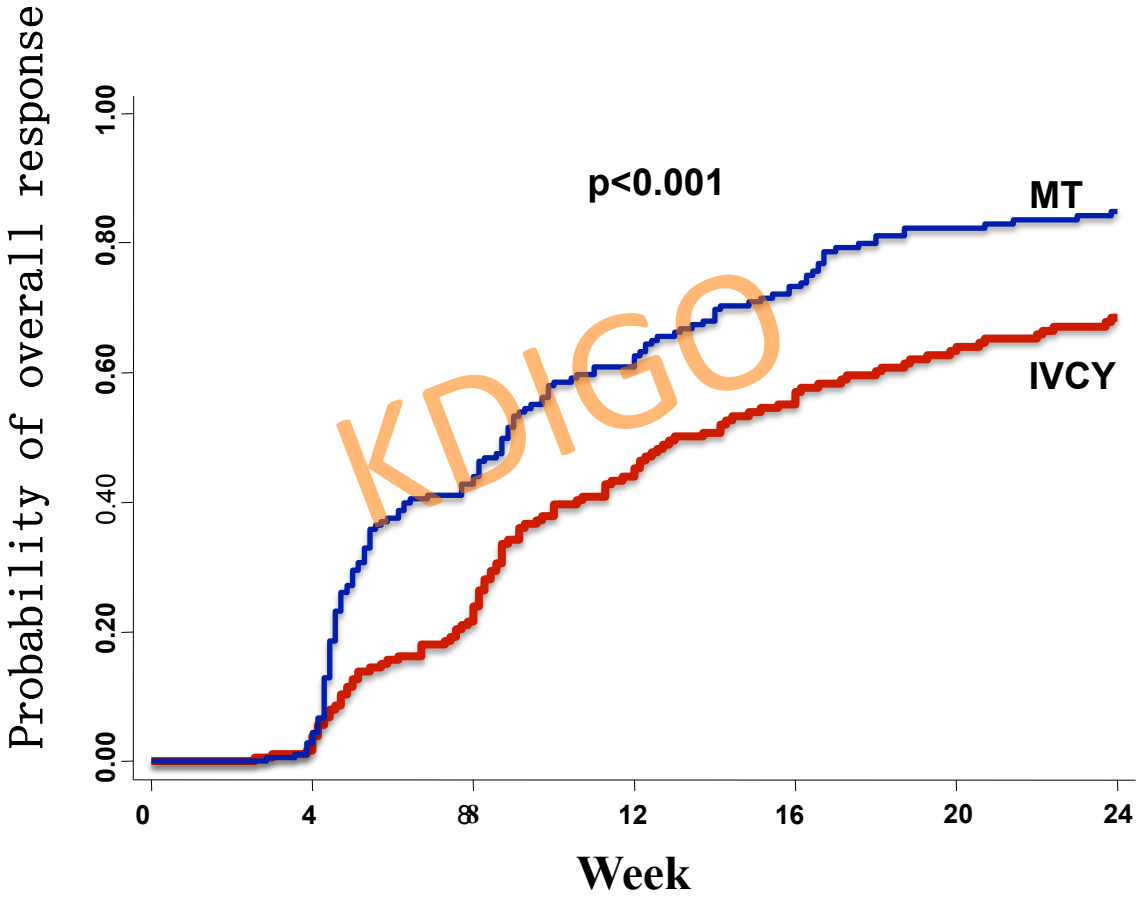
CR Incidence at 24 Weeks in All Patients With LN and per Pathologic Class Subgroup by Treatment (MT or IVCY)



CR : MT group 45.9%

IVCY group 25.6%, (P < 0.001)

Probability of achieving overall remission



overall remission： MT group 85.0%
IVCY group 68.6% ($P < 0.001$)

The incidence of complete remission in pathologic class subgroup

The incidence of complete remission was higher in the multitarget group than in the IVCY group among patients with class **IV LN** (51.5% vs. 29.9%); class **V LN** (33.1% vs. 7.8%) and class **IV+V LN** (45.2% vs. 26.5%).

The multitarget therapy may be a valuable treatment approach in patients with class IV (proliferative LN) and class V (membranous LN) lesions.

