BLISS-LN: A randomised, double-blind, placebo-controlled Phase 3 trial of intravenous belimumab in patients with active lupus nephritis

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Disclosures

- DR, BJ, SWB, YG and CB are employees of GSK and hold stocks and shares in the company
- CK is a former employee of GSK and holds stocks in the company
- RF has received consulting fees and grant/research support from GSK
- YKOT has received consultancy fees from GSK, Aurinia Pharmaceutincals Inc, and Novartis and grant/research support from GSK
- GC has received consultancy fees and grant/research support from Genentech and Merck
- ZA has received grant/research support from Amgen, GSK, Roche, Pfizer and Novartis, and consulting fees and speaker bureau from AstraZeneca and GSK
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- FH, BHR, AM and AS have received reimbursement for GSK advisory board participation
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Background

- A *post hoc* analysis of belimumab trials demonstrated improvements in renal parameters[1]
- Increased serum BAFF levels and heightened intra-renal BAFF production promote renal inflammation
  - Neutralising BAFF and down-regulating auto-reactive B-cell function in kidneys represents a compelling therapeutic approach to LN[2,3,4]
- Belimumab, a recombinant human IgG1λ monoclonal antibody that inhibits BAFF, is approved for the treatment of active autoantibody-positive SLE[5]

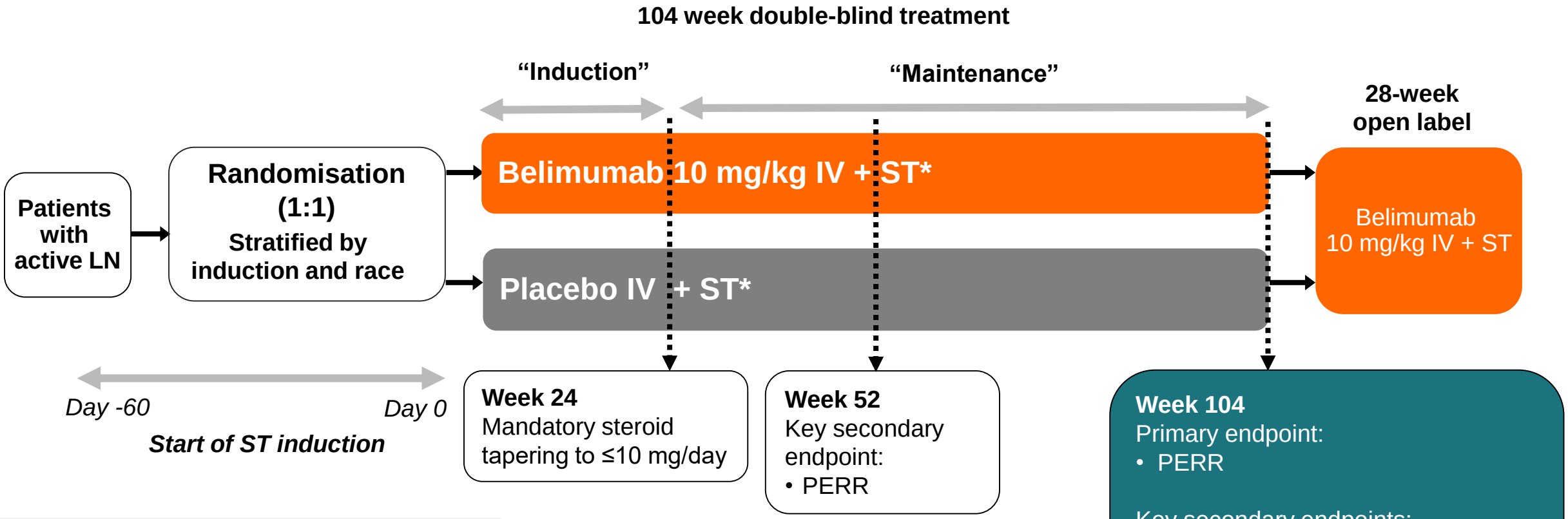
BLISS-LN is a Phase 3, randomised, double-blind, placebo-controlled, 104-week study that assessed the efficacy and safety of belimumab in adult patients with SLE and LN

1. Dooley MA, *et al*. *Lupus*. 2013; 22(1): 63–72. 2. Kang S, *et al*. *J Immunol.* 2017; 198: 2602-11. 3. Schwarting A, *et al*. *Lupus.* 2018 ;27: 243-56. 4. Sun CY *et al*. *Int J Rheumatol.* 2013; 954292. 5. Benlysta Prescribing Information. 2019. Accessed Apr 24, 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125370s067,761043s005lbl.pdf)

BAFF, B-cell-activating factor; IgG, immunoglobulin G; LN, lupus nephritis; SLE, systemic lupus erythematosus.

Study objectives and design

To assess the efficacy and safety of belimumab during induction and maintenance of LN



Key eligibility criteria:

- ≥18 years of age
- Clinically active LN (uPCR≥1 at screening)
- Class III, IV, V or III+V or IV+V on renal biopsy and requiring induction therapy

* Induction with HDCS+CYC, followed by LDCS+AZA maintenance; or induction with HDCS+MMF, followed by LDCS+MMF maintenance

AZA, azathioprine; BEL, belimumab; CRR, Complete Renal Response; CYC, cyclophosphamide; HDCS, high dose corticosteroids; LDCS, low dose corticosteroids; LN, lupus nephritis; IV, intravenous; MMF, mycophenolate mofetil; ORR, Ordinal Renal Response; PERR, Primary Efficacy Renal Response; ST, standard therapy; uPCR, urinary protein:creatinine ratio.

