60TH ERA CONGRESS
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Estimating delay in time to kidney failure or death for treatment effects on proteinuria in IgA nephropathy

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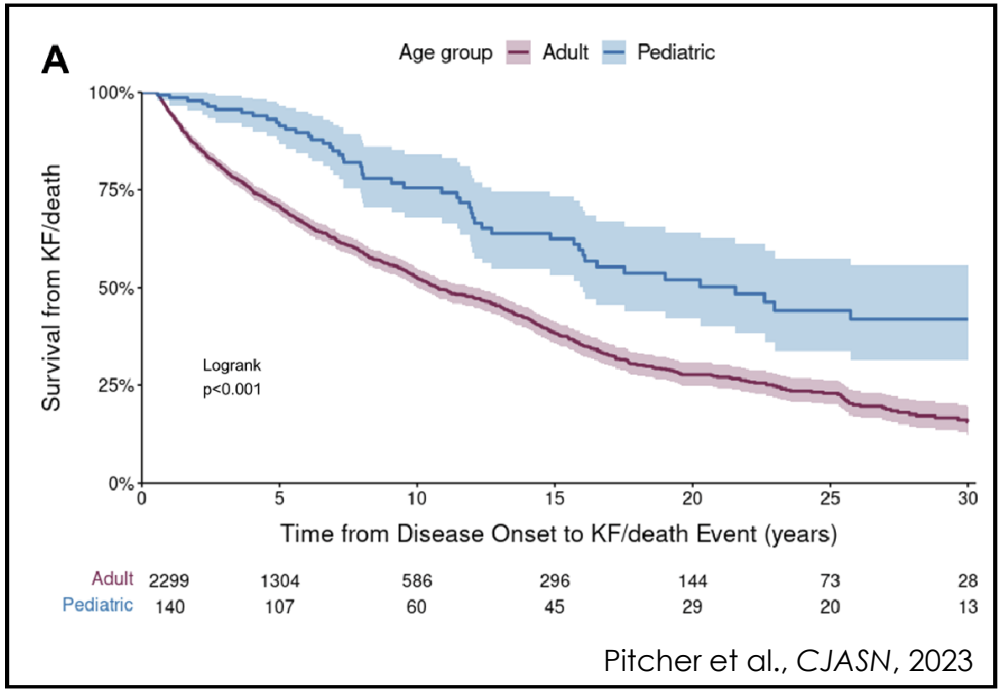
Disclosure of Interest

- Consultant to Travere Therapeutics and Vera Therapeutics.

Introduction

- IgAN is a serious, progressive, and life-limiting disease with a poor prognosis[1] and high unmet medical need in Europe and worldwide.[2]
- Median kidney survival time of 11.4 years.[3]
- IgAN is a disease in need of new medicines.

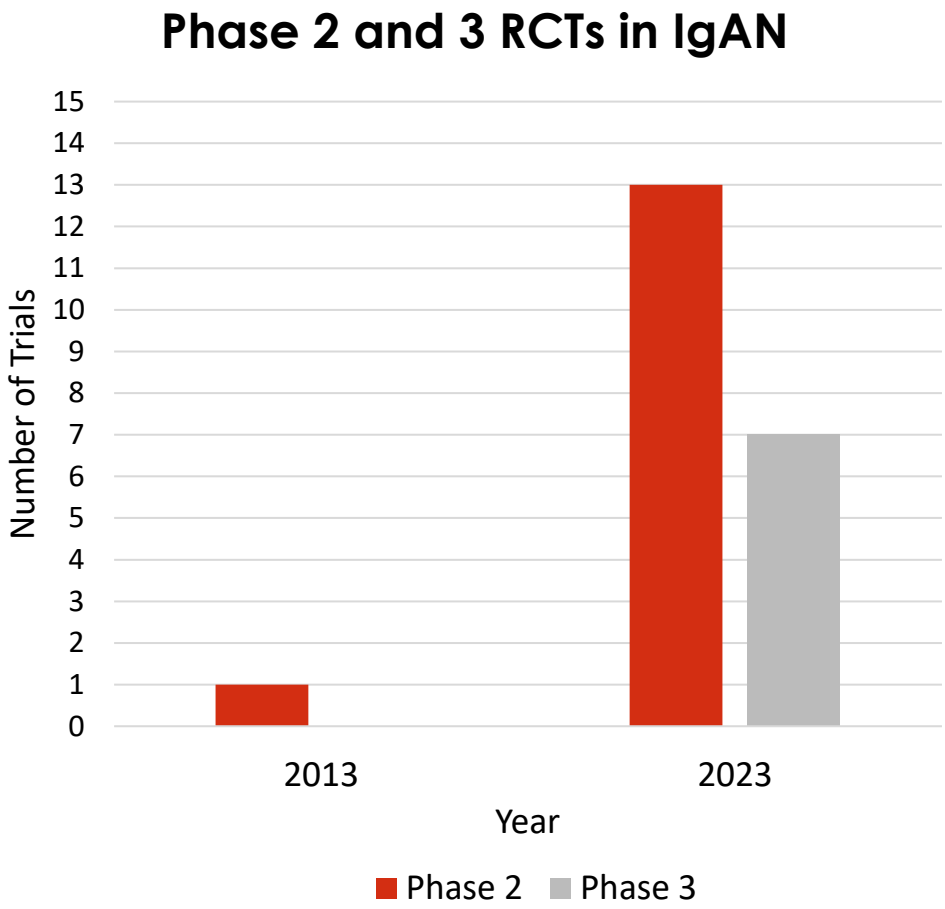


Pitcher et al., *CJASN*, 2023

1. Rajasekaran A, Julian BA, Rizk DV. *Am J Med Sci.* 2021;361(2):176-194. **2.** McGrogan A, et al. *Nephrol Dial Transplant.* 2011;26(2):414-430. **3.** Pitcher D, et al. *CJASN.* 2023;10.2215/CJN.0000000000000135.

Introduction

- IgAN is a serious, progressive, and life-limiting disease with a poor prognosis[1] and high unmet medical need in Europe and worldwide.[2]
- Median kidney survival time of 11.4 years.[2]
- IgAN is a disease in need of new medicines.
- Clinical development programs for IgAN have increased over the last 10 years:
  - 2013: 1 randomized controlled trial (RCT) in phase 2
  - 2023: 13 RCTs in phase 2 and 8 in phase 3



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Introduction

- Surrogate endpoint development has had a substantial impact on drug development in IgAN.