Median time to overall response

Median time to overall response was **8.9 weeks** (CI, 7.7 to 9.9 weeks) in the multitarget group and **13.0 weeks** (CI, 11.3 to 16.1 weeks) in the IVCY group (difference, - 4.1 weeks [CI, - 7.9 to - 2.1 weeks]).

Other Secondary End Points

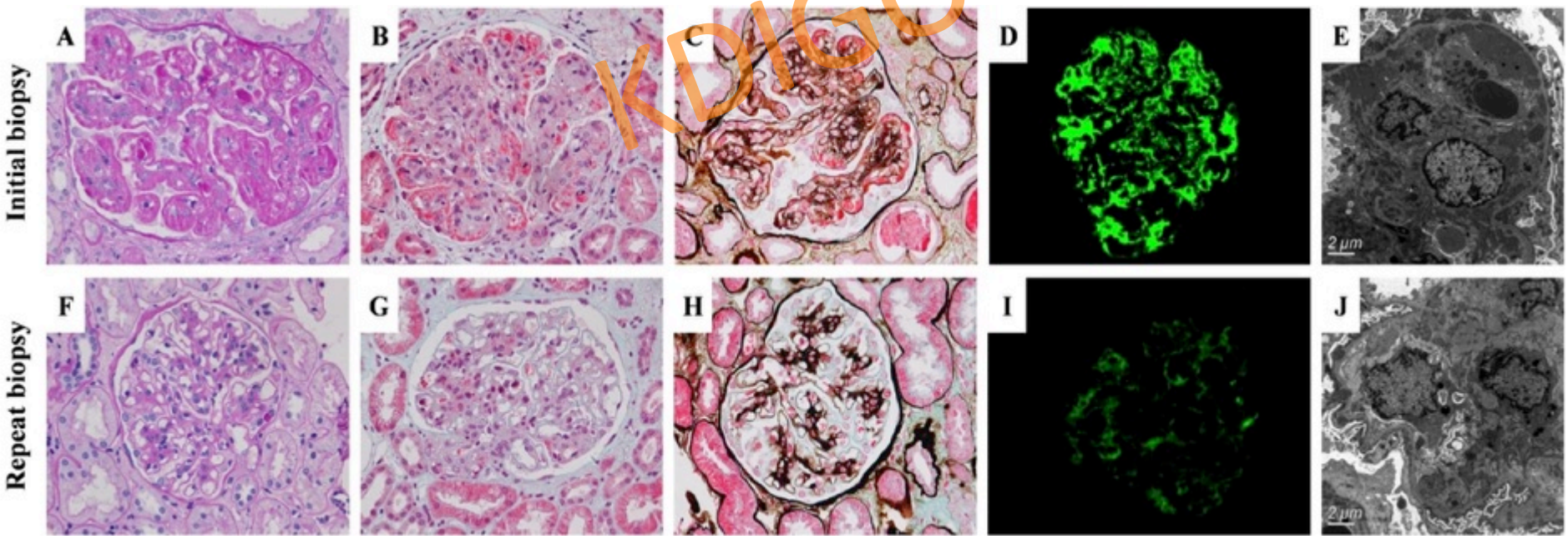
Change From Baseline to Week 24	Multitarget (n = 181)	IVCY (n = 181)	Difference (95% CI)	P value
Proteinuria, mean (SD), g/d,	-3.38 (2.77)	-2.68 (2.69)	-0.70 (-1.31 to -0.09)	0.025
Albumin mean (SD), g/L,	15.15 (7.11)	13.51 (6.84)	1.63 (0.07 to 3.19)	0.040
Serum creatinine mean (SD), μmol/L	-6.33 (26.39)	-9.92 (24.68)	3.59 (-2.12 to 9.30)	0.22
eGFR mean (SD), mL/min per 1.73 m^2	5.39 (37.20)	9.35 (33.63)	-3.95 (-11.88 to 3.97)	0.33
SLE-DAI mean (SD)	-11.01 (6.07)	-8.55 (5.05)	-2.46 (-3.77 to -1.15)	<0.001
C3 mean (SD), g/L	0.38 (0.30)	0.31 (0.25)	0.08 (0.01 to 0.14)	0.022
C4 mean (SD), g/L	0.08 (0.19)	0.06 (0.15)	0.02 (-0.02 to 0.06)	0.37
Negative conversion ratio of anti-dsDNA from baseline to 24 wk, n(%)	50 (64.1)	45 (52.3)	11.78 (3.59 to 26.71)	0.155