Key efficacy outcomes and testing hierarchy

- **PERR** defined as:
  - uPCR ≤0.7, *and*
  - eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m^2, *and*
  - Not a treatment failure

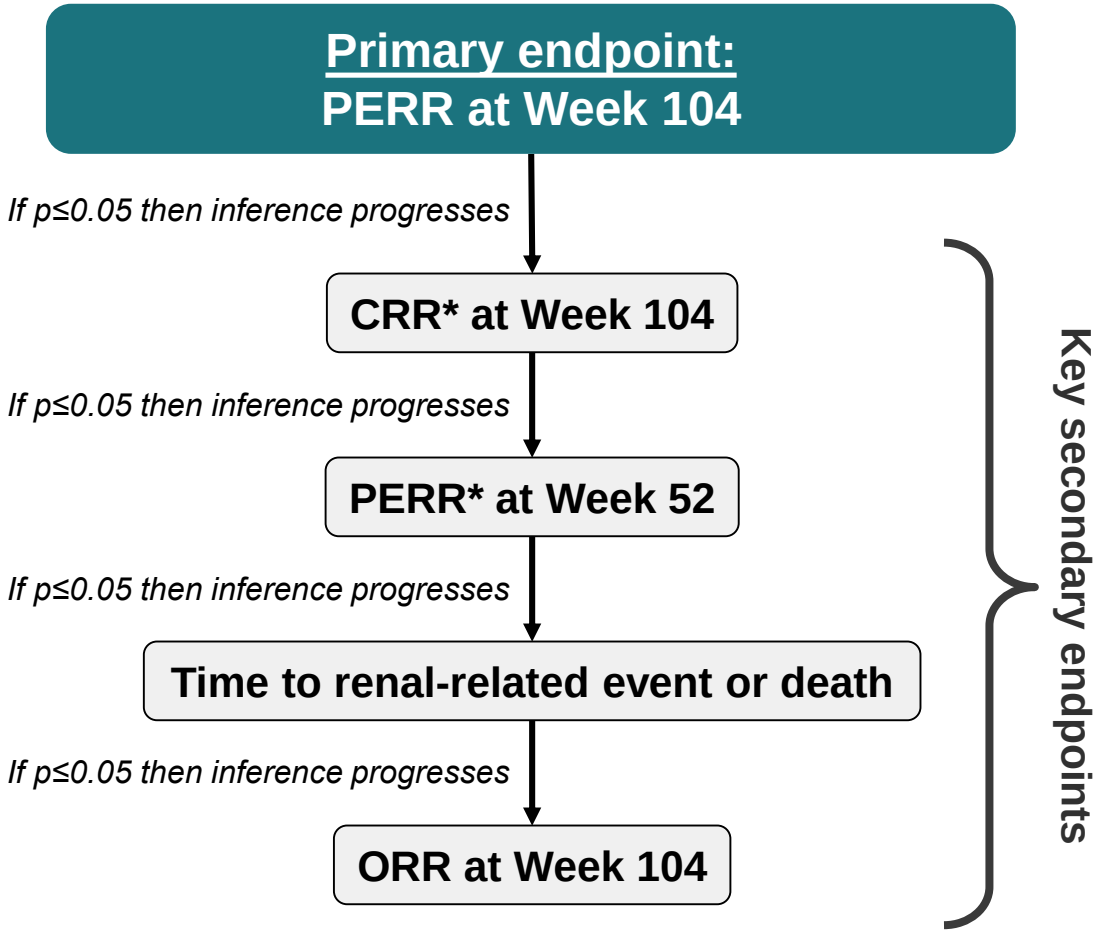
- **CRR** defined as:
  - uPCR <0.5, *and*
  - eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, *and*
  - Not a treatment failure

- **Renal-related event** defined as:

  First incidence of: i) ESRD, ii) doubling of serum creatinine, iii) renal worsening as evidenced by increased proteinuria and/or impaired renal function, *or* iv) renal disease-related treatment failure

- **ORR** defined as 'Complete', 'Partial' or 'No renal response'

  Partial ORR defined as:
  - eGFR no worse than 10% below baseline value or within normal range, *and*
  - ≥50% decrease in uPCR with: uPCR <1.0, if baseline ratio ≤3.0, *or* uPCR <3.0, if baseline ratio >3.0, *and*
  - Not a treatment failure, *and*
  - Not a CRR



CRR, Complete Renal Response; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ORR, Ordinal Renal Response; PERR, Primary Efficacy Renal Response; uPCR, urinary protein:creatinine.