Composite of first occurrence of

- **Doubling of serum creatinine**
- **eGFR <15 mL/min/1.73m^2**
- **Kidney replacement therapy**

Δ proteinuria over 9 months

Full approval

- Large, long controlled trials
- Feasible for diabetic kidney disease
- Challenging and prohibitive in rare kidney diseases

- Meta-regression "trial level analysis" of IgAN RCTs
- Established that treatment effect on proteinuria predicts a treatment effect on clinical outcome[4,5]

Accelerated / conditional approval

- Smaller sample size required
- Early readout
- RCT possible in rare kidney diseases, e.g., IgAN

4. Inker L A, et al. *Am J Kidney Dis.* 2016;68(3):392-401. **5.** Thompson A, et al. *CJASN.* 2019;14(3):469-481.
Abbreviations: eGFR, estimated glomerular filtration rate; **IgAN**, IgA nephropathy

Introduction

Kidney Health Initiative Study:

Meta-regression trial level analysis of IgAN RCTs

(Thompson A, et al. *CJASN*. 2019;14(3):469-481)

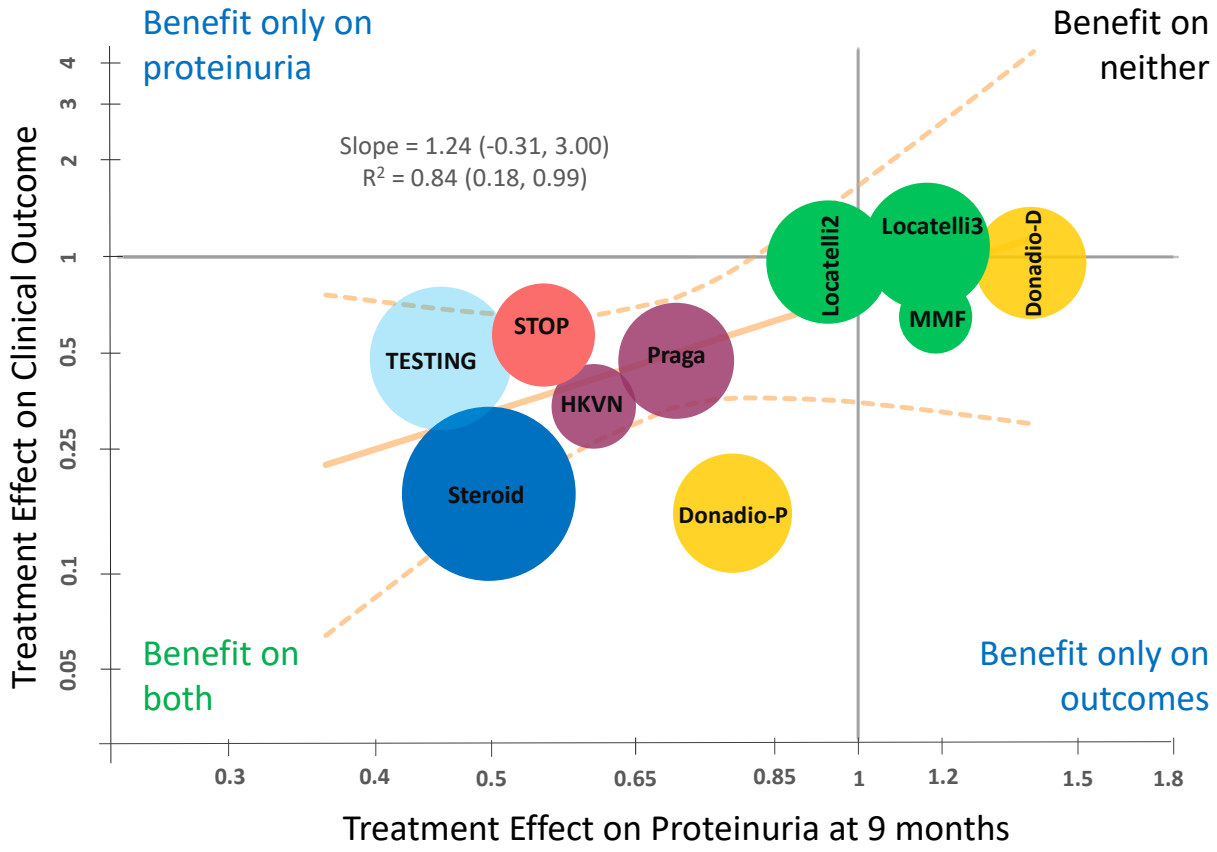
Key Finding

- Treatment effect on proteinuria at 9 months associated with treatment effect on clinical outcomes.

Conclusion

- Supports proteinuria reduction as a "reasonably likely surrogate endpoint".
- May be allowed as basis for "accelerated (conditional) approval".
- Requires clinical benefit to be verified.

Bayesian mixed-effect regression model



- Each bubble corresponds to an RCT or group of RCTs (bubble size relates to number of events)
- Dotted lines represent 95% Bayesian credibility interval

Abbreviations: IgAN, IgA nephropathy; **RCT**, randomized controlled trial

Objective

- To estimate the **delay in time to KF or death** associated with treatment effects of **40% and 50% reduction of proteinuria at 9 months** in an IgAN population **representative of a typical phase 3 RCT**
    - Allows estimation of future benefit in delay to KF/death for proteinuria results generated in ongoing phase 3 RCTs

Table 1. Ongoing phase 3 RCTs evaluating early change in proteinuria

Trial	Drug	Timing of Proteinuria Assessment
PROTECT in IgAN	Sparsentan	36 weeks
APPLAUSE - IGAN	Iptacopan	9 months
ARTEMIS - IGAN	Narsoplimab	36 weeks
IMAGINATION	RO7434656	37 weeks
ORIGIN	Atacicept	9 months
Visionary Study	Sibeprenlimab	9 months
NCT05799287	Telitacicept	39 weeks
ALIGN	Atrasentan	36 weeks

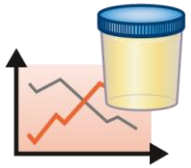
Abbreviations: IgAN, IgA nephropathy; **KF**, kidney failure; **RCT**, randomized controlled trial

Methods:

Two Step Approach

1. Apply trial level analysis to predict treatment effects for risk of clinical outcome expressed as a hazard ratio (HR) for hypothesized treatment effects on proteinuria.