Both treatment groups had stable renal function and did not differ with respect to serum creatinine and eGFR changes

Repeated Renal Biopsy

Variable, median (25th, 75th percentiles)	Multitarget (n = 14)		IVCY (n = 9)	
	Initial Biopsy	Repeat Biopsy	Initial Biopsy	Repeat Biopsy
Activity index	11.5 (7, 16)	2 (1,3) †	11 (5, 15)	3 (2, 4)‡
Chronicity index	1 (0, 2)	2 (1, 2)	1 (1, 3)	3 (2, 3)

A marked reduction in the pathologic activity index in both treatment groups, with numerically more pronounced changes in the MT group



Result suggest that the multitarget therapy induces not only clinical remission but also histologic remission.

Adverse Events

Variable	Multitarget (n = 181), n (%)	IVCY (n = 181), n (%)
All adverse events (include serious adverse events)	**91 (50.3)**	**95 (52.5)**
Infections	51 (28.2)	46 (25.4)
Upper gastrointestinal symptoms‡	7 (3.9)	37 (20.4)
Diarrhea	14 (7.7)	6 (3.3)
Liver dysfunction	1 (0.6)	6 (3.3)
Hyperglycemia	5 (2.8)	4 (2.2)
New-onset hypertension	10 (5.5)	4 (2.2)
Myalgia	2 (1.1)	0
Headache	3 (1.7)	0
Alopecia	6 (3.3)	9 (5.0)
Leukopenia†	1 (0.6)	12 (6.6)
Tremor†	8 (4.4)	1 (0.6)
Menstrual disorder	2 (1.1)	7 (3.9)
Gingival hyperplasia	2 (1.1)	0
Osteonecrosis	1 (0.6)	0
Arthralgia	3 (1.7)	1 (0.6)
Doubling of serum creatinine level	2 (1.1)	0
Thrombocytopenia	1 (0.6)	0
Others	20 (11.0)	11 (6.1)

† **P < 0.05**
‡ **P < 0.001**

Hong Zhang and Vlado Perkovic
on behalf of the TESTING study group

Late Breaking Clinical Trials

ERA-EDTA Meeting, Vienna 2016

TESTING trial

- Aim:
  - Long-term efficacy and safety of oral methylprednisolone on a background of RAS inhibitor therapy, in patients with IgA nephropathy at a high risk of progression

- Design:
  - Investigator-initiated, international, randomized, double-blind, placebo-controlled trial

Study population

IgA nephropathy at high risk of progression:

- Biopsy proven IgA nephropathy
- eGFR 20-120 mls/min/1.73 m^2
- Proteinuria > 1g/day after at least 3 months of maximum labelled or tolerated RAS blockade

Intervention

- **Methylprednisolone or Placebo (double blind)**
  - 0.6-0.8 mg/kg/day (maximal 48mg/day) for 2 months
  - Tapered at 8mg daily/month and stopped within 6-8 months

- **Background therapy**
  - Optimal blood pressure control target <130/80mmHg
  - ACE inhibitors or ARBs adjusted to the maximum labeled or tolerated dose

Efficacy outcomes

- **Primary end points:**
  - Composite of a persistent **40%** decrease in eGFR, ESKD, or death due to kidney disease

- **Secondary end points:**
  - 40% decrease in eGFR, ESKD or all-cause death
  - 50% decrease in eGFR, ESKD or all-cause death
  - Each of 40% decrease in eGFR, ESKD or all-cause death
  - Annual rate of eGFR decline
  - Proteinuria reduction