Results

Baseline demographics and disease characteristics (mITT population)

- 448 patients were randomised to treatment and received ≥1 dose of study treatment
  - 446 (belimumab, n=223; placebo, n=223) were included in the mITT population
  - Induction regimen for each treatment group: CYC/AZA, n=59 (26.5%); MMF, n=164 (73.5%)
- Baseline characteristics were balanced between groups

Characteristic	Placebo n=223	Belimumab 10 mg/kg IV n=223
Age (years), mean (SD)	33.1 (10.6)	33.7 (10.7)
Female, n (%)	196 (87.9)	197 (88.3)
LN disease duration (years), median (IQR)	0.2 (0.1, 3.4)	0.2 (0.1, 3.3)
Renal biopsy class, n (%)		
Class III or IV	132 (59.2)	126 (56.5)
Class III and V or Class IV and V	55 (24.7)	61 (27.4)
Class V	36 (16.1)	36 (16.1)
eGFR (mL/min/1.73 m^2), median (IQR)	98.0 (67.0, 127.0)	99.0 (72.0, 124.0)
eGFR <60, n (%)	41 (18.4)	33 (14.8)
uPCR (g/g), median (IQR)	2.5 (1.4, 4.8)	2.6 (1.1, 4.4)
uPCR ≥3, n (%)	92 (41.3)	91 (40.8)

AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IV, intravenous; LN, lupus nephritis; mITT, modified intent-to-treat; MMF, mycophenolate mofetil; SD, standard deviation; SLE, systemic lupus erythematosus; uPCR, urinary protein:creatinine ratio.

Primary and key secondary endpoints

Prespecified testing hierarchy (alpha controlled)

	Response rate (%)		Treatment difference (%)	OR/HR (95% CI)	p-value
	Placebo n=223	Belimumab 10 mg/kg IV n=223			
PERR* at Week 104	32.3	43.0	10.76	OR 1.55 (1.04, 2.32)	0.03
CRR† at Week 104	19.7	30.0	10.31	OR 1.74 (1.11, 2.74)	0.02
PERR* at Week 52	35.4	46.6	11.21	OR 1.59 (1.06, 2.38)	0.02
Time to renal-related event or death	28.3	15.7		HR 0.51 (0.34, 0.77)	0.001
ORR at Week 104					
Complete response	19.7	30.0	10.31		0.01
Partial response	17.0	17.5	0.45		
Non-responders‡	63.2	52.5	-10.76		

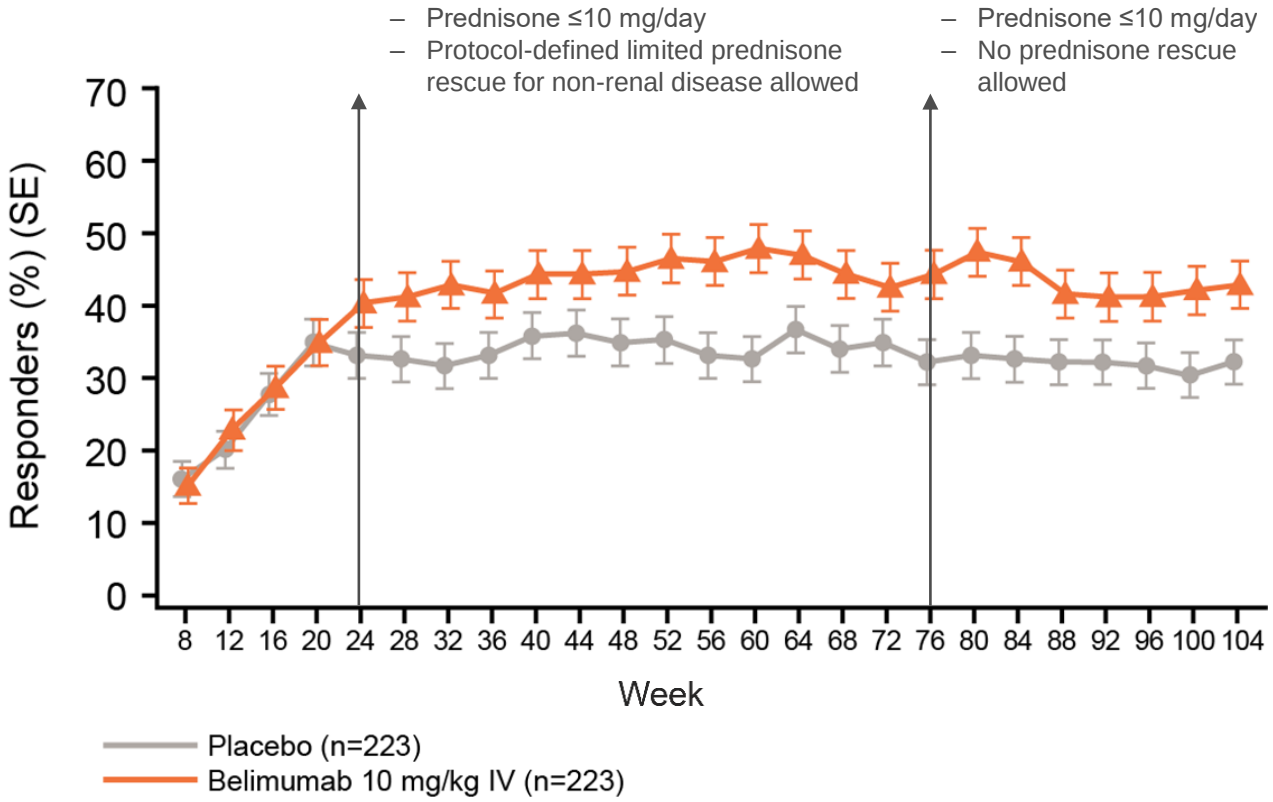
- All models are for the comparison of belimumab vs placebo controlling for induction regimen (CYC vs MMF), race (black vs non-black), baseline uPCR, and baseline eGFR
- PERR and CRR endpoints used logistic regression. Time to renal-related event or death was a Cox regression analysis. ORR was rank ANCOVA