2. For the HRs from Step 1, estimate the delay to KF or death by applying accelerated failure time (AFT) modelling to an IgAN population cohort with long follow-up.



Treatment effect on proteinuria

1 ↓

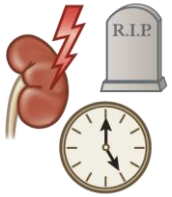
Trial level analysis of 13 RCTs in IgAN[5]

HR
KF or Death

2 ↓

UK RaDaR IgAN cohort (n=545)
- UPCR ≥100 mg/mmol (0.88 g/g)
- eGFR ≥30 ml/min/1.73m^2

AFT Modelling



Δ median time free from KF or Death

5. Thompson A, et al. *CJASN.* 2019;14(3):469-481.

Abbreviations: eGFR, estimated glomerular filtration rate; **IgAN,** IgA nephropathy; **KF**, kidney failure; **RCT**, randomized controlled trial

Methods:
Data Sources & Eligibility Criteria

1

- Published findings of trial level analysis applying patient level data from 13 RCTs in IgAN.[5]

2

- Patient level data from UK National Registry of Rare Kidney Disease (RaDaR) IgAN cohort.
- Inclusion criteria:
  - Adult biopsy proven-IgAN patients
  - UPCR ≥100 mg/mmol (0.88g/g) ≥6 months from diagnosis
    - First UPCR ≥100 mg/mmol ≥6 months defines baseline
  - eGFR ≥30 mL/min/1.73m^2 at baseline

5. Thompson A, et al. *CJASN.* 2019;14(3):469-481.

Abbreviations: eGFR, estimated glomerular filtration rate; **IgAN,** IgA nephropathy; **RCT**, randomized controlled trial; **UPCR**, urine protein-creatinine ratio

Methods:

Clinical Measures & Statistical Analyses

1

- Clinical outcome defined as doubling of serum creatinine, KF or death.

2

- KF defined as first occurrence of chronic KRT, confirmed eGFR <15 mL/min/1.73m^2, or KF/CKD stage 5 recorded in RaDaR.
- AFT modelling used to analyze time to KF/death during follow up in the RaDaR IgAN study population and estimate effect changes in HR had on median survival time and 5-year survival rates.
- Weibull, Log-Logistic and Log-Normal distributions applied with fitted survivor function reported from the model with lowest AIC.
- Time gained for a given reduction in risk in KF/death and 5-year survival was estimated under proportional hazards.

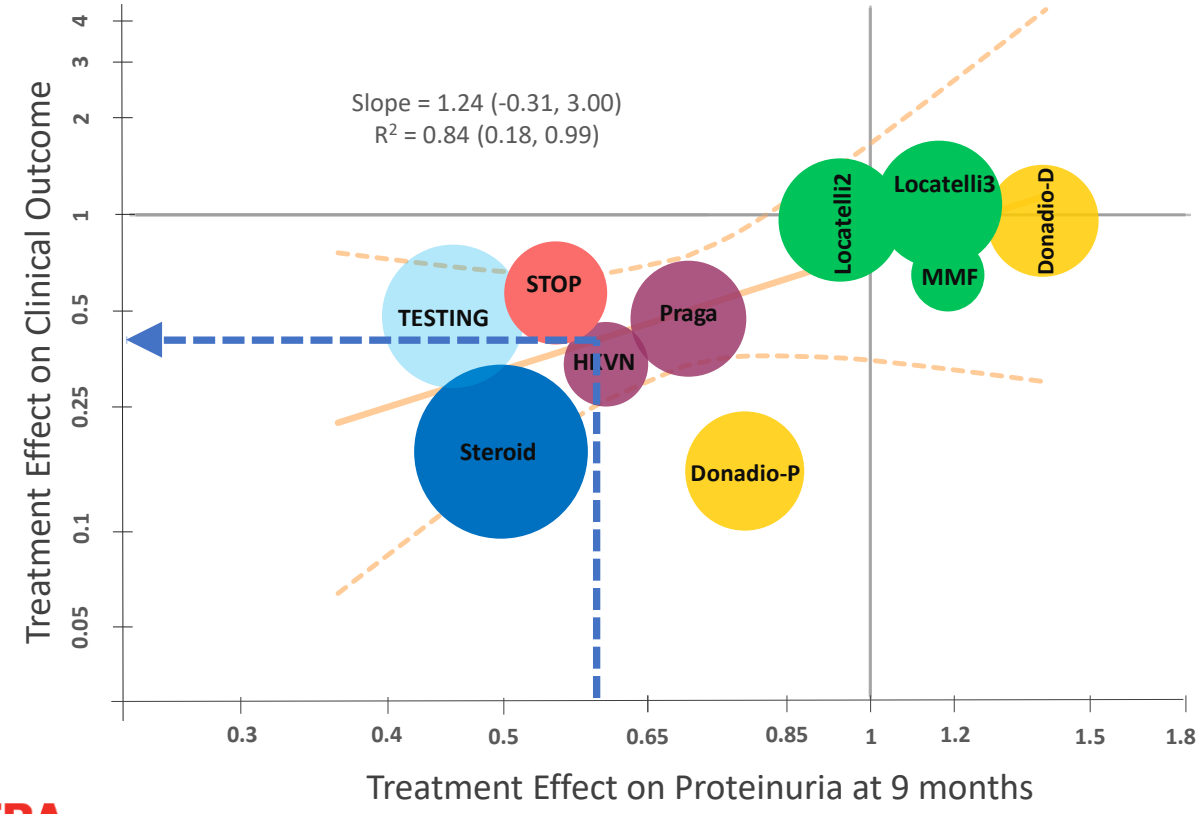
Abbreviations: AIC, Akaike information criterion; **AFT**, accelerated failure time; **CKD**, chronic kidney disease; **eGFR** , estimated glomerular filtration rate; **HR**, hazard ratio, **IgAN,** IgA nephropathy; **KF**, kidney failure, **KRT**, kidney replacement therapy

1

Results:

Predicting outcomes HR for ↓40% and ↓50% in proteinuria

- Trial level analysis cohort (n=1153)
- Geometric mean (ITR) proteinuria 1.8 (1.0–3.2) g/day, eGFR 63 (47-86) ml/min/1.73m^2