RESULTS

IDMC communication

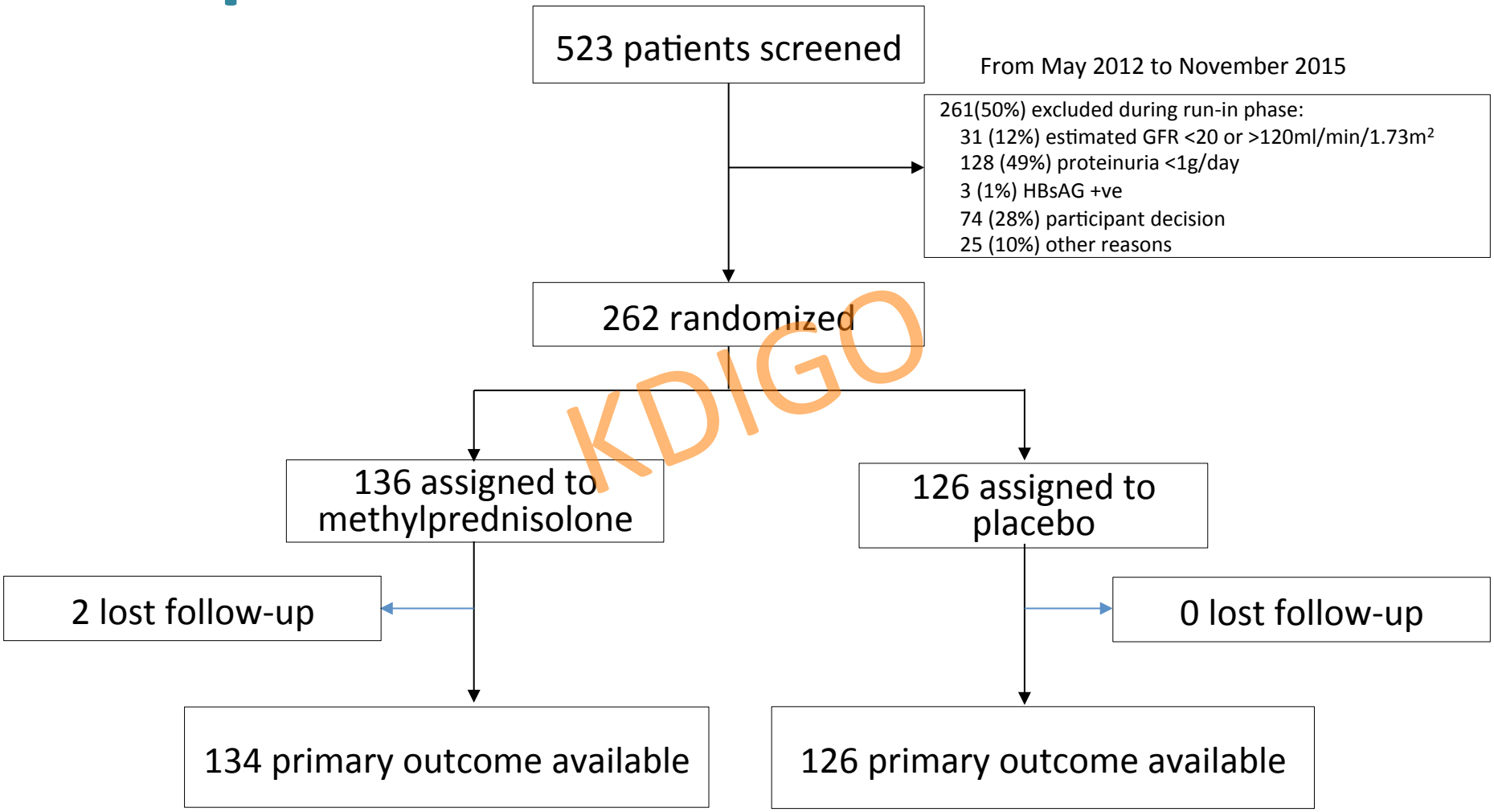
November, 2015

'…….Concern over an imbalance in severe adverse events between the test and control treatment groups and attribution of the majority of the severe adverse events to the test medication, methylprednisolone, has led the DSMB to conclude that the trial should not continue in its current form…….'

