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PROTECT and NefIgArd 2-Year Proteinuria and eGFR Outcomes in Adults With IgA Nephropathy: Matching-Adjusted Indirect Comparison

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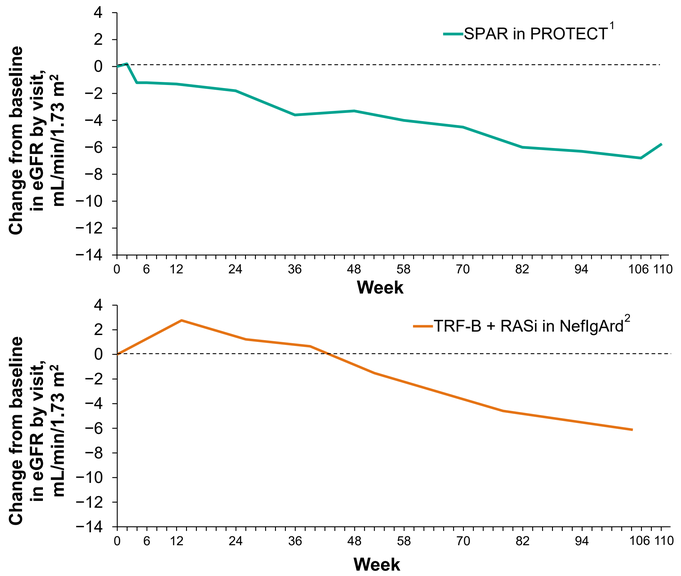
INTRODUCTION

- The Phase 3 PROTECT and NefIgArd RCTs investigated the efficacy (including effects on kidney function decline and proteinuria) and safety of sparsentan (SPAR) and targeted-release formulation budesonide (TRF-B), respectively, in patients with IgA nephropathy[1,2]

eGFR by Visit for SPAR in PROTECT and TRF-B + RASi in NefIgArd



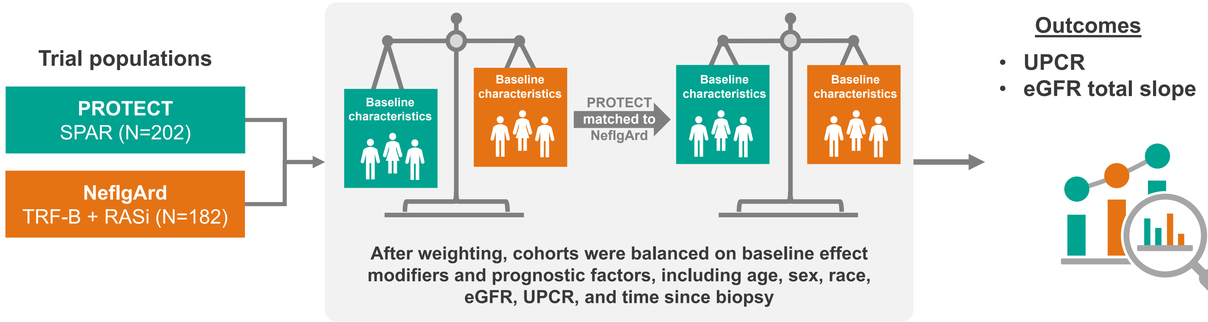
- SPAR[3,4] and TRF-B[5,6] are approved for the treatment of IgA nephropathy in the US and Europe

AIM

To compare 2-year efficacy outcomes between SPAR in PROTECT[1] and TRF-B + real-world optimized and stable RASi SOC in NefIgArd[2] using unanchored matching-adjusted indirect comparisons (MAICs)

METHODS

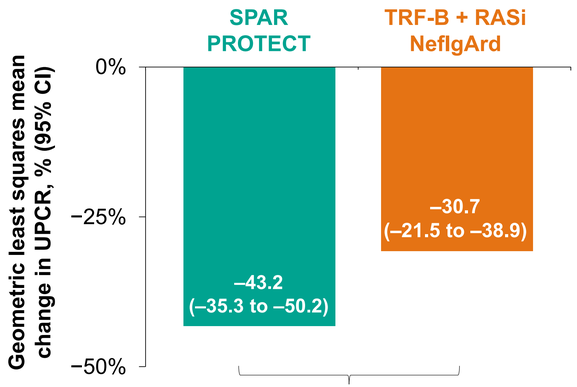
Weighted matching of key baseline characteristics



After weighting, cohorts were balanced on baseline effect modifiers and prognostic factors, including age, sex, race, eGFR, UPCR, and time since biopsy