Drug vs Control Treatment Effect on Proteinuria at 9 Months	Corresponding % Treatment Effect for Drug if Control Ineffective	Predicted HR for Clinical Outcome	95% CI
0.9	10%	0.68	(0.36, 1.25)
0.8	20%	0.58	(0.36, 0.93)
0.7	30%	0.50	(0.34, 0.73)
0.6	**40%**	**0.41**	**(0.26, 0.65)**

Abbreviations: eGFR, estimated glomerular filtration rate; **HR**, hazard ratio; **ITR**, interterrtile range; **KF**, kidney failure

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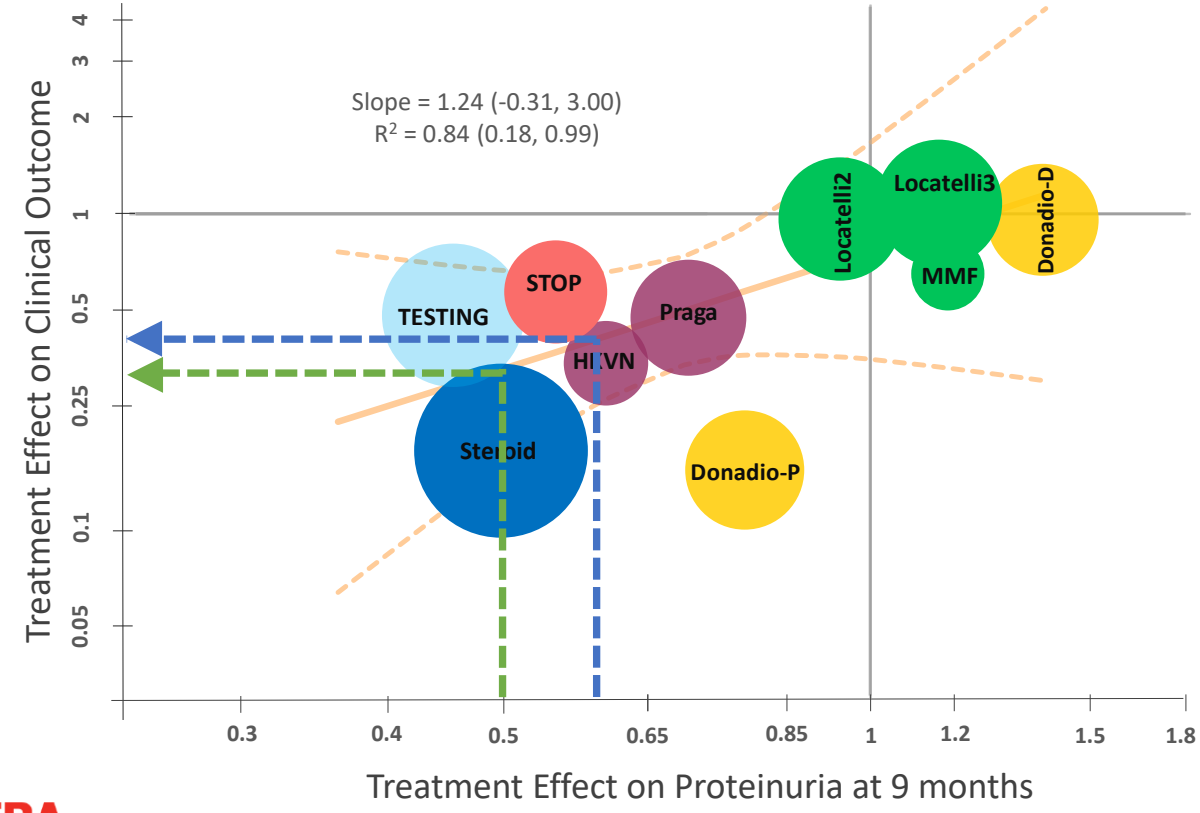

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0.5	**50%**	**0.33**	**(0.16, 0.67)**

Abbreviations: eGFR, estimated glomerular filtration rate; **HR**, hazard ratio; **ITR**, intertertile range; **KF**, kidney failure

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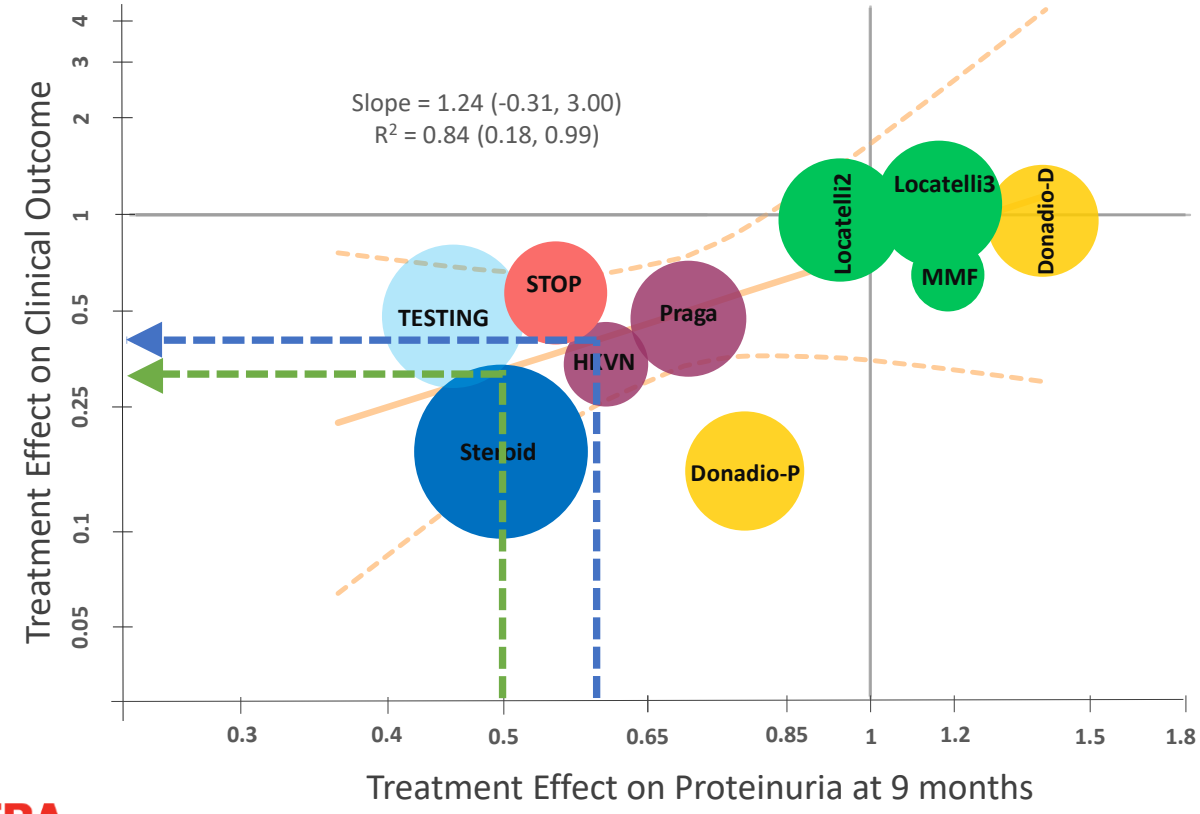

