KIDNEY WEEK 2025

Zanubrutinib in Anti–Phospholipase A2 Receptor (PLA2R)–Associated Primary Membranous Nephropathy: Preliminary Results of a Phase 2/3, Multicenter, Randomized, Open-Label Study

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- Dr Lafayette reports the following:
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Introduction

- PMN is a kidney-specific, autoimmune, glomerular disease characterized by increased protein in the urine, glomerular injury, and, in most patients, elevated serum anti-PLA2R antibodies[1]
- Although effective response rates are seen with rituximab or CNIs in the first-line setting in PMN, relapse rates are high, highlighting the need for novel therapies[2,3]
- BTK plays a key role in B-cell modulation and has emerged as a potential therapeutic target in PMN[4]
- Zanubrutinib, a highly selective and irreversible inhibitor of BTK,[4,5] is currently being evaluated in a two-part phase 2/3 study in patients with PMN (NCT05707377); here we present results from part 1 of the study at 76 weeks

BTK, Bruton tyrosine kinase; PLA2R, phospholipase A2 receptor; PMN, primary membranous nephropathy.

1. Couser WG. Clin J Am Soc Nephrol. 2017;12:983-997; 2. Floege J and Rovin BH. Kidney Int. 2021;99:811-813; 3. Allinovi M, et al. Kidney Int Rep. 2025 May 6;10:2621-2629; 4. Tam CS, et al. Blood Cancer J. 2023;13:141; 5. Brukinsa (zanubrutinib). Prescribing information. BeOne Medicines Ltd; 2024.

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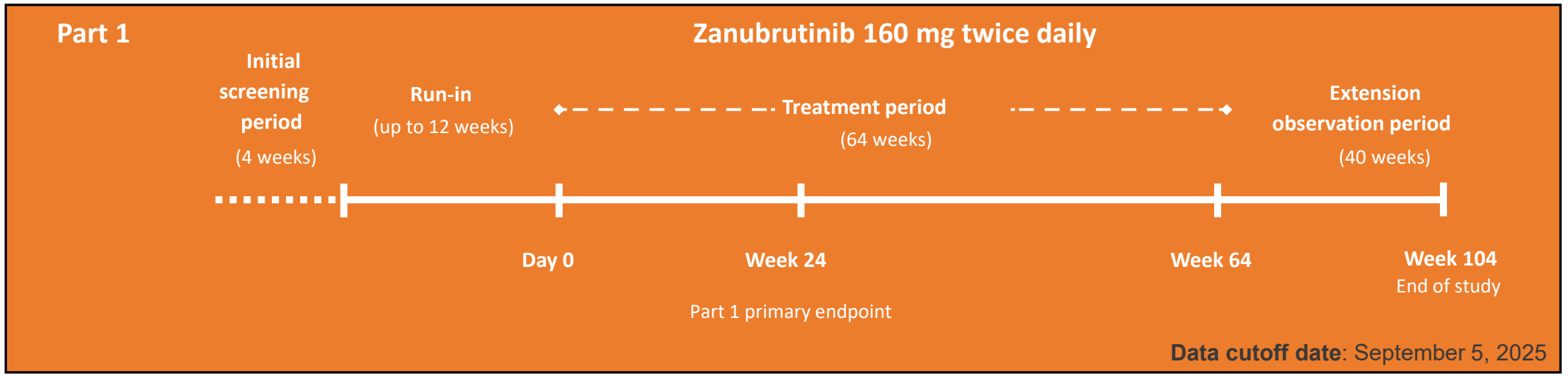
Study Design and Methods



Eligibility criteria

- Adults (aged 18-75 years)
- Anti-PLA2R antibody level of >50 RU/mL
- UPCR of >3.5 mg/mg, based on 24-hour urine collection

Endpoints

- **Primary:** Change from baseline in UPCR at 24 weeks
- **Secondary:** Immunologic response status (an anti-PLA2R antibody titer <14 RU/mL), clinical remission status,[a] and safety[b]

- In total, 30 patients were enrolled in the study; 23 patients entered the extension observation period and had completed the assessment at week 76 (includes four patients who completed the assessment at week 104)
- Overall, 12 patients (40.0%) discontinued study treatment prematurely[c]