SC decision in response

- Discontinue study treatment
- Continue follow-up of all participants off treatment
- Analyse and report results to date
  - All participants recalled for a study visit
  - Transitional study analysis

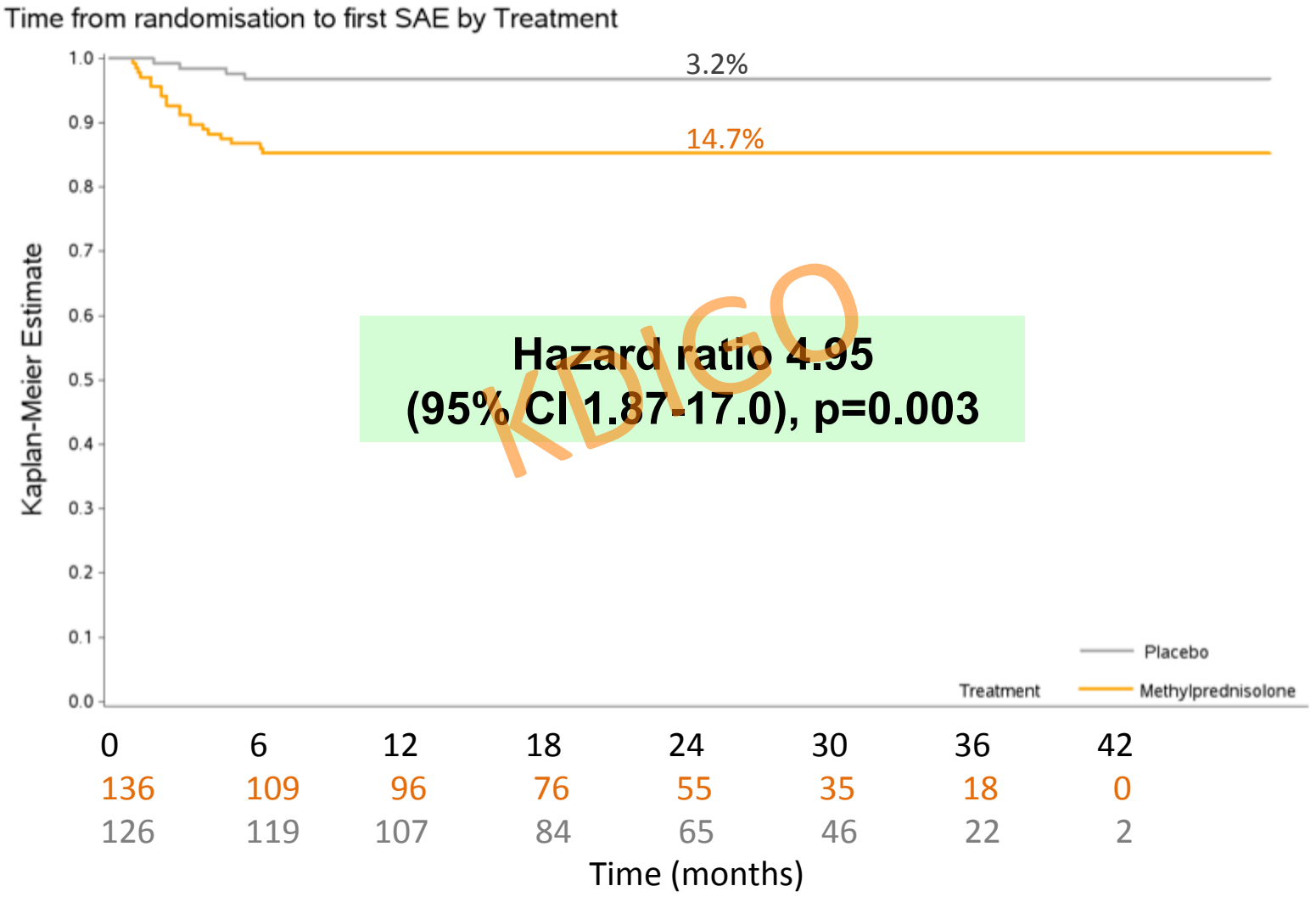
Trial profile



Baseline characteristics

Characteristics	Methylprednisolone group (N=136)	Placebo group (N=126)
Age - yr	38.6 ±11.5	38.6±10.7
Female sex – no. (%)	50 (36.8%)	46 (36.5)
Race – no. (%)		
Chinese	130 (95.6)	121(96.0)
Caucasian	5 (3.7)	3 (2.4)
South-East Asian	1 (0.7)	12(1.6)
Smoker - %	34 (25.0)	31 (24.6)
Body-mass index	24.4 ± 4.5	23.4 ± 3.7
Hypertension-no.(%)	71 (52.2)	52 (41.3)
Blood pressure - mmHg		
systolic	123.9 (14.7)	124.3 (11.6)
diastolic	79.3 (10.5)	79.8 (9.9)
Urine protein excretion – g/day	2.55 (2.45)	2.23 (1.11)
Serum creatinine – mg/dl	1.5 (0.6)	1.6 (0.6)
Estimated GFR – ml/min/1.73m^2	59.6 (24.1)	58.5 (23.1)
Total Cholesterol – mg/dl	188.9 (39.0)	191.8 (51.1)