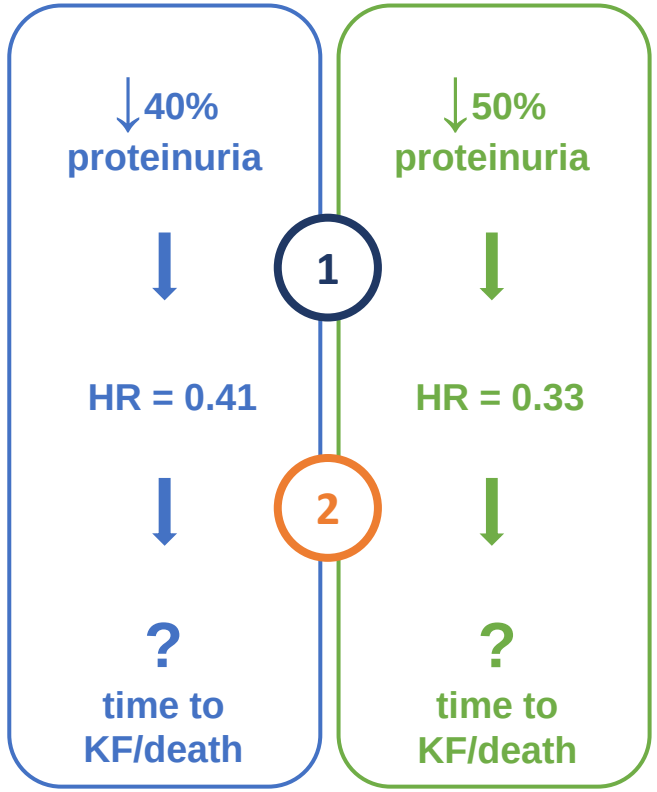

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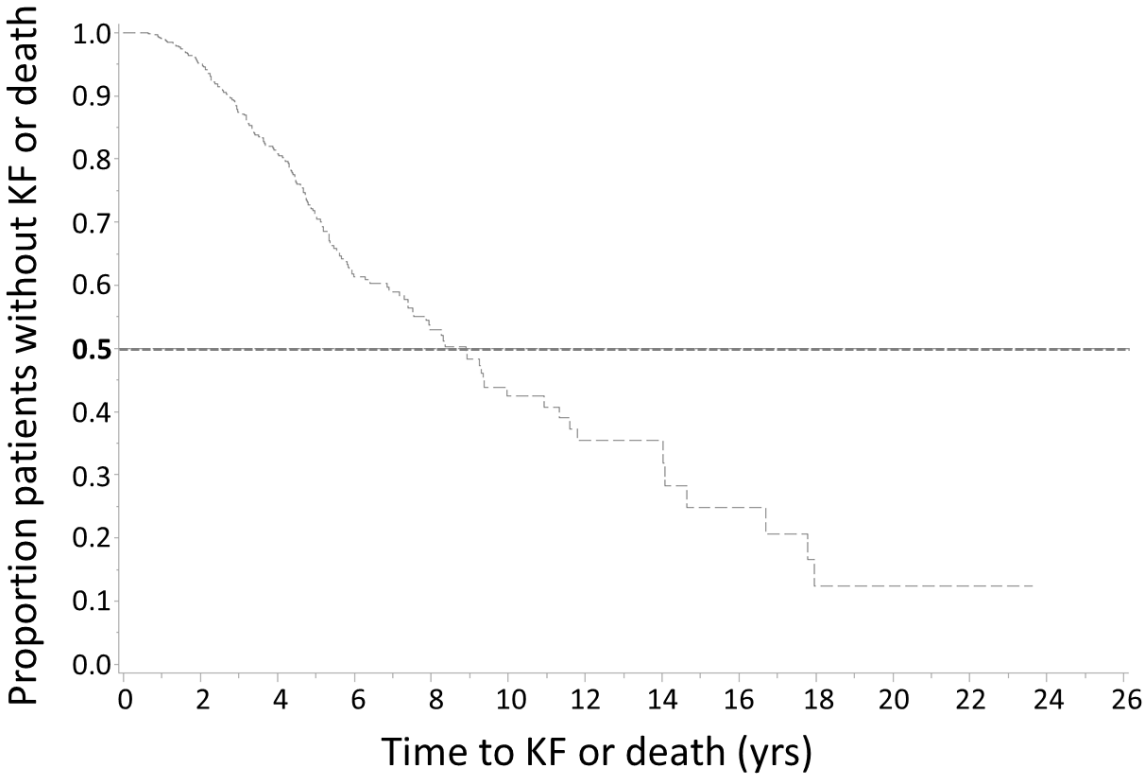
Results:

Estimating time to KF/death for predicted HRs associated with 0%, ↓40% and ↓50% treatment effect on proteinuria

- RaDaR IgAN cohort – phase 3 representative population (n=535, events=171)
- Median (IQR) UPCR 1.5 (1.1–2.2) g/g; Mean (SD) eGFR 61 (26) ml/min/1.73m^2



