Estimating Delay in Time to ESKD for Treatment Effects on Proteinuria in IgA Nephropathy and FSGS

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Disclosures

- Jonathan Barratt: Consultancy/Advisory Board - Alnylam, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra; Steering Committee: Internal IgA Nephropathy Network; Editorial Board- Kidney International, CJASN, Clinical Science, Glomerular Diseases.
- Moin A. Saleem is the Chief Scientific Officer for Purespring Therapeutics. He has received consultancy fees and speaker's honoraria from Travere Therapeutics Inc.
- Leah Conley is an employee of Travere Therapeutics Inc and may have an equity or other financial interest in Travere Therapeutics Inc.
- Kevin Carroll provides statistical consultancy services to Travere Therapeutics and other biotech companies. He does not hold stock in Travere Therapeutics or any other biotech/pharma company. He is not an employee, board member or non-executive board member of any pharma/biotech company or any clinical research service provider

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Background

- Reduction in proteinuria is associated with lower risk of end-stage kidney disease (ESKD) in focal segmental glomerulosclerosis (FSGS) (Troost et al, 2017) and IgA nephropathy (Thompson et al, 2019)

Objective

- Estimate the delay in time to ESKD conferred by hypothesized treatment effects on proteinuria endpoints that are currently being applied in FSGS and IgAN phase 3 trials:

- **Mean percent change in proteinuria from baseline at 9 months**
- **Achieving UP/C <1.5 g/g associated with a 40% reduction in UP/C from baseline at 9 months (FSGS Partial Remission of Proteinuria Endpoint (FPRE))**

ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; UP/C, urine protein:creatinine ratio; FPRE, FSGS partial remission of proteinuria endpoint

Methods

Individual Patient Data

FSGS: National UK Registry of Rare Kidney Diseases (RaDaR)

Patient Criteria (FSGS)	N (pts)
Number of patients in the Idiopathic Nephrotic Syndrome cohort	**3,907**
Number of FSGS patients in NephroS sub-cohort	**420**
Number of patients meeting inclusion criteria: • Patients with primary or genetic FSGS with UP/C ≥1.5 g/g and eGFR ≥30 mL/min/m^2 • Follow-up proteinuria value within 6-12 months from baseline	**36**

IgAN: Leicester University Hospitals, UK

Patient Criteria (IgAN)	N (pts)
Number of patients in Leicester University Hospitals dataset	**339**
Number of patients meeting inclusion criteria: • IgAN patients with proteinuria value ≥1.0 g/day or UP/C ≥1.0 g/g and eGFR ≥30 mL/min/1.73m^2 at the initiation of RAS blockade • Follow-up proteinuria value within 6-12 months from baseline	**81**

Statistical Methods

- Time to ESKD (eGFR <15 mL/min, initiation of dialysis, transplantation) or death from any cause over the patient follow-up period analysed using accelerated failure time (AFT) modelling; Weibull, Log Logistic and Log Normal distributions were applied with fitted survivor function reported from the model with lowest AIC.
- Time gained for a given reduction in risk in ESKD/death and 5-year survival was estimated under proportional hazards

FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; UP/C, urine protein:creatinine ratio; eGRF, estimated glomerular filtration rate; RAS, renin-angiotensin system; ESKD, end stage kidney disease; AFT, accelerated failure time; AIC, Akaike's Information Criterion