RESULTS

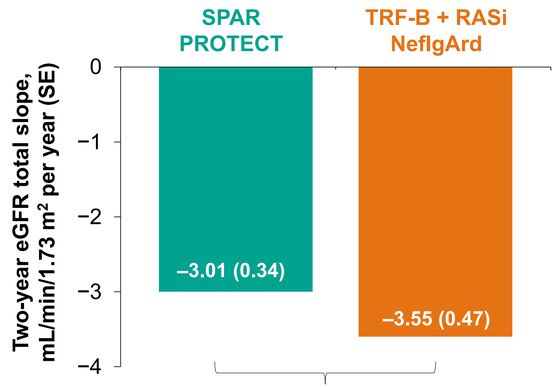
Percentage Reduction in UPCR From Baseline to 2 Years



Relative reduction (95% CI)
−18.1% (−31.6% to −1.9%); *P*=.03

After weighting, patients treated with SPAR had a greater relative percentage reduction in UPCR vs those treated with TRF-B + RASi SOC

Annualized 2-Year eGFR Total Slope



Difference (95% CI)
0.54 (−0.60 to 1.68); *P*=.35

After weighting, patients treated with SPAR had a slower decline in kidney function vs those treated with TRF-B + RASi SOC

CONCLUSIONS

- At 2 years, SPAR was associated with a greater relative reduction in UPCR compared with TRF-B + RASi SOC
  - These data are consistent with previously reported 9-month MAIC outcomes[7]
- Patients treated with SPAR had numerically slower kidney function decline (eGFR total slope) vs those treated with TRF-B + RASi SOC; however, this difference was not statistically significant
- Further analysis comparing eGFR chronic slope may provide a better indication of the long-term nephroprotective value of both therapies

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eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; MAIC, matching-adjusted indirect comparisons; RASi, renin-angiotensin system inhibitor; RCT, randomized controlled trial; SOC, standard of care; SPAR, sparsentan; TRF-B, targeted-release formulation budesonide; UPCR, urine protein-to-creatinine ratio.

PROTECT and NefIgArd Two-Year Proteinuria and eGFR Outcomes in Adults with IgA Nephropathy: Matching-Adjusted Indirect Comparison

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INTRODUCTION

- Immunoglobulin A nephropathy (IgA) nephropathy is characterized by deposition of IgA in the glomeruli, resulting in progressive loss of renal function and increased risk of kidney failure[1,2]
- The Phase 3 PROTECT and NefIgArd trials investigated the efficacy (including effects on kidney function decline and proteinuria) and safety of sparsentan (SPAR) and targeted-release formulation budesonide (TRF-B), respectively, in patients with IgA nephropathy[3,4]
- In the absence of head-to-head trials, the aim of this study was to compare 2-year efficacy outcomes between SPAR in PROTECT and TRF-B + optimized and stable renin-angiotensin system inhibition (RASi) in NefIgArd using unanchored matching-adjusted indirect comparisons (MAICs)

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METHOD

Data source

- The following data were utilized in this study:
  - Individual patient-level data from the SPAR (N=202) arm of the phase III, randomized, double-blind PROTECT trial (NCT03762850) in patients with IgA nephropathy[3]
  - Published aggregated data from the treatment arm (i.e., TRF-B + optimized and stable renin-angiotensin system inhibitor [RASi]; N=182) of the phase III, randomized, double-blind NefIgArd trial (NCT03643965) in patients with IgA nephropathy[4]

Study outcomes

- The following data were utilized in this study:
  - Percentage reduction in urine protein-creatinine ratio (UPCR): the percentage change in UPCR from baseline to 2 years in the PROTECT and NefIgArd trials
  - Annualized 2-year estimated glomerular filtration rate (eGFR) total slope: the annualized rate of decline in eGFR over the 2-year period following randomization in the PROTECT and NefIgArd trials

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METHOD

Statistical analysis

- Assessment of the PROTECT and NefIgArd trials indicated sufficient similarity in key sample selection criteria and outcome definitions, making indirect treatment comparisons feasible between these two trials
- However, the control arm in PROTECT was gold standard optimized RASi, while the control arm in NefIgArd was placebo + optimized and stable RASi. Due to the lack of comparability between control arms (and evidence of different outcomes),[5] an unanchored MAIC was implemented in this study
- Specifically, patients in the SPAR arm of the PROTECT trial were weighted to match key baseline effect modifiers and prognostic factors of patients in the TRF-B + RASi arm of the NefIgArd trial
    - Matching weights were estimated using the method of moments[6]
- Percentage reduction in UPCR from baseline to 2 years and annualized 2-year eGFR total slope estimated from the weighted SPAR cohort were compared against those reported for the TRF-B + RASi arm of the NefIgArd trial
    - Percentage reduction in UPCR was estimated using a mixed model for repeated measures (MMRM)
    - Annualized 2-year eGFR total slope was estimated using a random effect coefficient model
- P-values were estimated by the two-tailed z-test with a pooled standard error