[a]Complete remission was defined as UPCR ≤0.3 mg/mg and stable eGFR, and partial remission was defined as UPCR of >0.3 to ≤3.5 mg/mg, with ≥50% decrease from baseline,and stable eGFR. [b]Assessed by monitoring the incidence and severity of adverse events. [c]Treatment failure (n=5); patient decision (n=3); adverse events (n=3); physician decision (n=1). The adverse events were peripheral swelling and pneumonia (one patient each); epilepsy and intracranial mass occurred in one patient with a medical history of cerebral glioma resection over 12 years ago.
eGFR, estimated glomerular filtration rate; PLA2R, phospholipase A2 receptor; UPCR, urine protein-creatinine ratio.

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Results

Baseline demographics and disease characteristics

- The data cutoff date was September 5, 2025[a]

Characteristic	Zanubrutinib 160 mg BID (N=30)
Age, median (range), years	47 (32.0-74.0)
≥50 years, n (%)	13 (43.3)
Male, n (%)	20 (66.7)
Race, n (%)	
Asian	28 (93.3)
White	2 (6.7)
Region, n (%)	
Asia	27 (90.0)
Europe	2 (6.7)
North America	1 (3.3)
UPCR, mean (SD)[b]	8 (3.0)
Serum anti-PLA2R Ab titer, median (range), RU/mL	161 (51-1220)
Serum albumin, mean (SD), g/L	25 (7.2)
eGFR, median (range), mL/min/1.73[2c]	85 (40-123)

[a]At data-cut off, the median duration of exposure was 64 weeks (range, 4-65 weeks) [b]Based on 24-hour urine collection. [c]eGFR was calculated using CKD-EPI formula.
Ab, antibody; BID, twice daily; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; PLA2R, phospholipase A2 receptor; UPCR, urine protein-creatinine ratio.

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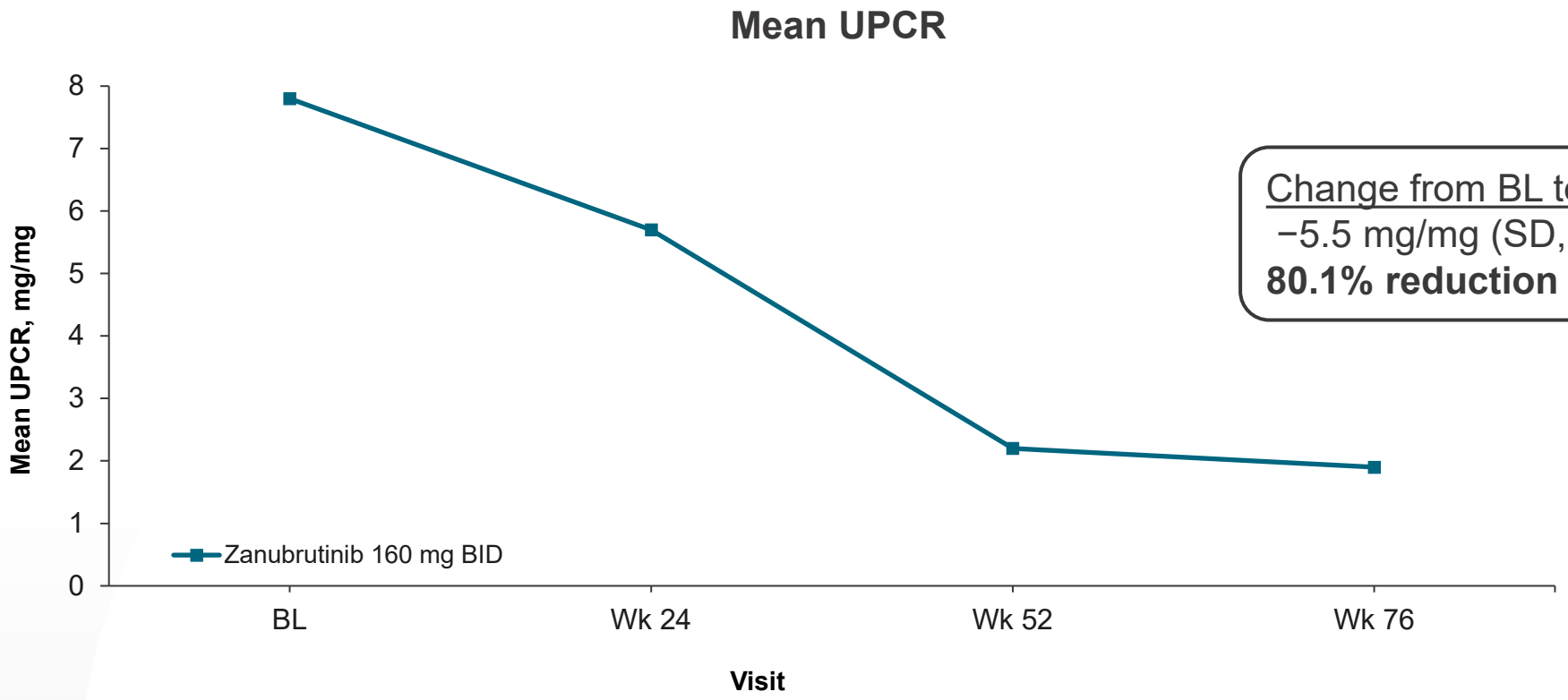
Results