*uPCR ≤0.7, eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m^2, not a TF; †uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, not a TF; ‡Study WD, TF, and IPD were imputed as non-responders. ANCOVA, analysis of covariance; CI, confidence interval; CRR, Complete Renal Response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HR, hazards ratio; IPD, investigational product discontinuation; IV, intravenous; mITT, modified intent-to-treat; MMF, mycophenolate mofetil; OR, odds ratio; ORR, Ordinal Renal Response; PERR, Primary Efficacy Renal Response; TF, treatment failure; uPCR, urinary protein:creatinine; WD, withdrawal

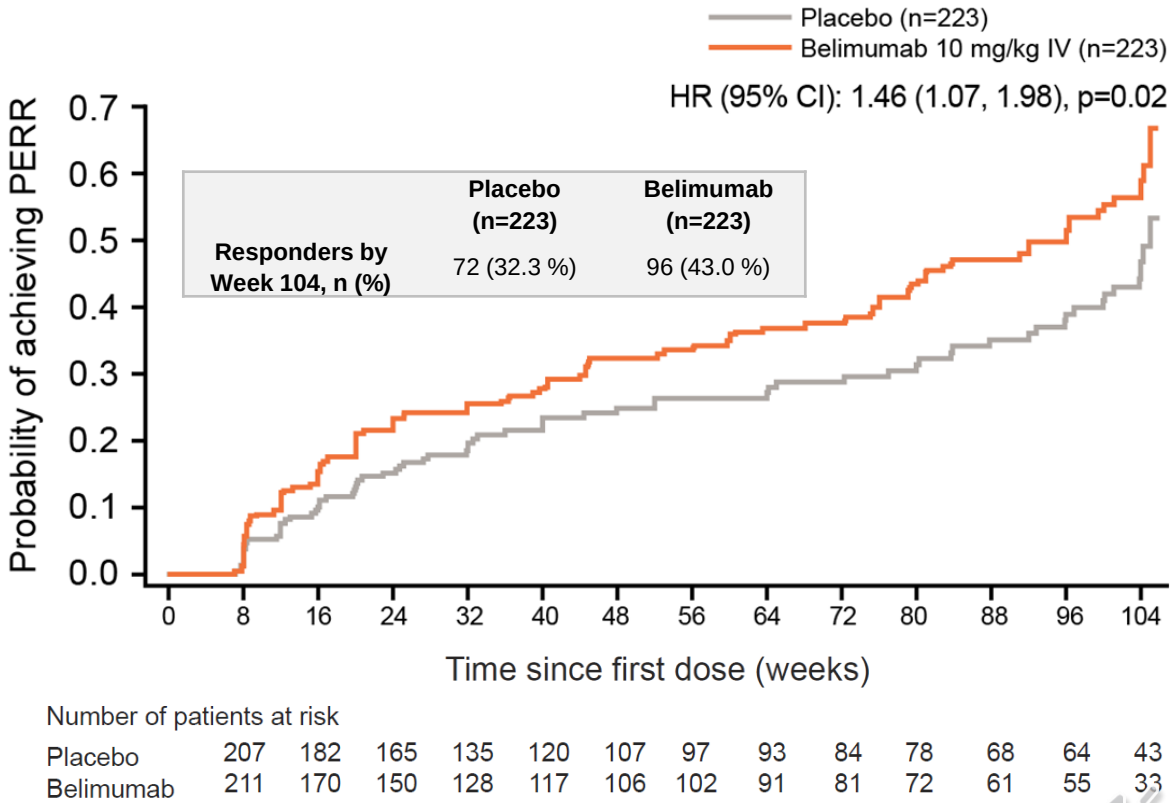
PERR*

Supportive analyses *(IPD/TF/WD=NR)*

PERR* by visit



Time to PERR* maintained through Week 104



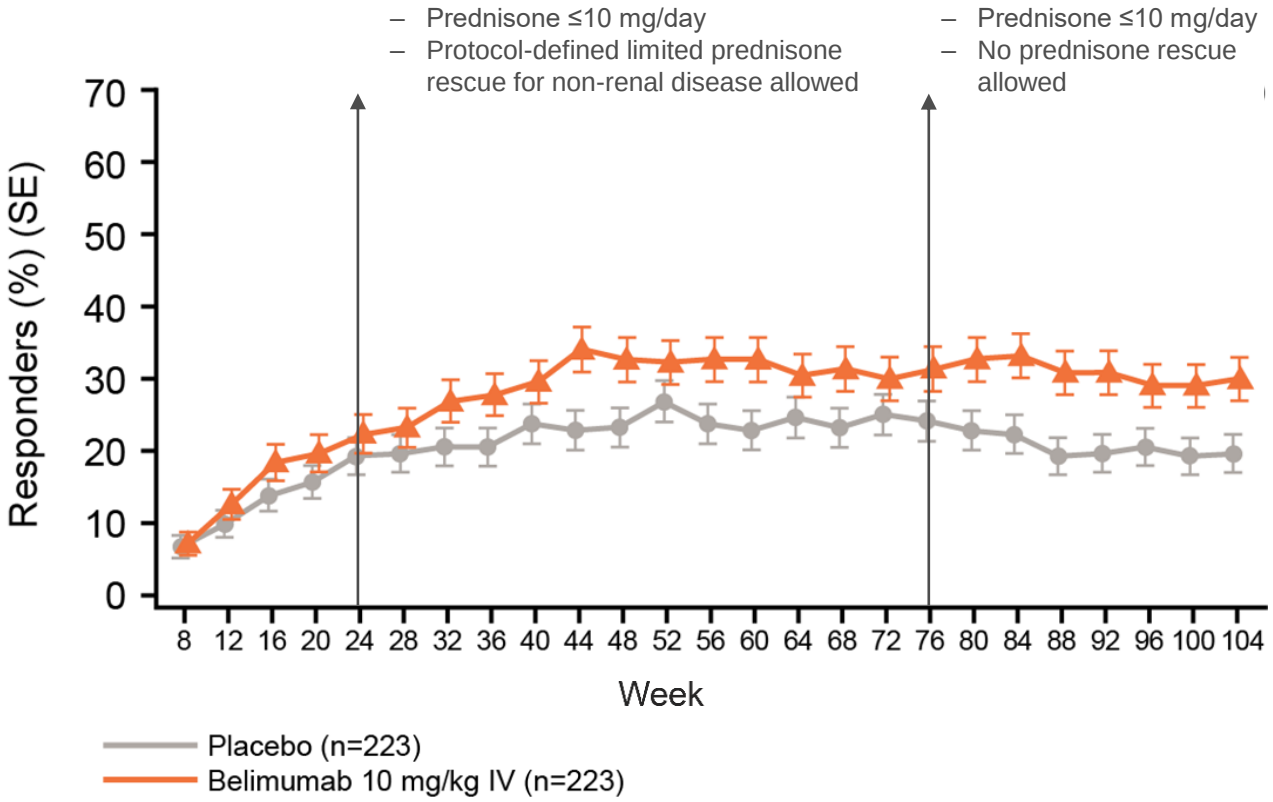
*uPCR ≤0.7, eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m^2, not a TF.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPD, investigational product discontinuation; IV, intravenous; NR, non-responder; PERR, Primary Efficacy Renal Response; SE, standard error; TF, treatment failure; uPCR, urinary protein:creatinine ratio; WD, withdrawal.