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RESULTS

Patient characteristics and effective sample size

- Compared with patients treated with TRF-B + RASi in NefIgArd, patients treated with SPAR in PROTECT were older and had higher median blood pressure, lower median eGFR, lower median urine protein, and a longer duration of time since biopsy (**Table 1**)
- After weighting, all matched baseline effect modifiers and prognostic factors were balanced between the 2 cohorts

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RESULTS

Table 1. Baseline patient characteristics of SPAR arm from PROTECT and TRF-B + RASi arm from NefIgArd

	TRF-B + optimized and stable RASi	SPAR			
		Before matching		After matching	
		Summary statistic (N=202)	Difference	Summary statistic (ESS=90.1)	Difference
Age (years), median [Q1, Q3]	43.00 [36.00, 50.00]	47.00 [37.00, 57.00]	-4.00 [-1.00, -7.00]	43.00 [36.00, 51.00]	0.00 [0.00, -1.00]
Male, %	64	69	-5	64	0.00
Race, %					
White	76	64	11	76	0.00
Asian	24	33	-10	24	0.00
Systolic blood pressure, median	126.00	128.00	-2.00	126.00	0.00
Diastolic blood pressure, median	79.00	81.00	-2.00	79.00	0.00
eGFR (mL/min/1.73m^2), median [Q1, Q3]	56.14 [45.50, 70.97]	50.00 [38.00, 71.00]	6.14 [7.50, -0.03]	56.00 [45.00, 71.00]	0.14 [0.50. -0.03]
UPCR, mean (SD)	1.48 (0.85)	1.43 (0.90)	0.05 (-0.05)	1.48 (0.85)	0.00 (0.00)
Urine protein (mg/dL), median [Q1, Q3]	2.29 [1.61, 3.14]	1.76 [1.18, 2.86]	0.53 [0.43, 0.28]	2.24 [1.60, 3.14]	0.05 [0.02, -0.00]
Presence of diabetes, %	9	9	-0.00	9	0.00
Time from biopsy (years), median [Q1, Q3]	2.40 [0.60, 6.90]	4.13 [1.48, 9.49]	-1.73 [-0.88, -2.59]	2.46 [0.65, 6.92]	-0.06 [-0.05, -0.02]

eGFR: estimated glomerular filtration rate; Q: quarter; RASi: renin-angiotensin system inhibitor; TRF-B: targeted-release formulation budesonide; SPAR: sparsentan; UPCR: urine protein-creatinine ratio

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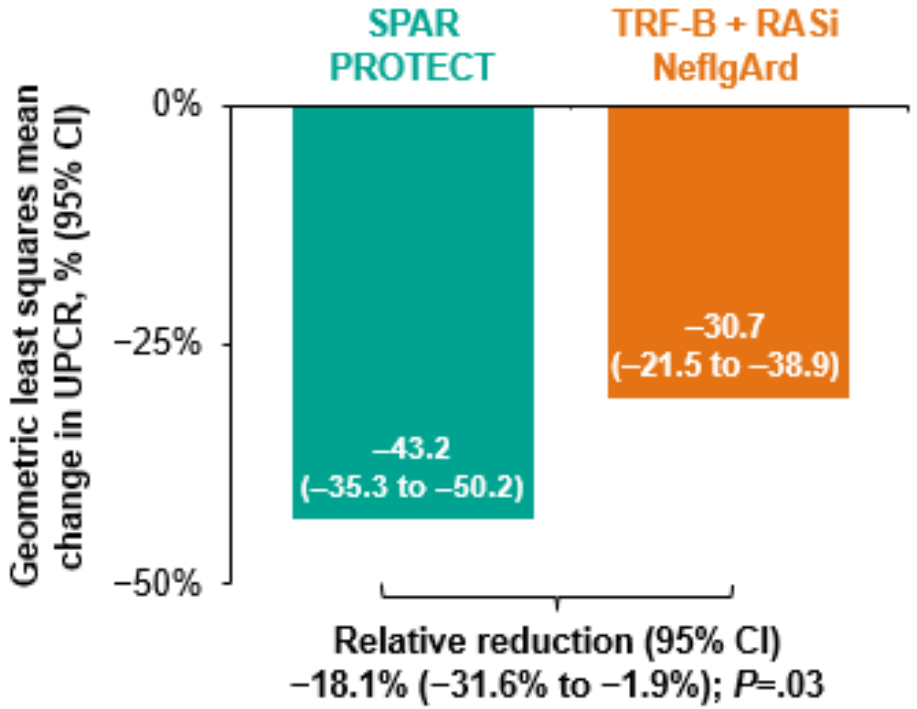
RESULTS