Efficacy: urine protein-creatinine ratio



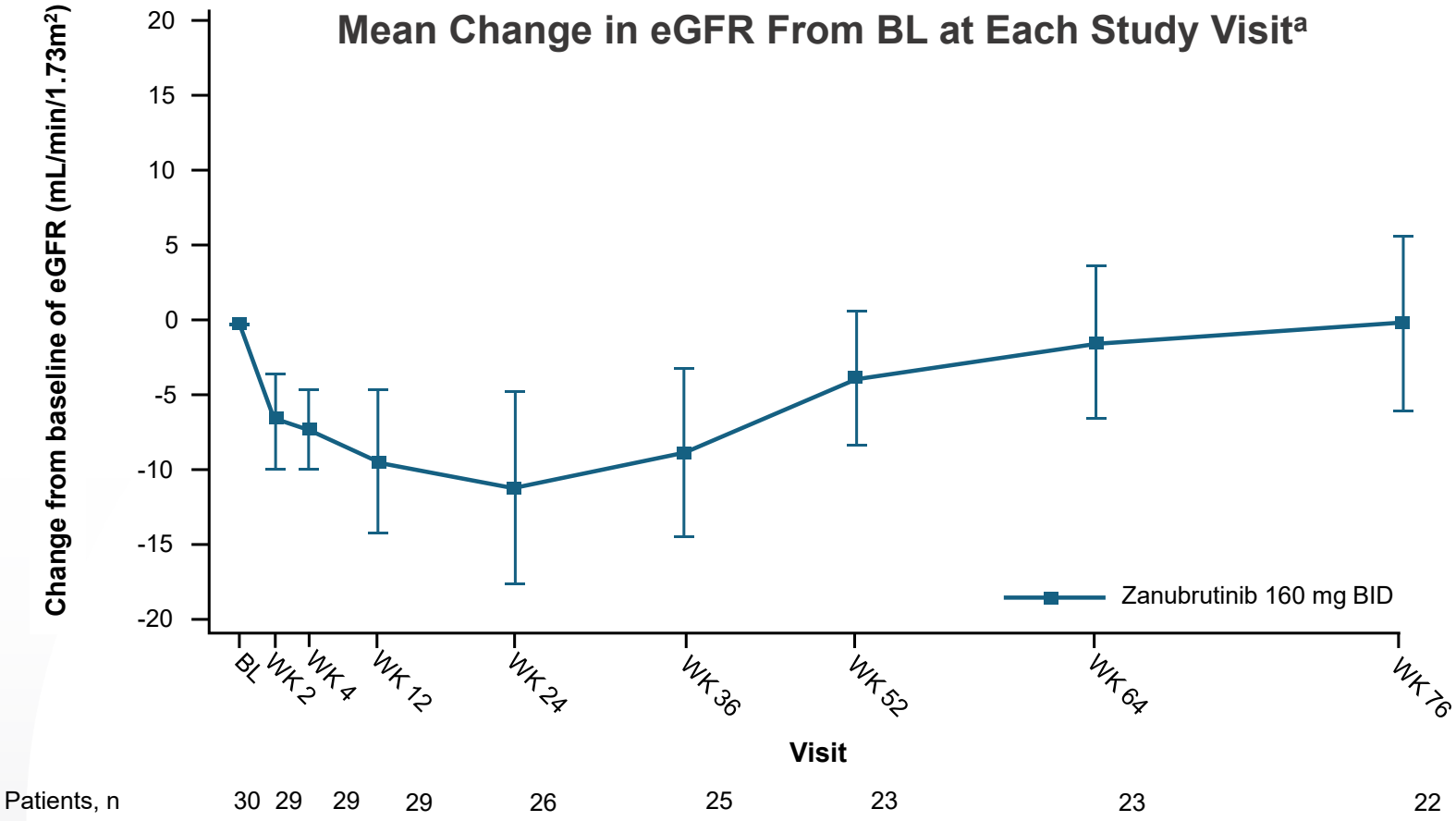
Change from BL to 76 weeks:
−5.5 mg/mg (SD, 2.3);
80.1% reduction

