Combination of Zanubrutinib + Venetoclax for Treatment-naive CLL/SLL With del(17p) and/or *TP53*: Preliminary Results From SEQUOIA Arm D

Richard Greil,[1,2] Shuo Ma,[3] Talha Munir,[4] Masa Lasica,[5] Mazyar Shadman,[6,7] Emmanuelle Ferrant,[8] Ian W. Flinn,[9] Wojciech Janowski,[10] Monica Tani,[11] Tadeusz Robak,[12] Jennifer R. Brown,[13] Constantine S. Tam,[14] Tian Tian,[15] Emily Mantovani,[15] Stephanie Agresti,[15] Linlin Xu,[15] Aileen Cohen,[15] Wojciech Jurczak,[16] Paolo Ghia[17,18]

[1]Third Medical Department with Hematology, Medical Oncology, Rheumatology and Infectiology, Paracelsus Medical University, Salzburg, Austria; [2]Salzburg Cancer Research Institute Center for Clinical Cancer and Immunology Trials, Salzburg, Austria; Cancer Cluster Salzburg; [3]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [4]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [5]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [6]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [7]University of Washington, Seattle, WA, USA; [8]Département Hématologie, CHU de Lyon-Sud, Lyon-Sud, France; [9]Tennessee Oncology/OneOncology, Nashville, TN, USA; [10]Calvary Mater Newcastle Hospital, Waratah, NSW, Australia; [11]Hematology Unit, Department of Onco-Hematology, Santa Maria delle Croci Hospital, Ravenna, Italy; [12]Copernicus Memorial Hospital, Medical University of Łódź, Łódź, Poland; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [15]BeiGene USA, Inc, San Mateo, CA, USA; [16]Maria Sklodowska-Curie National Research Institute of Oncology, Kraków, Poland; [17]Università Vita-Salute San Raffaele, Milan, Italy; [18]IRCCS Ospedale San Raffaele, Milan, Italy

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Disclosures for Richard Greil