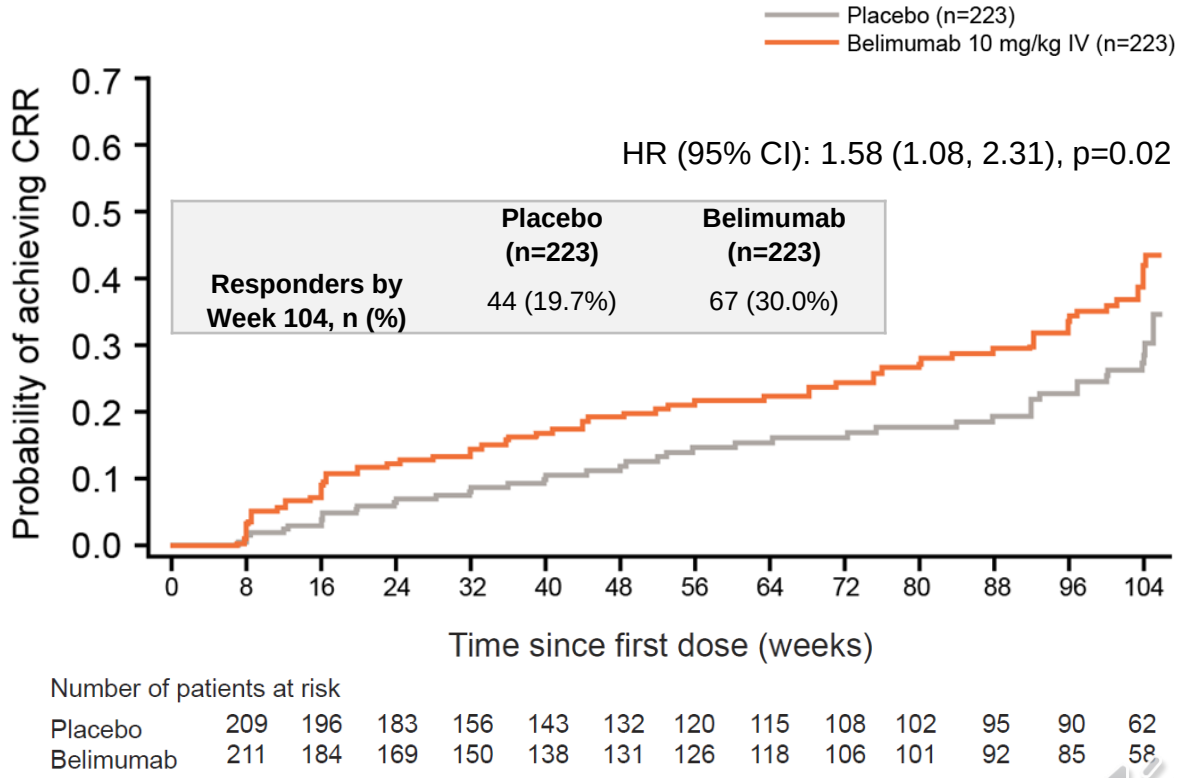
CRR*

Supportive analyses *(IPD/TF/WD=NR)*

CRR* by visit



Time to CRR* maintained through Week 104

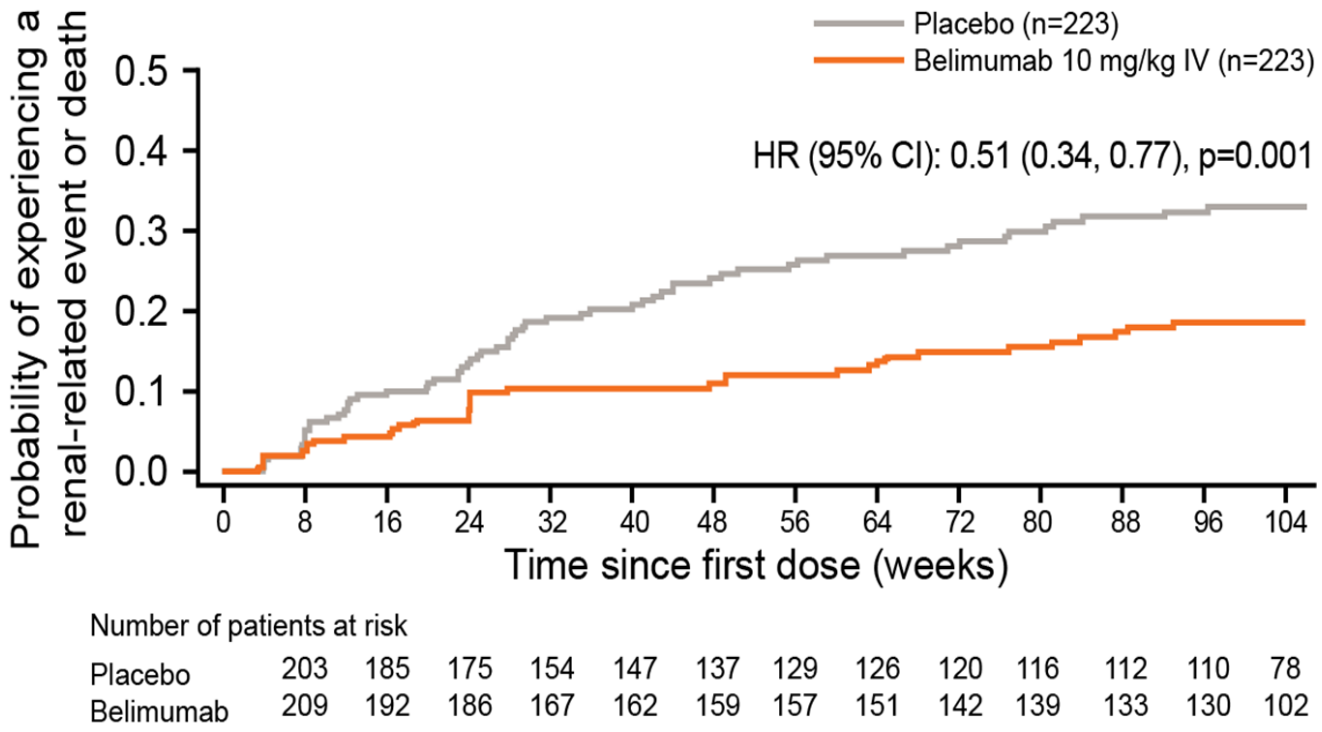


*uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, not a TF.

CI, confidence interval; CRR, Complete Renal Response; eGFR, estimated glomerular filtration rate; HR, hazards ratio; IPD, investigational product discontinuation; IV, intravenous; NR, non-responder; SE, standard error; TF, treatment failure; uPCR, urinary protein:creatinine ratio; WD, withdrawal.

Time to renal-related event or death

(IPD/TF not related to renal disease/WD were censored)



	Placebo (n=223)	Belimumab (n=223)
Patients with an event by Week 104, n (%)	63 (28.3%)	35 (15.7%)

	Placebo n=223	Belimumab 10 mg/kg IV n=223
Total events*	63	35
Renal worsening†	39	17
Treatment failure related to renal event‡	20	16
Doubling of serum creatine from baseline	1	1
Progression to ESRD	1	0
Death for any reason	2	1

*Represents first event for each patient with an event. †Defined by increased proteinuria (a reproducible increase in uPCR to >1 g if the baseline value was <0.2 g, to >2 g if the baseline value was 0.2–1 g, or more than twice the value at baseline if the baseline value was >1 g), or impaired renal function (a reproducible decrease in GFR of >20%, accompanied by proteinuria >1 g), and/or cellular [red blood cell and/or white blood cell] casts). ‡Based on adjudication of treatment failures. CI, confidence interval; ESRD, end stage renal disease; GFR, glomerular filtration rate; HR, hazards ratio; IPD, investigational product discontinuation; IV, intravenous; TF, treatment failure; uPCR, urinary protein:creatinine; WD, withdrawal.