Patients, n	30	26	22[a]	23
CR, n	-	0	5	6
PR, n	-	7	8	9

[a]*One patient missed the UPCR sample collection.*
BID, twice daily; BL, baseline; CR, complete remission; PR, partial remission; UPCR, urine protein-creatinine ratio.

Results

Efficacy: eGFR



At week 76, eGFR levels were similar to baseline levels

[a]*Error bars represent the 95% confidence interval.*
BID, twice daily; BL, baseline; eGFR, estimated glomerular filtration rate.

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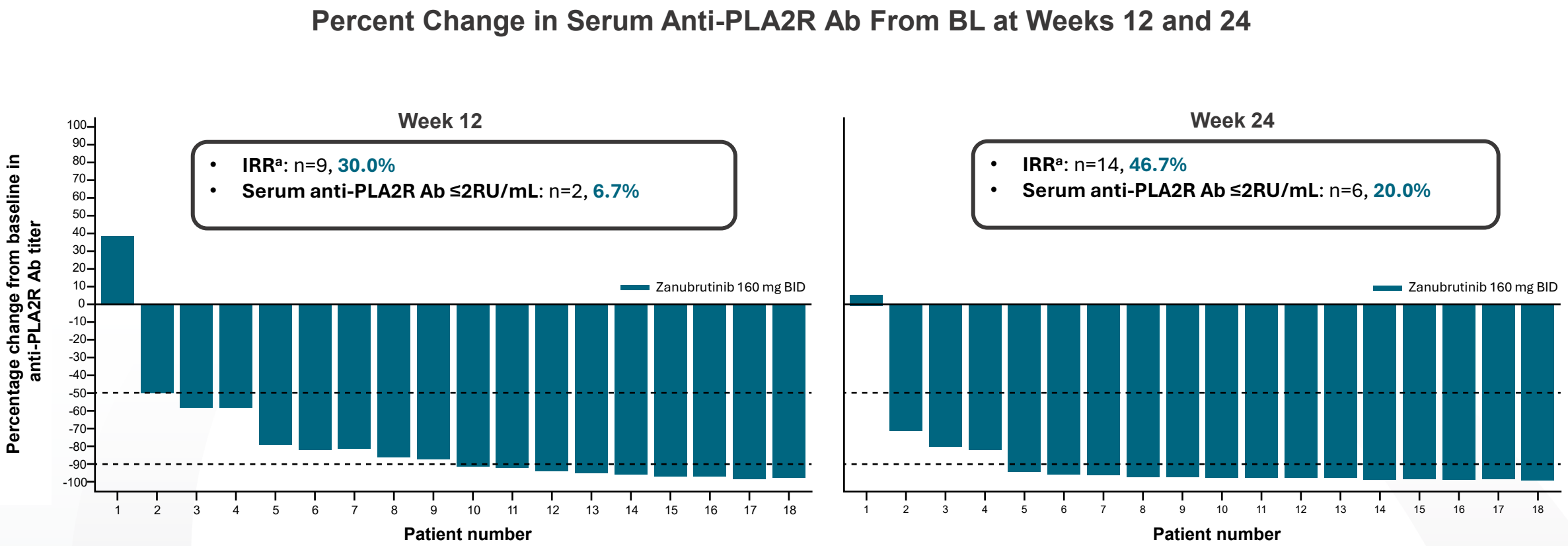
Results

Efficacy: individual serum anti-PLA2R antibody titer



[a]*Anti-PLA2R titer reduction to <14 RU/mL.*
Ab, antibody; BID, twice daily; PLA2R, phospholipase A2 receptor; IRR, immunologic response rate.