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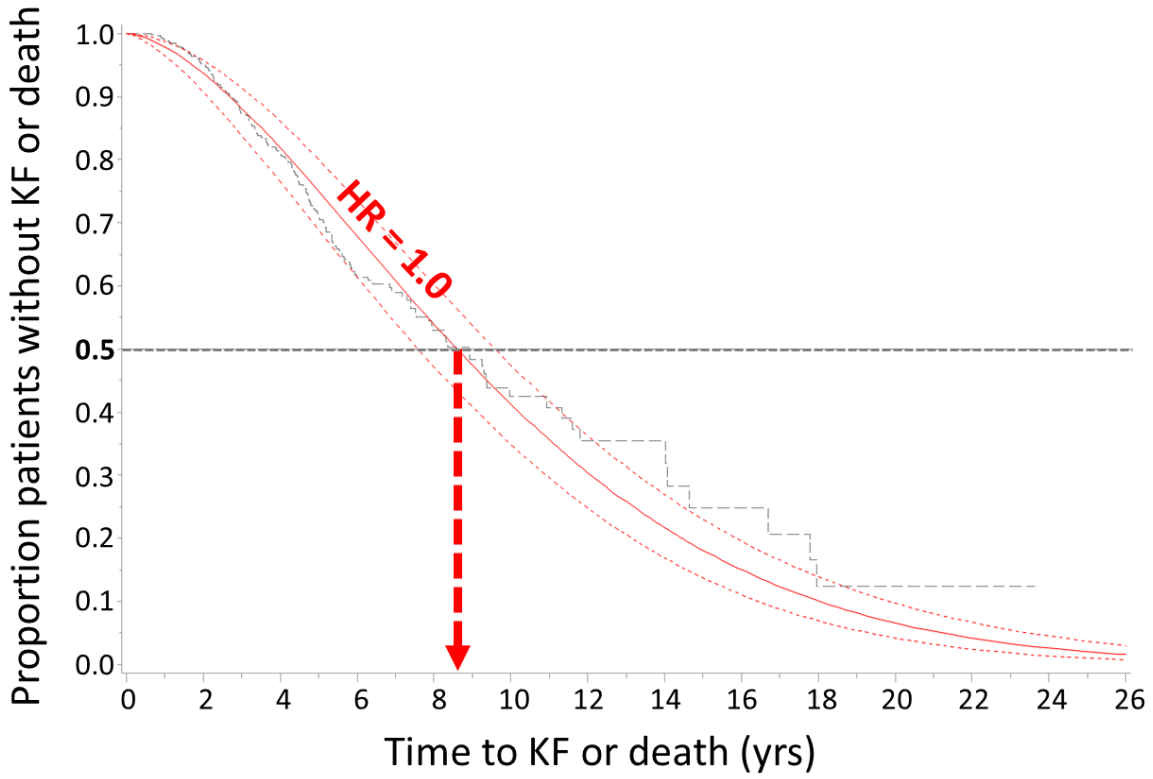