Oxford histological Score		
M1 lesion – no. (%)	76 (57.6)	75 (61.0)
E1 lesion – no. (%)	43 (31.6%)	30 (23.8%)
S1 lesion – no. (%)	94 (71.2)	89 (72.4)
T0/T1/T2 lesion – no. (%)	51(38.6%)/58(43.9)/23(17.4)	43(35.0)/60(48.8)/20(16.3)
Therapy with RAS-blocking agents - %		
ACE inhibitor	83 (61.0%)	77 (61.1%)
ARB	55 (40.4%)	49(38.9%)

Serious adverse events

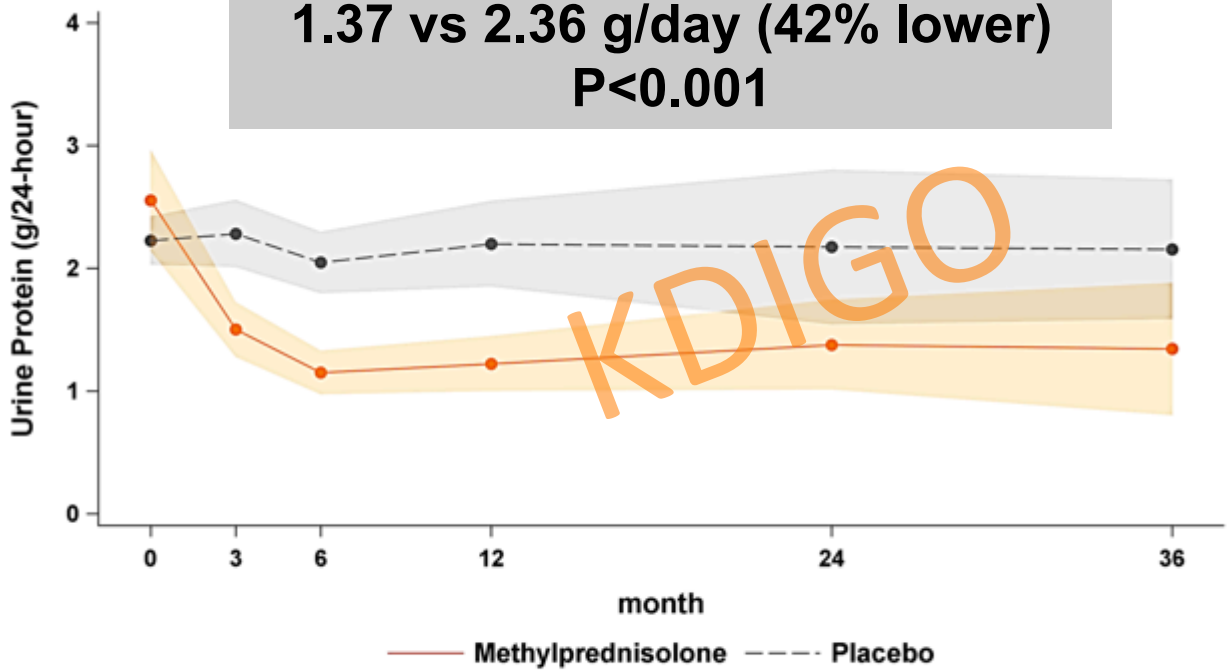


Safety outcomes

Outcome	Methylprednisolone group (N=136)	Placebo group (N=126)	P Value
Total patients with serious adverse events – no.	**20**	**4**	**0.001**
Serious adverse events of infection	**11**	**0**	**<.001**
Fatal infection	2	0	NS
Pneumocystis jirovecii pneumonia	3	0	NS
Other lung infection	2	0	NS
Septic arthritis	1	0	NS
Perianal infection	1	0	NS
Gastrointestinal serious adverse events	**3**	**1**	**NS**
Bone disorders			
Avascular necrosis	3	0	NS
Fracture	1	0	NS
New onset diabetes mellitus	**2**	**3**	**NS**