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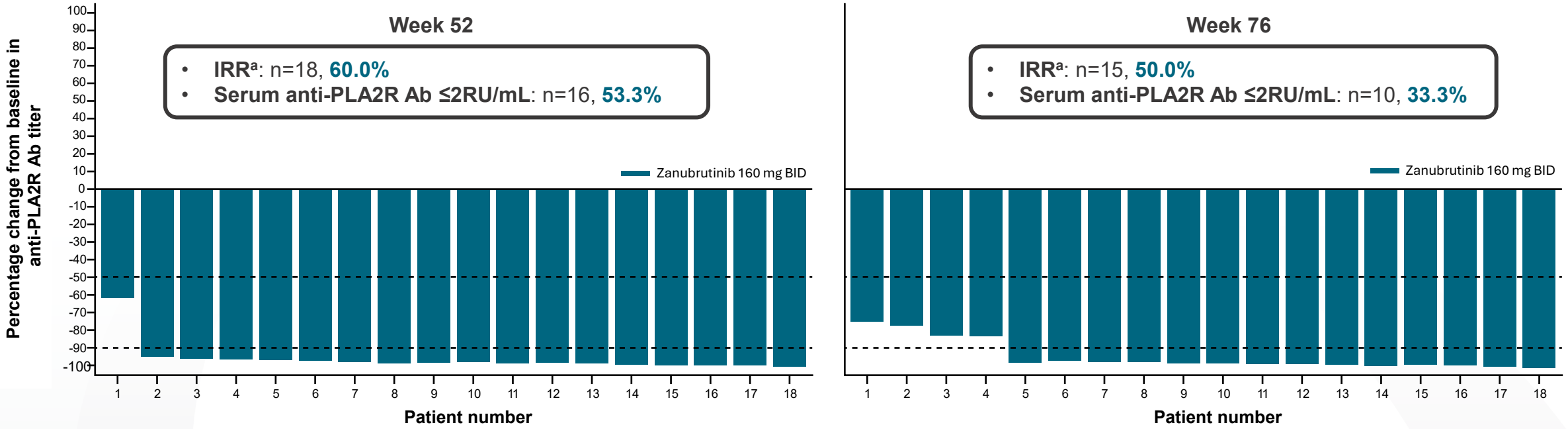
Results

Efficacy: individual serum anti-PLA2R antibody titer (continued)

Percent Change in Serum Anti-PLA2R Ab From BL at Weeks 52 and 76



[a]*Anti-PLA2R titer reduction to <14 RU/mL.*
Ab, antibody; BID, twice daily; PLA2R, phospholipase A2 receptor; IRR, immunologic response rate.