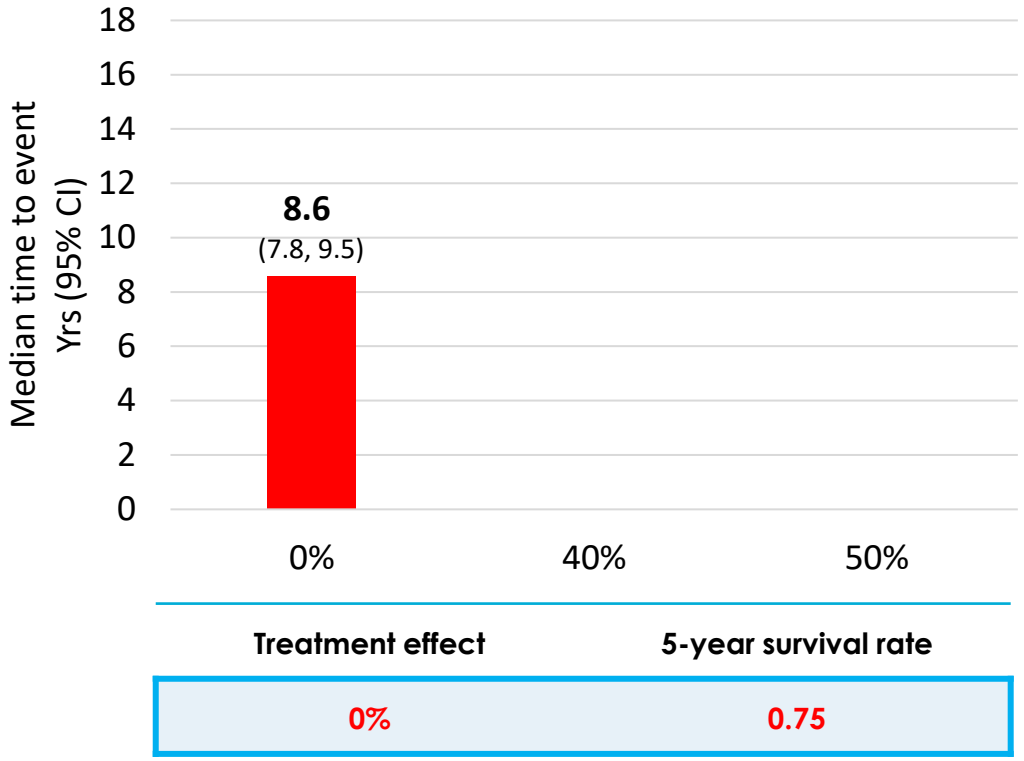

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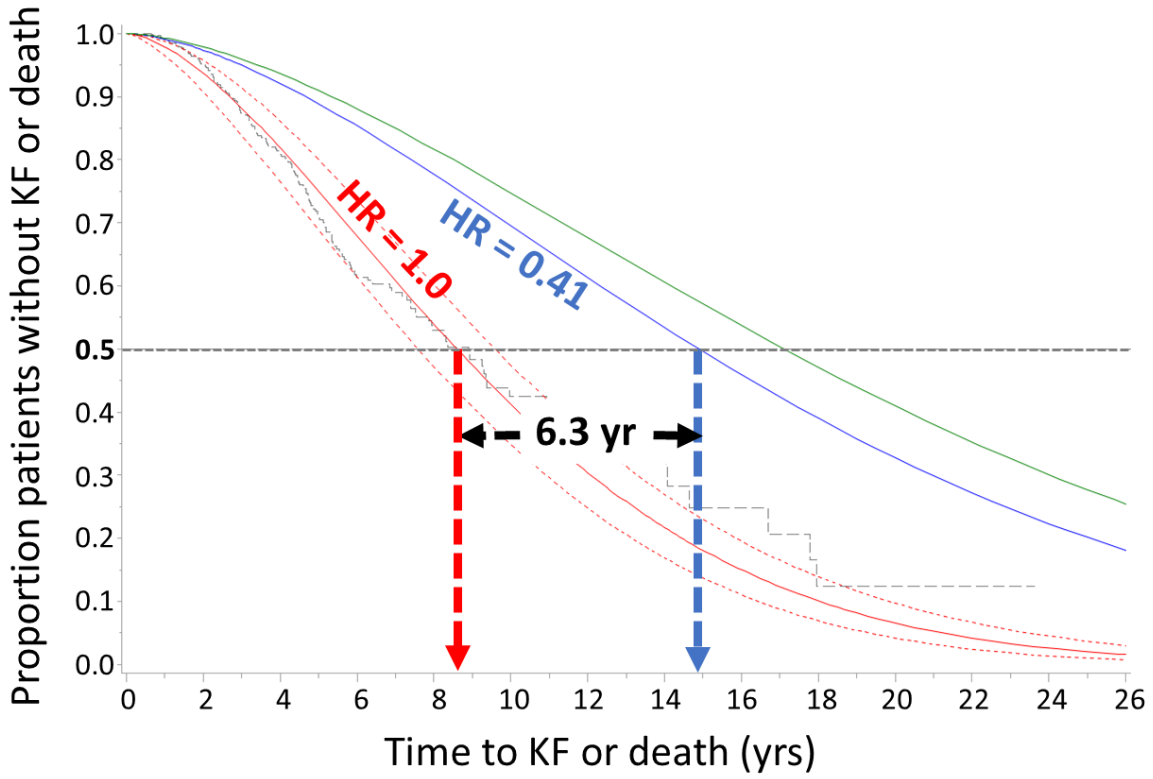

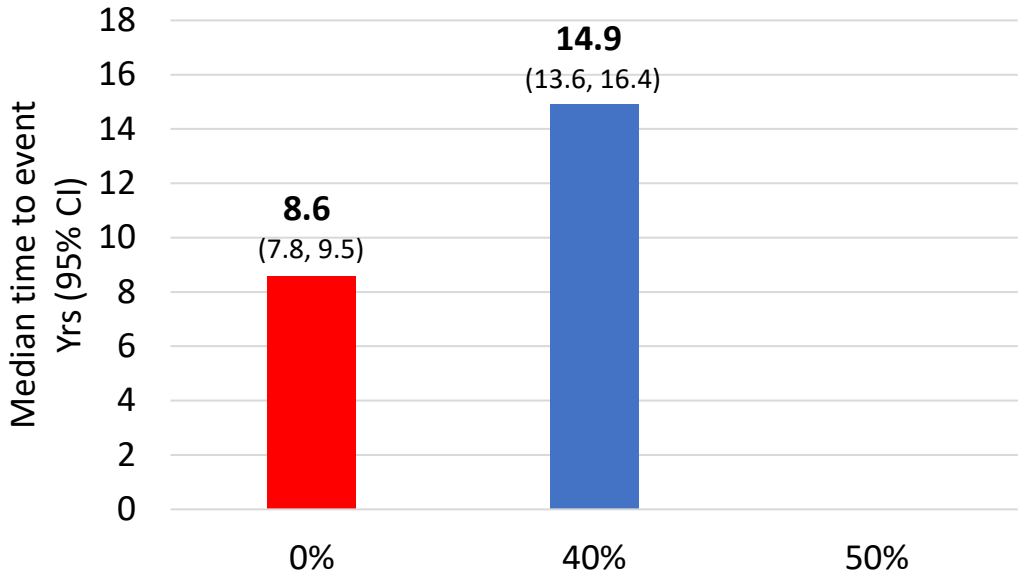

Treatment effect	5-year survival rate
0%	0.75
40%	0.89

Abbreviations: eGFR, estimated glomerular filtration rate; **HR**, hazard ratio; **IgAN,** IgA nephropathy; **IQR**, interquartile range; **KF**, kidney failure; **SD**, standard deviation; **UPCR**, urine protein-creatinine ratio