Safety

Incidence of AEs, AESIs and suicidality (safety population*)

- Safety profiles were similar for each treatment group, with no noted safety concerns

n (%)	Placebo (n=224)	Belimumab 10 mg/kg IV (n=224)
≥1 AE	211 (94.2)	214 (95.5)
≥1 treatment-related AE	119 (53.1)	123 (54.9)
≥1 SAE	67 (29.9)	58 (25.9)
≥1 treatment-related SAE	25 (11.2)	23 (10.3)
AE resulting in study drug discontinuation	29 (12.9)	29 (12.9)
AESI		
Malignancies excluding NMSC†	0	2 (0.9)
Malignancies including NMSC†	0	3 (1.3)
Post-infusion reactions‡	29 (12.9)	26 (11.6)
All infections of special interest (OI, HZ, TB, sepsis)	34 (15.2)	30 (13.4)
Serious infections	7 (3.1)	9 (4.0)
Depression/suicide/self-injury§	16 (7.1)	11 (4.9)
All deaths	5 (2.2)	6 (2.7)
Death on-treatment	3 (1.3)	4 (1.8)
Death post-treatment	2 (0.9)	2 (0.9)
C-SSRS suicidal ideation or behavior on-treatment	12 (5.4)	7 (3.1)

*Placebo group, n=224; belimumab group, n=224; †Includes tumours of unspecified malignancy; per CMQ or sponsor adjudication; ‡adjudicated as malignant; per CMQ or sponsor adjudication; §One attempted suicide in a patient receiving belimumab with pre-existing depression and self-discontinuation of an anti-depressant.
AE, adverse event; AESI, adverse event of special interest; CMQ, Custom MedDRA query; C-SSRS, Columbia-Suicide Severity Rating Scale; HZ, herpes zoster; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Affairs; NMSC, non-melanoma skin cancer; OI, opportunistic infection; SAE, serious adverse event; TB, tuberculosis.

Conclusions

In the largest LN study to date, data from BLISS-LN demonstrate that belimumab plus standard therapy significantly improved multiple LN renal responses versus standard therapy alone, while maintaining an acceptable safety profile

LN, lupus nephritis.

Acknowledgments

- The authors would like to thank the participating patients and their families, and the central biopsy consortium, clinicians and study investigators of BLISS-LN

Thank you

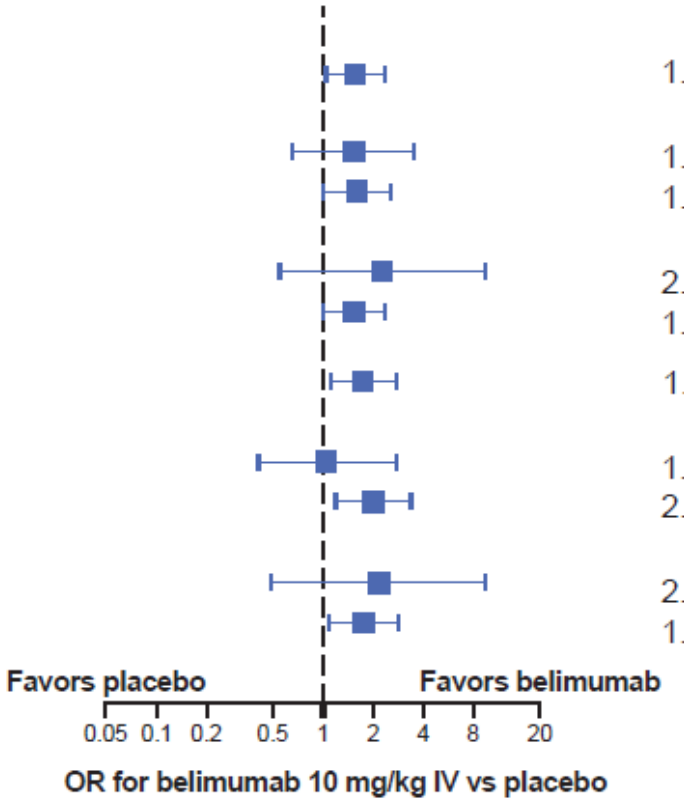
Questions?