Percentage reduction in UPCR from baseline to 2 years

- After matching, patients treated with SPAR exhibited a greater mean percentage reduction in UPCR from baseline to 2 years (-43.2%) compared to those treated with TRF-B + RASi (-30.7%), representing a relative percentage reduction of -18.1% (p=.03; **Figure 1**)

Figure 1. Comparison of percentage reduction in UPCR from baseline to 2 years associated with SPAR vs. TRF-B + RASi



CI: confidence interval; RASi: renin-angiotensin system inhibitor; TRF-B: targeted-release formulation budesonide; SPAR: sparsentan; UPCR: urine protein-creatinine ratio

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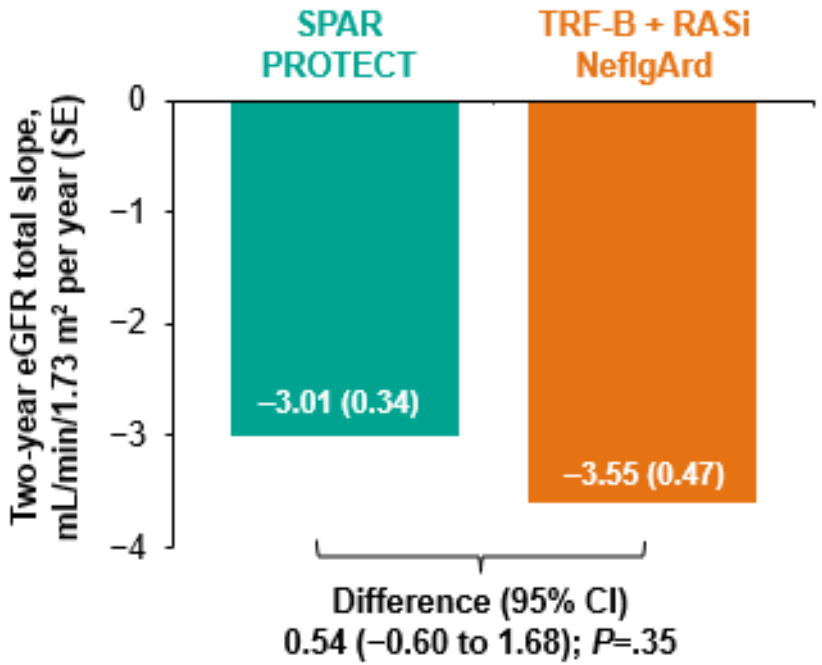
RESULTS

Annualized 2-year eGFR total slope

- After matching, patients treated with SPAR exhibited a slower decline in kidney function (2-year eGFR total slope: -3.01 mL/min/1.73m^2) compared to TRF-B + RASi (2-year eGFR total slope: -3.55 mL/min/1.73m^2), representing a difference of 0.54 mL/min/1.73m^2 per year (**Figure 2**)
    - However, this difference was not statistically significant (p=.35)

Figure 2. Comparison of 2-year eGFR total slope associated with SPAR vs. TRF-B + RASi



CI: confidence interval; RASi: renin-angiotensin system inhibitor; TRF-B: targeted-release formulation budesonide; SPAR: sparsentan; UPCR: urine protein-creatinine ratio

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LIMITATIONS

- Like all indirect treatment comparisons, MAICs assume exchangeability of patients between studies, which is difficult to conclusively validate
- Only consistently reported baseline factors could be matched; results may be impacted by unreported or unmeasured variable
- Given that this analysis was based on participants enrolled in the PROTECT and NefIgArd trials, its findings might not apply universally to the general IgA nephropathy population

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CONCLUSIONS

- At 2 years, SPAR was associated with a greater relative reduction in UPCR compared
- with TRF-B + RASi
  - These data are consistent with previously reported 9-month MAIC outcomes[7]
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