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Introduction

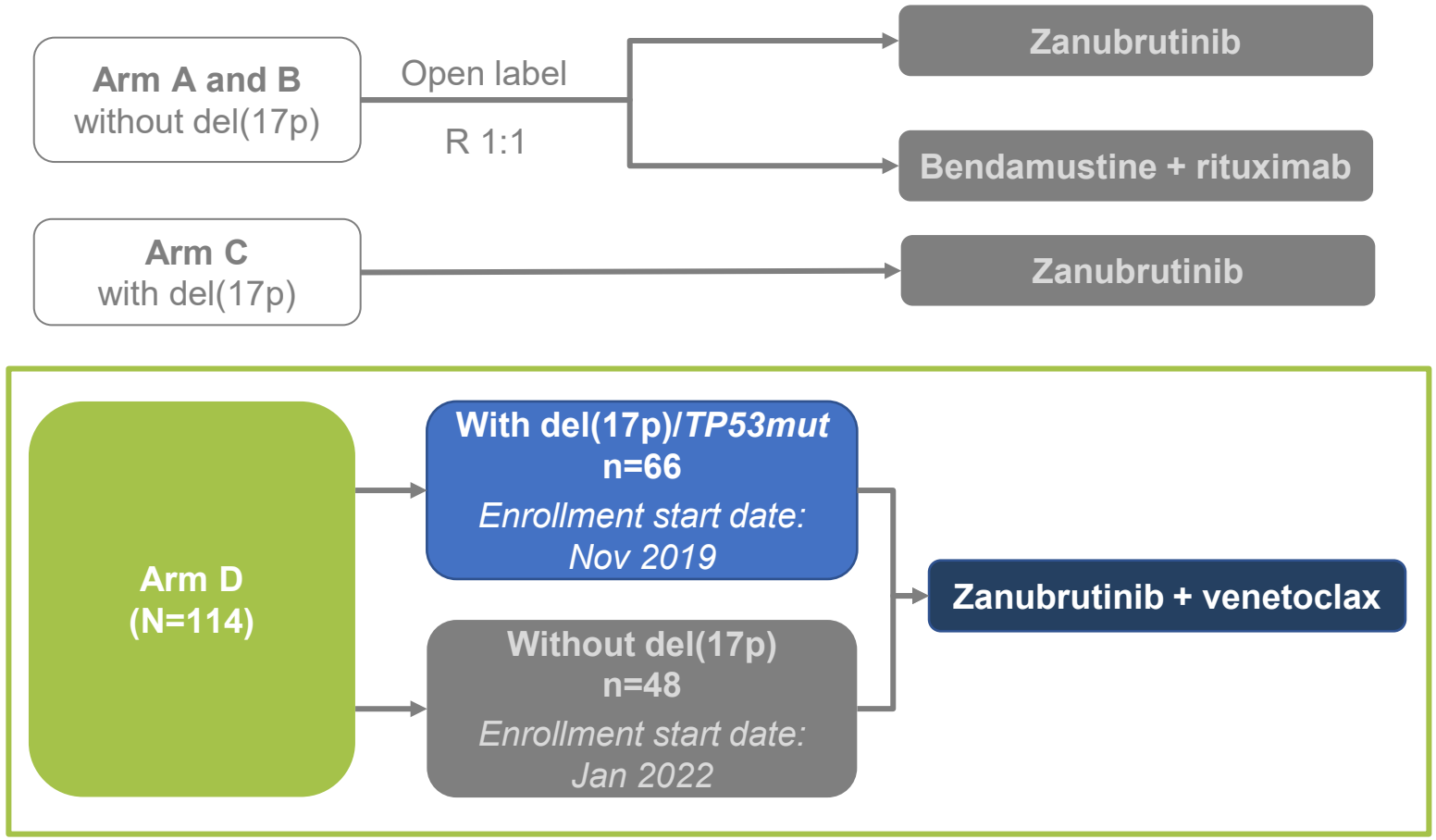
- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor approved in TN and R/R CLL as monotherapy[1,2] that was designed to provide complete and sustained BTK occupancy, with fewer off-target AEs and improved efficacy compared with other BTK inhibitors[3,4]
- In Arm C of the phase 3 SEQUOIA trial, zanubrutinib monotherapy was well tolerated and achieved a high ORR (95%) and 18-month PFS estimate (89%) in patients who had untreated CLL/SLL with del(17p)[5], which were consistent with outcomes in patients without del(17p)[6]
- Monotherapy with venetoclax, the first-generation BCL2 inhibitor, has also been shown to be well tolerated with durable responses achieved in patients with del(17p) and/or *TP53* mutation[7], but data on venetoclax + ibrutinib combination therapy in this high-risk population has been limited
- Combination therapy with a BCL2 inhibitor in patients with high-risk CLL may provide deep responses and improve outcomes in patients treated with zanubrutinib
- Preliminary results in patients with del(17p) and/or *TP53* mutation who received zanubrutinib + venetoclax combination treatment in Arm D of the SEQUOIA trial are presented

1. Brukinsa. Prescribing information. BeiGene, Ltd; 2024; 2. Brukinsa. Summary of product characteristics. BeiGene, Ltd; 2021; 3. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940;
4. Tam CS, et al. *Expert Rev Clin Pharmacol*. 2021;14(11):1329-1344; 5. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363; 6. Tam CS, et al. *LancetOncol*. 2022;23(8):1031-1043;
7. Stilgenbauer S, et al. *J Clin Oncol*. 2018;36(19):1973-1980.