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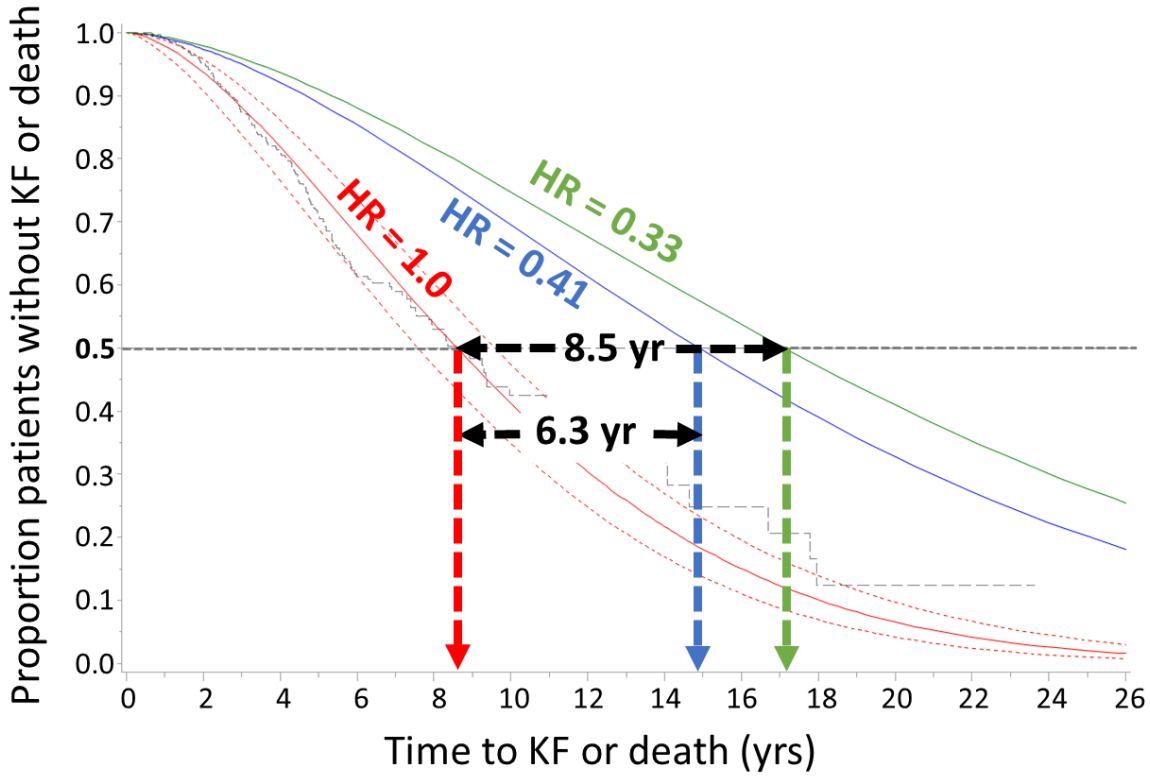
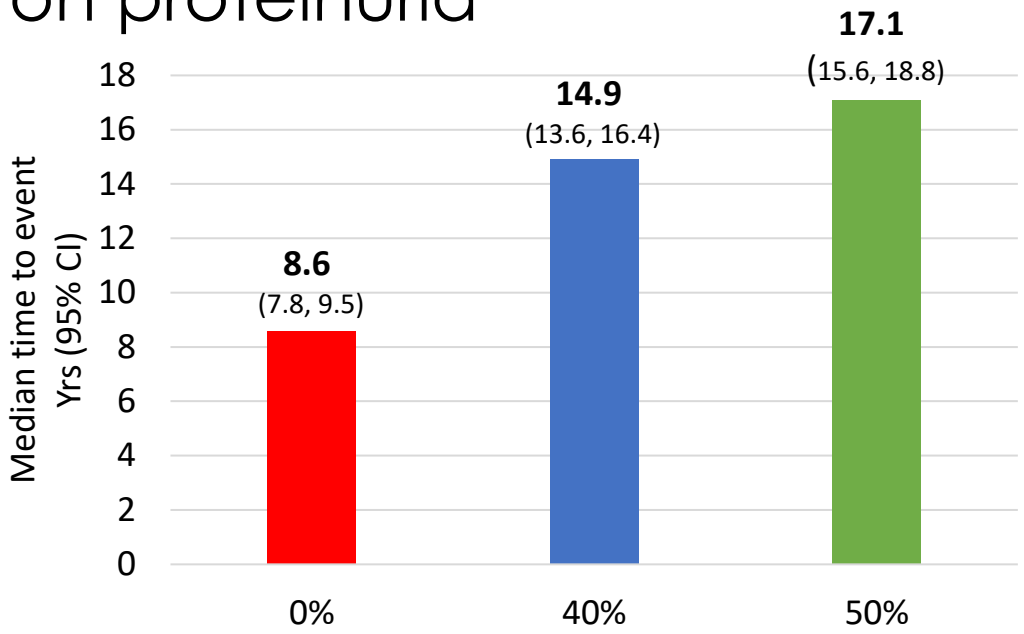


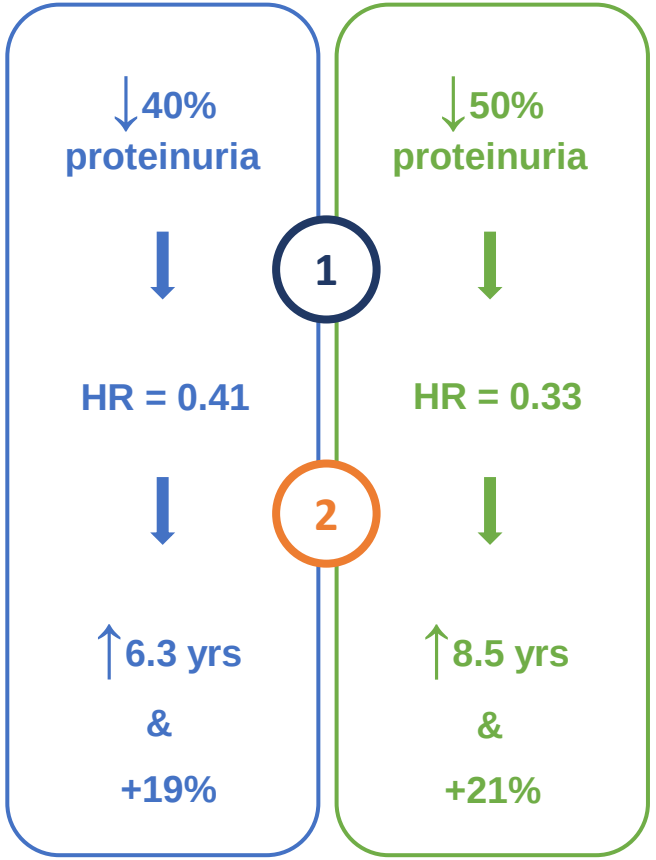


Treatment effect	5-year survival rate
0%	0.75
40%	0.89
50%	0.91

Abbreviations: eGFR, estimated glomerular filtration rate; **HR**, hazard ratio; **IgAN,** IgA nephropathy; **IQR**, interquartile range; **KF**, kidney failure; **SD**, standard deviation; **UPCR**, urine protein-creatinine ratio

Results:

Achieving a ↓40% or ↓50% treatment effect on proteinuria is associated with significant delay to KF



- **Achieving a 40% and 50% reductions in proteinuria at 9 months is associated with markedly improved outcomes**
- Substantially lower risk of KF/death
- Increased median time to KF/death

&

- Increased 5-year KF-free survival probability

Abbreviations: HR, hazard ratio; **KF**, kidney failure;

Discussion:
Limitations

- The trial level analysis included "doubling of serum creatinine" in composite outcome, which was not included in the AFT modelling.

- Estimates for delay to KF or death are applicable only to populations of comparable baseline proteinuria and eGFR.

Abbreviations: AFT, accelerated failure time; **eGFR**, estimated glomerular filtration rate; **KF**, kidney failure

Discussion:
Conclusions

- Therapeutic interventions that reduce proteinuria and risk of KF can confer important and clinically meaningful extensions in the time patients are alive and free from KF.

- Findings allow an estimation of future benefit in delay to KF/death for proteinuria results generated in ongoing phase 3 RCTs, provided baseline characteristics are comparable.

Abbreviations: KF, kidney failure; **RCT**, randomized controlled trial

Acknowledgements

- RaDaR was established with funding from the MRC, Kidney Research UK and Kidney Care UK.
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- Medical writing support was provided by Eve Hunter-Featherstone of Genesis Research which received compensation from Travere Therapeutics.