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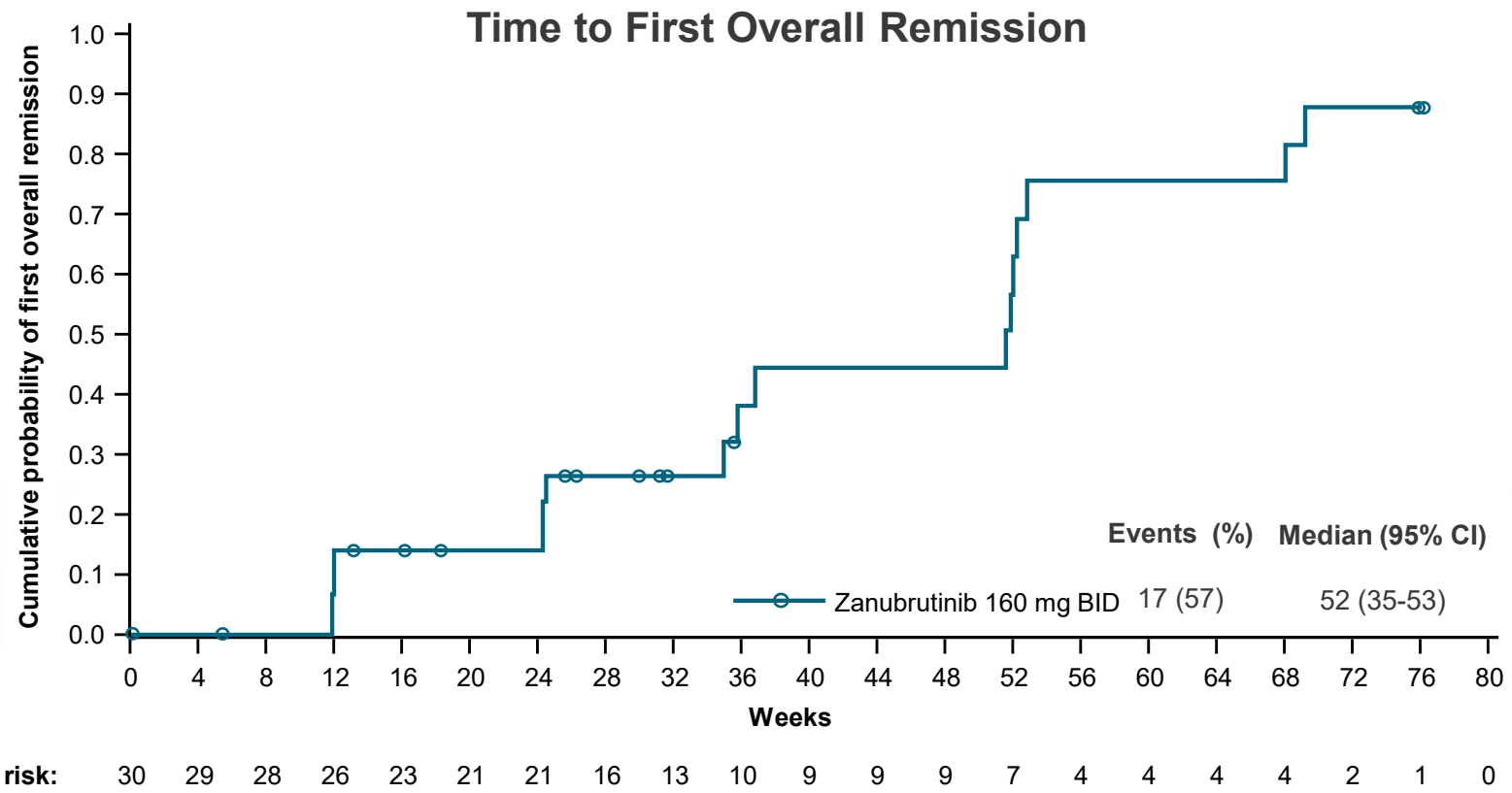
Results

Efficacy: overall remission



- At week 76, six patients (20.0%) had complete remission[a]; the overall remission rate was 50.0%

[a]Complete remission was defined as UPCR ≤0.3 mg/mg and stable eGFR.
BID, twice daily; eGFR, estimated glomerular filtration rate; UPCR, urine protein-creatinine ratio.