Effect on Proteinuria

Time averaged proteinuria:
1.37 vs 2.36 g/day (42% lower)
P<0.001



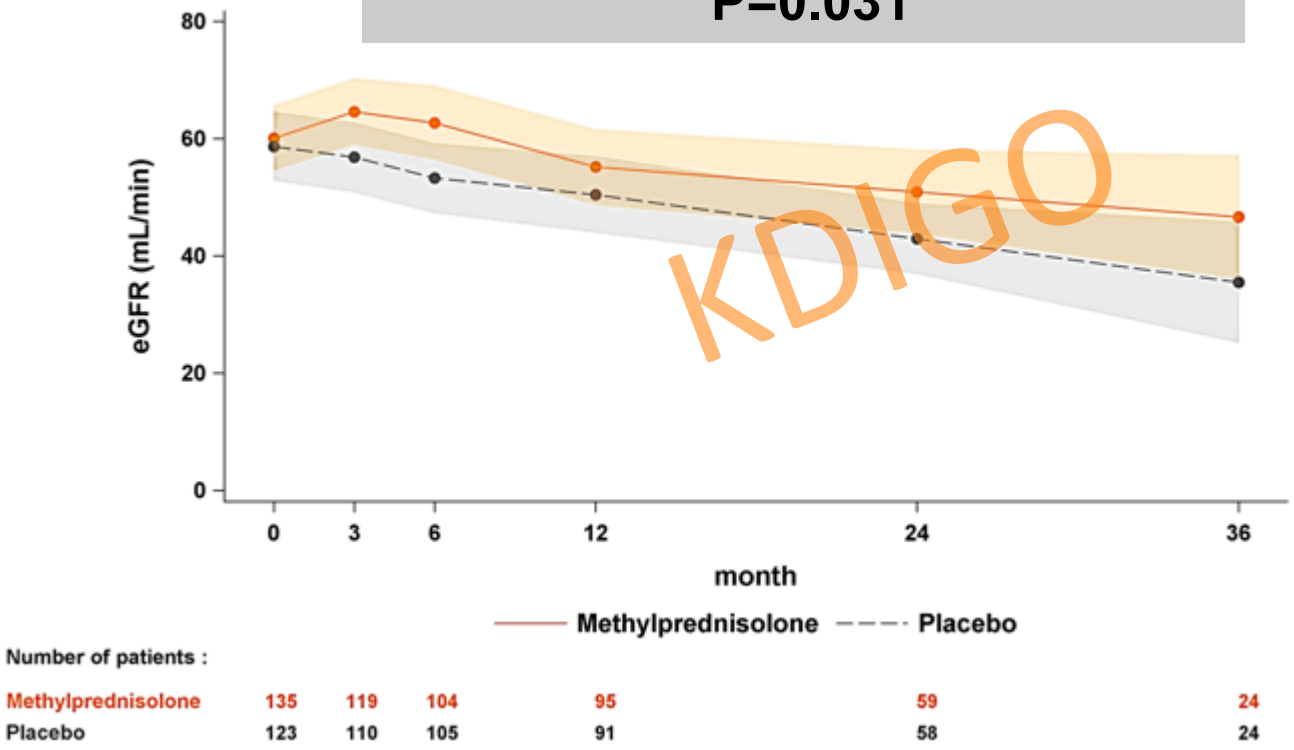
Number of patients :

Methylprednisolone	135	117	103	93	55	23
Placebo	123	109	99	88	55	23

Month	Mean Δ	p value
3	-0.83	<.0001
6	-1.00	<.0001
12	-1.20	<.0001
24	-1.03	<.0001
36	-0.93	0.0077