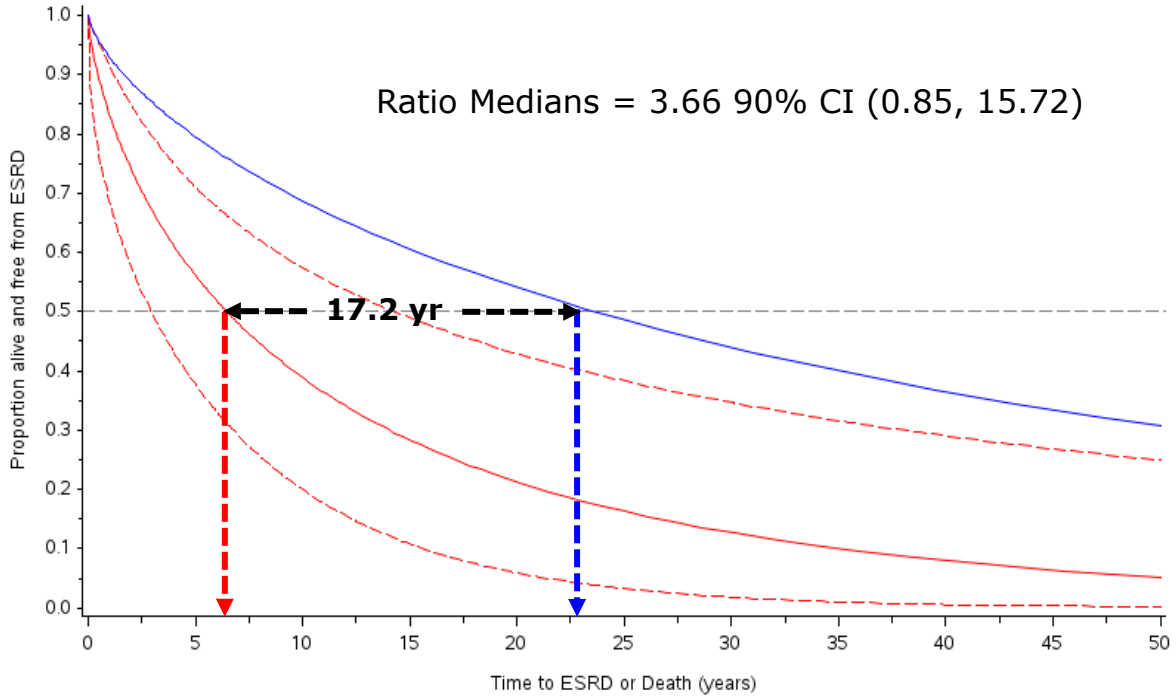
FSGS Analysis: *FSGS patients from the Nephrotic Syndrome NephroS cohort (n=36, incl. 14 events)*

Achieving FPRE is associated with an