Back-up slides

PERR* and CRR† subgroup analysis

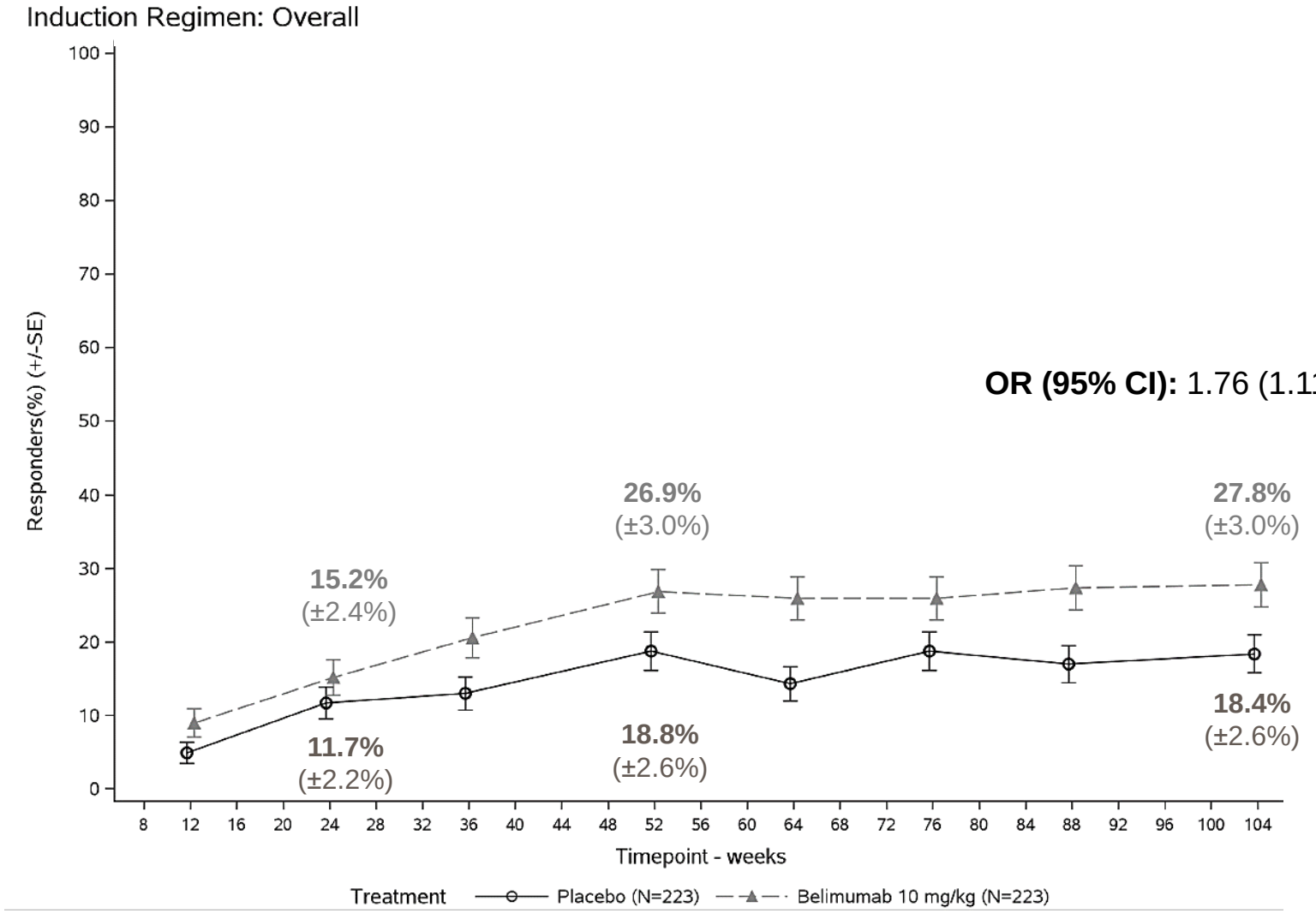
Variations in treatment difference between induction regimen and race subgroups were identified

		Response rate (%)		Treatment difference (%)		
		Placebo n=223	Belimumab 10 mg/kg IV n=223		OR (95% CI)	p-value
PERR	Overall	72/223 (32.3%)	96/223 (43.0%)	10.76%	1.55 (1.04, 2.32)	0.0311
	Induction					
	CYC	16/59 (27.1%)	20/59 (33.9%)	6.78%	1.52 (0.66, 3.49)	0.3272
	MMF	56/164 (34.1%)	76/164 (46.3%)	12.20%	1.58 (1.00, 2.51)	0.0501
	Race					
	Black	5/32 (15.6%)	7/31 (22.6%)	6.96%	2.24 (0.55, 9.19)	0.2613
	Non-black	67/191 (35.1%)	89/192 (46.4%)	11.28%	1.53 (1.01, 2.33)	0.0465
CRR	Overall	44/223 (19.7%)	67/223 (30%)	10.31%	1.74 (1.11, 2.74)	0.0167
	Induction					
	CYC	11/59 (18.6%)	11/59 (18.6%)	0%	1.07 (0.41, 2.78)	0.8843
	MMF	33/164 (20.1%)	56/164 (34.1%)	14.02%	2.01 (1.19, 3.38)	0.0085
	Race					
	Black	4/32 (12.5%)	6/31(19.4%)	6.85%	2.16 (0.49, 9.43)	0.3061
	Non-black	40/191 (20.9%)	61/192 (31.8%)	10.83%	1.75 (1.08, 2.83)	0.0225



*uPCR ≤0.7, eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m2, no rescue therapy; †uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, no rescue therapy. no rescue therapy. CI, confidence interval; CRR, Complete Renal Response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IV, intravenous; MMF, mycophenolate mofetil; OR, odds ratio; PERR, Primary Efficacy Renal Response; uPCR, urinary protein:creatinine.

SLEDAI-S2K* <4 by visit
(IPD/TF/WD=NR)



OR (95% CI): 1.76 (1.11, 2.78); p=0.02

*SELENA-SLEDAI using the SLEDAI-2000 scoring for proteinuria.
CI, confidence interval;; IPD, investigational product discontinuation; IV, intravenous; NR, non-responder; OR, odds ratio; SELENA, Safety of Estrogen in Lupus National Assessment trial; SE, standard error; SLEDAI-S2K, Systemic Lupus Erythematosus Disease Activity Index - SLEDAI-2K Responder Index-50; TF, treatment failure; WD, withdrawal.