SEQUOIA Study Design – Arm D Cohort With del(17p) and/or *TP53mut*

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- For Arm D: central confirmation of del(17p) by FISH and/or local *TP53* mutation



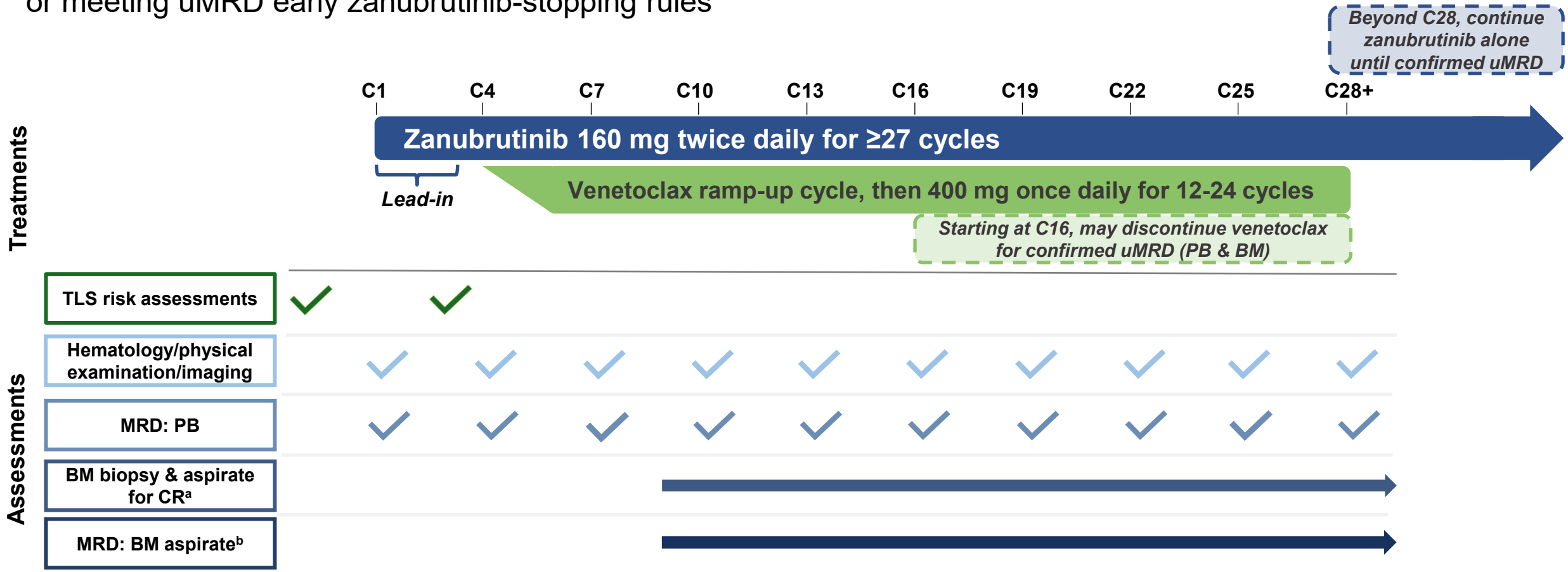
Endpoints for Arm D

- ORR (INV)[a]
- PFS (INV)
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety per CTCAE

[a] Reponses assessed per modified iwCLL criteria for CLL and Lugano criteria for SLL.

SEQUOIA Arm D Treatment Regimen and Assessment Schedule

- Zanubrutinib lead-in (3 cycles) followed by zanubrutinib + venetoclax (12-24 cycles dependent on uMRD early venetoclax-stopping rules), then zanubrutinib monotherapy until disease progression, unacceptable toxicity, or meeting uMRD early zanubrutinib-stopping rules