increase in median time to ESKD

AFT modelling & Weibull fit analysis

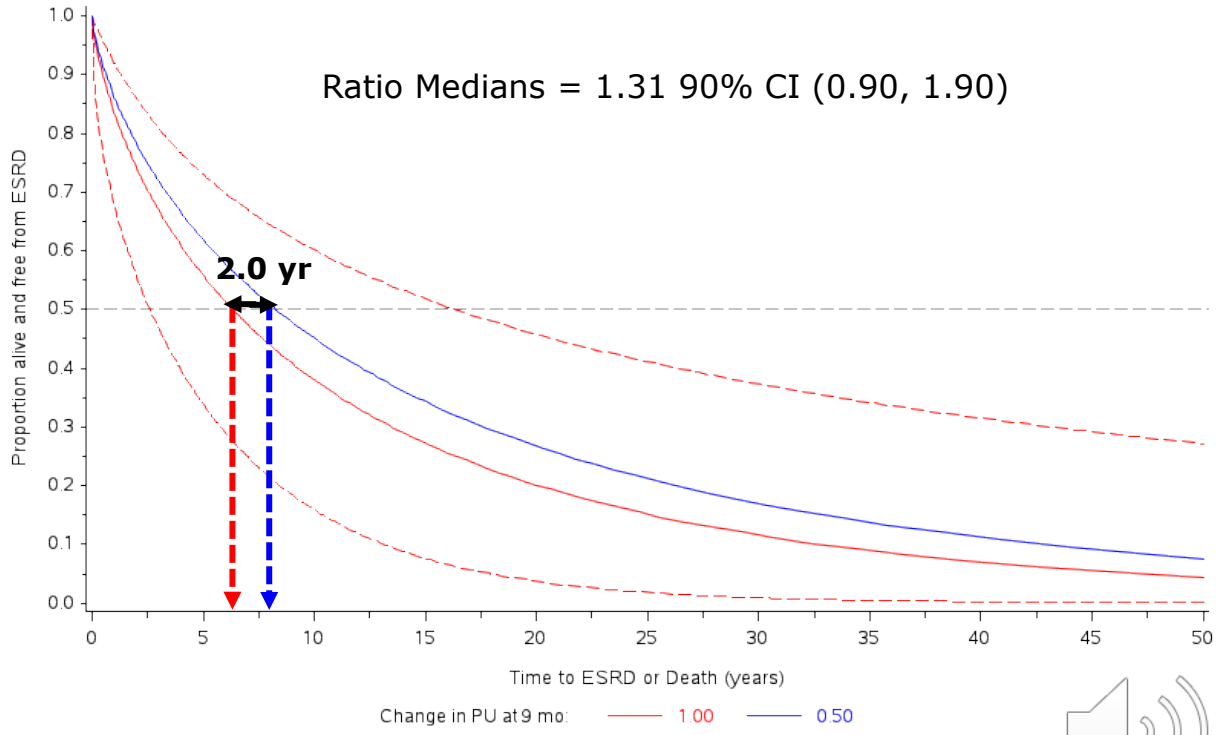
FPRE non-responder
Median time to event 6.5 yr, 90% CI (3.03, 13.8)