Effect on eGFR

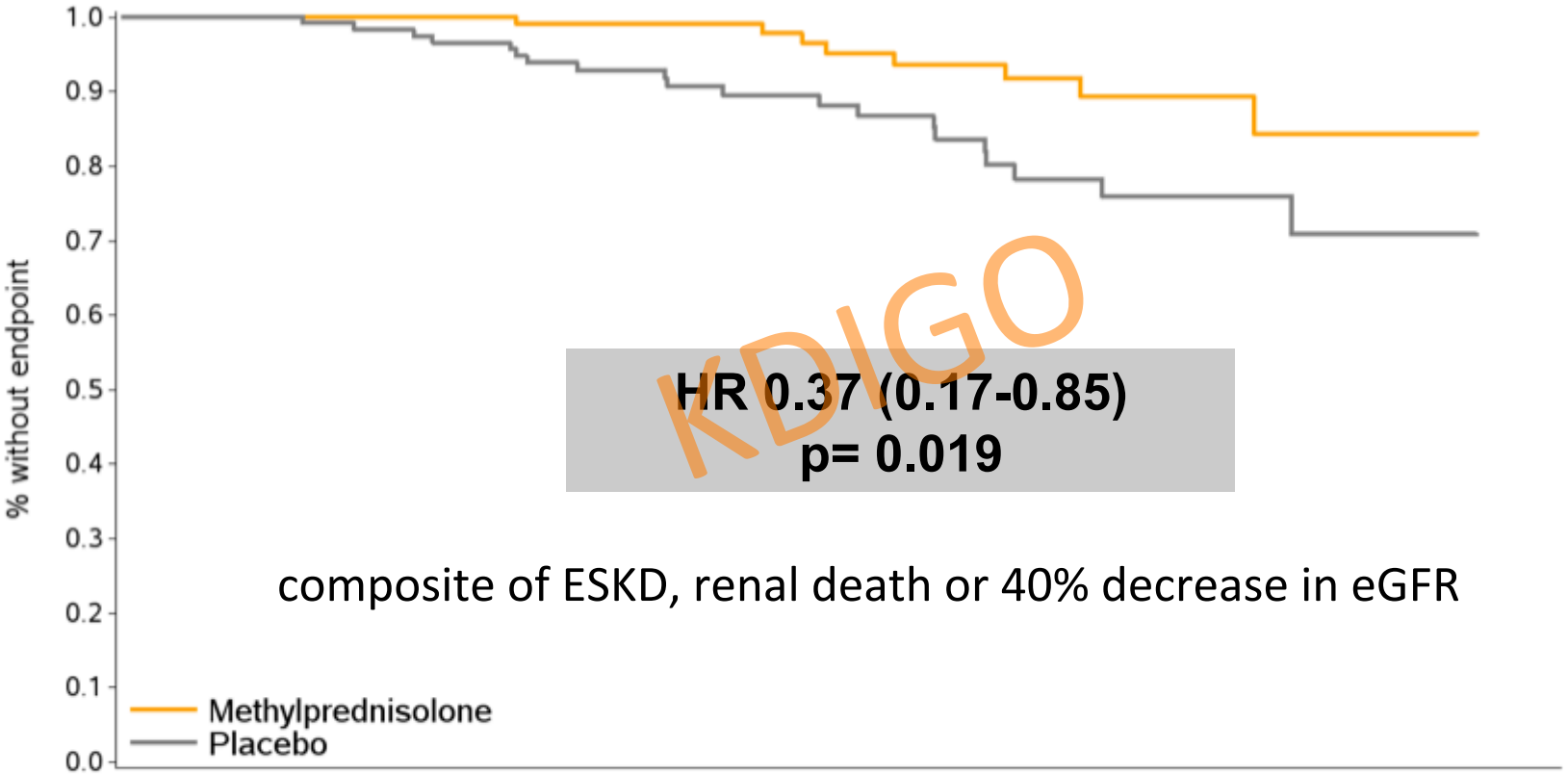
Annual eGFR slope*:
-1.7 vs -6.8 mls/min/1.73m^2/yr
P=0.031



Month	Mean Δ	p value
3	5.14	0.0019
6	6.74	<.0001
12	4.62	0.0091
24	5.43	0.0088
36	7.67	0.0092

*- defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time

Primary outcome



composite of ESKD, renal death or 40% decrease in eGFR

Conclusions

- Full dose steroid therapy was associated with significantly increased rates of serious adverse outcomes in patients with IgA nephropathy
- The results to date suggest renal benefit based on a modest number of events
- The ongoing, long-term follow-up will help to further define the balance of risks and benefits