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Results

Safety: safety summary

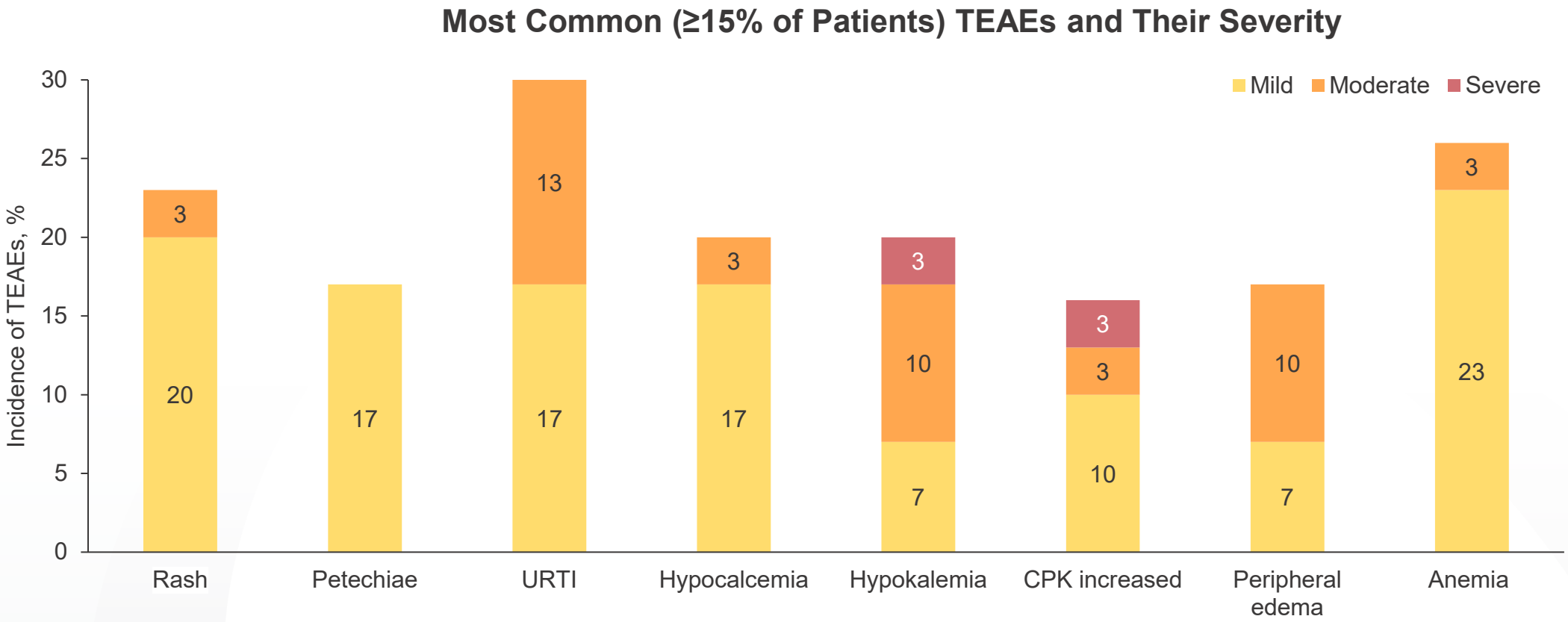
- Overall, 28 patients (93.3%) had TEAEs; four patients had severe TEAEs (two patients experienced severe TRAEs [pneumonia and blood creatinine phosphokinase increased])
- Three patients had serious TRAEs (pneumonia, n=2; skin infection, n=1); no fatal adverse events occurred

	Zanubrutinib 160 mg BID (N=30)
Any TEAE	28 (93.3)
Leading to dose modification	8 (26.7)
Leading to discontinuation	4 (13.3)
Serious	7 (23.3)
Any TRAE	17 (56.7)
Severe	2 (6.7)
Serious	3 (10.0)

BID, twice daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Results

Safety: most common treatment-emergent adverse events



- The majority of TEAEs (24/28 [86%]) were mild or moderate; the most common TEAEs were URTI (30%) anemia (27%), and rash (23%)

CPK, blood creatine phosphokinase; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

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Conclusions

- Findings from part 1 of this two-part phase 2/3 study demonstrate that zanubrutinib is generally well tolerated, with promising efficacy in patients with primary PMN
  - Mean UPCR levels showed an 80.1% reduction from baseline to week 76
  - At week 76, eGFR levels were similar to baseline levels
  - At week 76, the immunologic response rate (serum anti-PLA2R Ab ≤14 RU/mL) was 50.0% and 33.3% of patients had a deep immunologic response (serum anti-PLA2R Ab ≤2 RU/mL)
  - At week 76, six patients (20.0%) had complete remission, and the overall remission rate was 50.0%
  - The majority (86%) of TEAEs were mild or moderate
- Immunologic and clinical efficacy was seen in this study, despite evaluating zanubrutinib in a population with relatively severe disease characteristics for PMN (e.g high proteinuria and PLA2R Ab)
- Overall these results support the continued evaluation of zanubrutinib in PMN

Ab, antibody; eGFR, estimated glomerular filtration rate; PLA2R, phospholipase A2 receptor; PMN, primary membranous nephropathy; TEAE, treatment-emergent adverse event; UPCR, urinary protein-creatinine ratio.

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