FPRE responder
Median time to event 23.7 yr, 90% CI (3.60, 156)



0% change in PCR
Median time to event 6.3 yr, 90% CI (2.6, 15.4)

50% reduction in PCR
Median time to event 8.3 yr, 90% CI (2.8, 24.2)

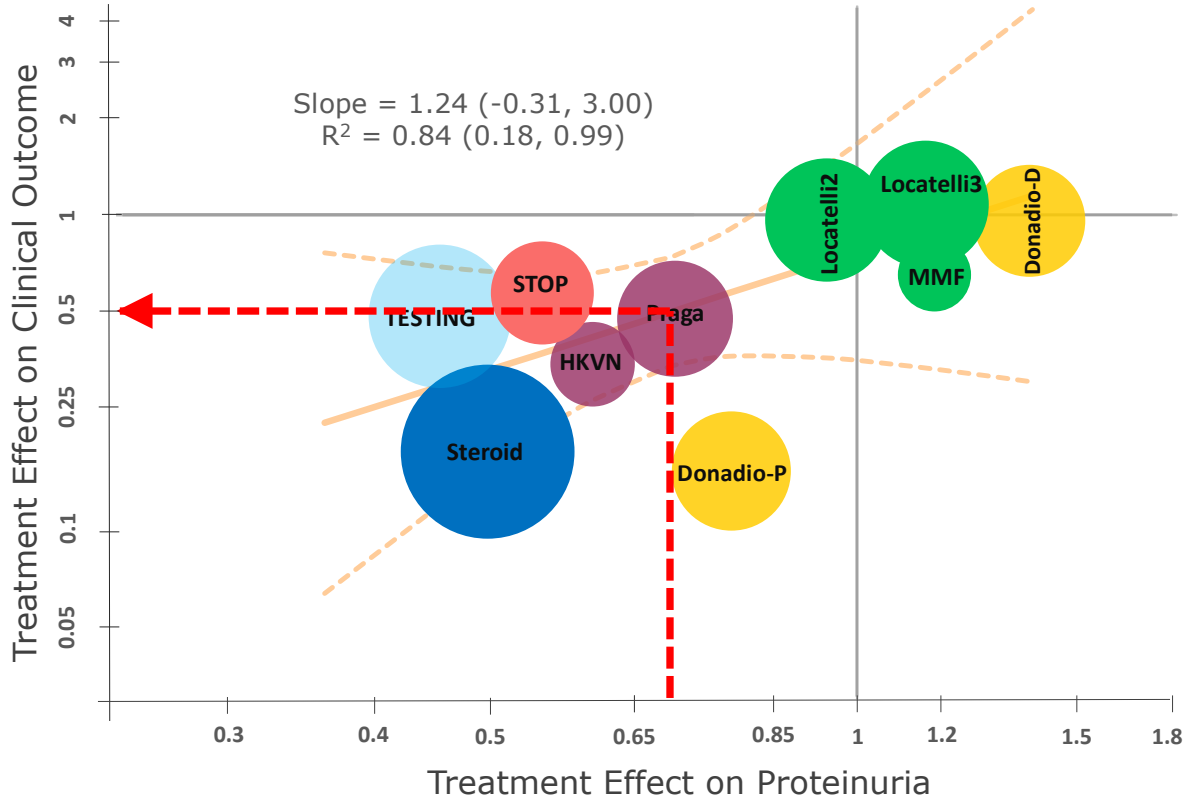


FSGS, focal segmental glomerulosclerosis; FPRE, FSGS partial remission of proteinuria endpoint; ESKD, end stage kidney disease; AFT, accelerated failure time; PCR, urine protein:creatinine ratio; yr, year; CI, confidence interval

IgAN Analysis: Thompson et al., Clin J Am Soc Nephrol (2019)

Kidney Health Initiative): Trial Level Analysis of RCTs in IgAN showing the relationship between treatments effects on proteinuria and risk of clinical outcomes

Treatment effect on proteinuria of 30% is estimated to confer a 50% reduction in risk of clinical outcomes



Drug vs Control Treatment Effect[1] on PU[2] at 9 months	Corresponding % Treatment effect for Drug if Control Ineffective	Predicted HR for ESRD	95% CI
0.90	10%	0.6750	(0.363, 1.252)
0.85	15%	0.6290	(0.366, 1.080)
0.80	20%	0.5840	(0.365, 0.934)
0.75	25%	0.5390	(0.356, 0.816)
0.70	30%	0.4950	(0.336, 0.730)
0.65	35%	0.4520	(0.302, 0.677)

[1]RASB: renin-angiotensin system blockade
[2]PU: proteinuria

IgAN, IgA nephropathy; RCT, randomized clinical trial; ESRD, end stage renal disease; CI, confidence interval

IgAN Analysis (cont'd): Leicester IgAN patients(n=81, incl. 23 events)

50% lower risk of ESKD is associated with increased median time to ESKD

Kaplan Meier plot & Weibull fit analysis

HR

HR = 1.0 represents no treatment effect on proteinuria from baseline:

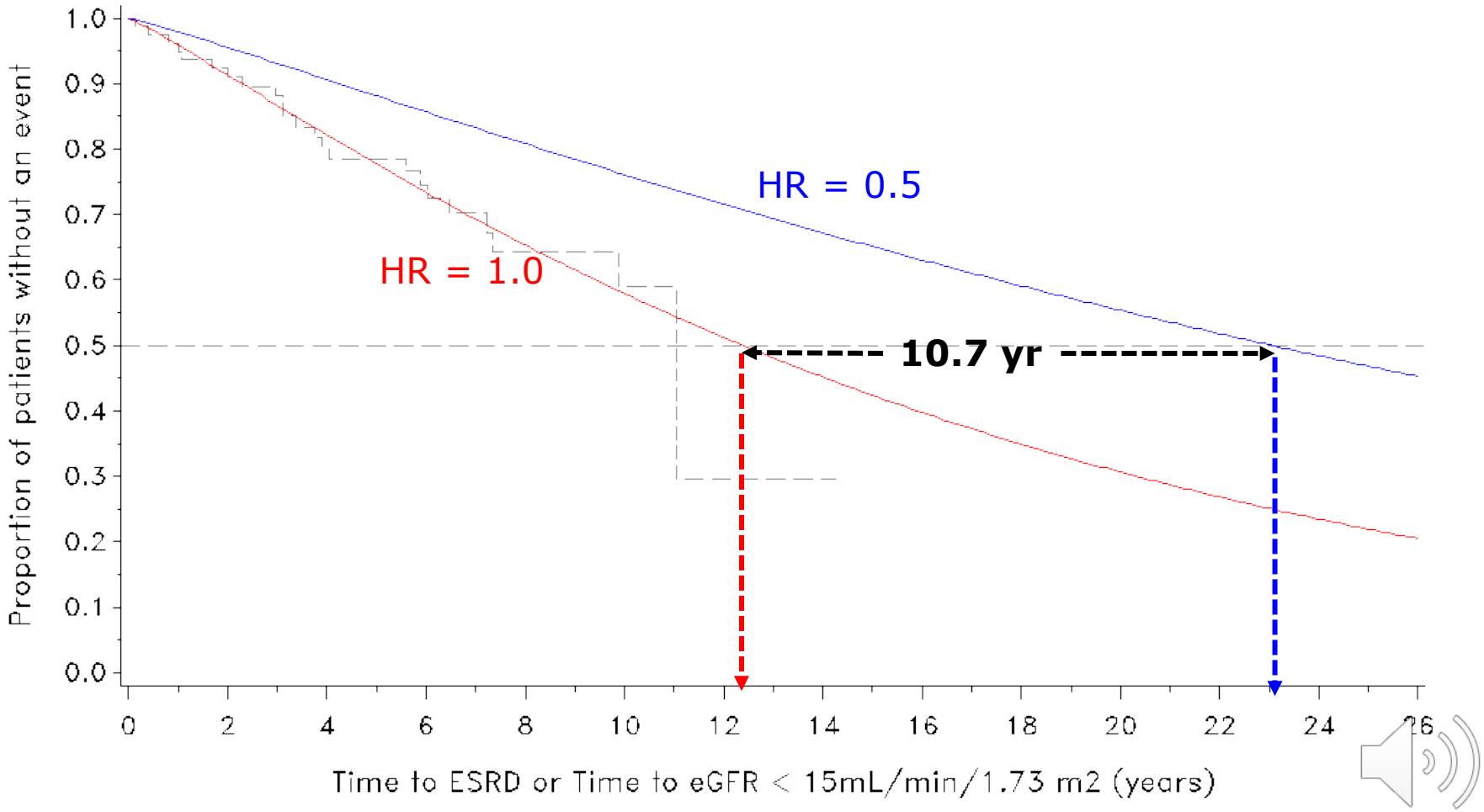
Median time to event 12.4 yr, 90% CI (15.9, 33.5)

HR

HR = 0.5 represents 30% treatment effect on proteinuria from baseline:

Median time to event 23.1 yr, 90% CI (13.5, 28.5)

Ratio of Medians 1.86 90% CI (1.55, 2.24)



IgAN, IgA nephropathy; ESKD, end stage kidney disease; HR, hazard ratio; yr, year; CI, confidence interval; ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate

Results

FSGS

Achieving FPRE at 9 months is associated with improved outcome

- Median time to ESKD is increased
- 5-year ESKD free survival rate is increased

IgAN

Achieving a 30% reduction in proteinuria at 9 months is associated with improved outcome

- 50% lower risk of ESKD
- Median time to ESKD is increased
- 5-year ESKD free survival rate is increased

Limitations

- Relatively low number of patients and events
- Wide confidence intervals for the ratio of medians relating to the delay to ESKD

Conclusion

- Therapeutic interventions that reduce proteinuria may confer important and clinically meaningful extensions in the time patients are alive and free from ESKD.

FSGS, focal segmental glomerulosclerosis; FPRE, FSGS partial remission of proteinuria endpoint; ESKD, end stage kidney disease; IgAN, IgA nephropathy