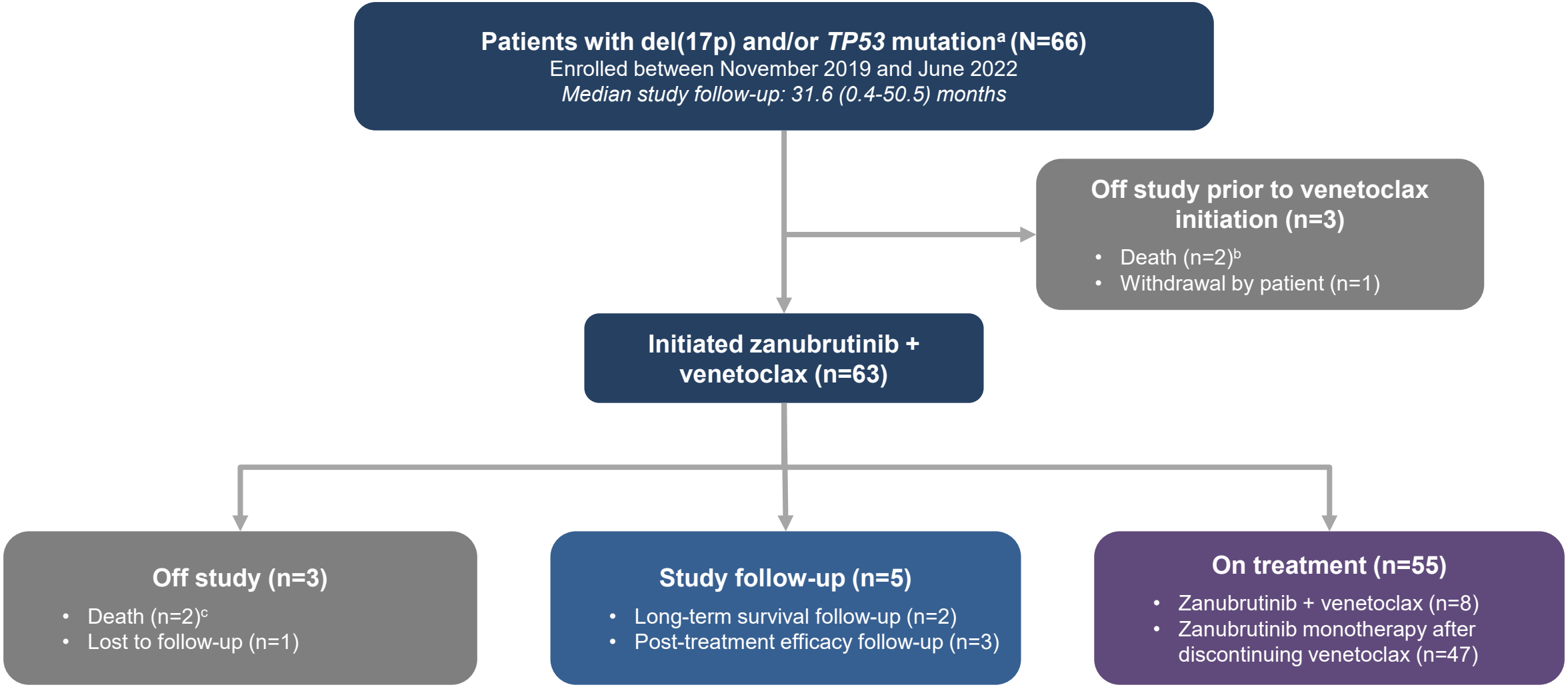
[a] BM biopsy and aspirate are required to confirm a suspected CR/CRi (BM collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed.
[b] Patients with confirmed CR/CRi and 2 consecutive PB uMRD ≥12 weeks apart.

uMRD[a]-guided Early Zanubrutinib- or Venetoclax-stopping Rules

- Zanubrutinib or venetoclax can be stopped early if all of the following conditions are met:
  - Response assessed as CR/CRi confirmed by a bone marrow biopsy
  - uMRD4 achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
  - uMRD4 achieved in 2 consecutive bone marrow aspirate MRD tests conducted ≥12 weeks apart
  - Received
    - ≥12 cycles of venetoclax (to stop venetoclax early)
    - ≥27 cycles of zanubrutinib (to stop zanubrutinib early)

[a] uMRD was assessed by flow cytometry.
CRi, complete response with incomplete hematopoietic recovery.

Patient Disposition



Data cutoff: January 31, 2024.

[a] Based on central assessment. [b] Due to AE. [c] Due to AE (n=1); due to PD (n=1).

Treatment Discontinuations

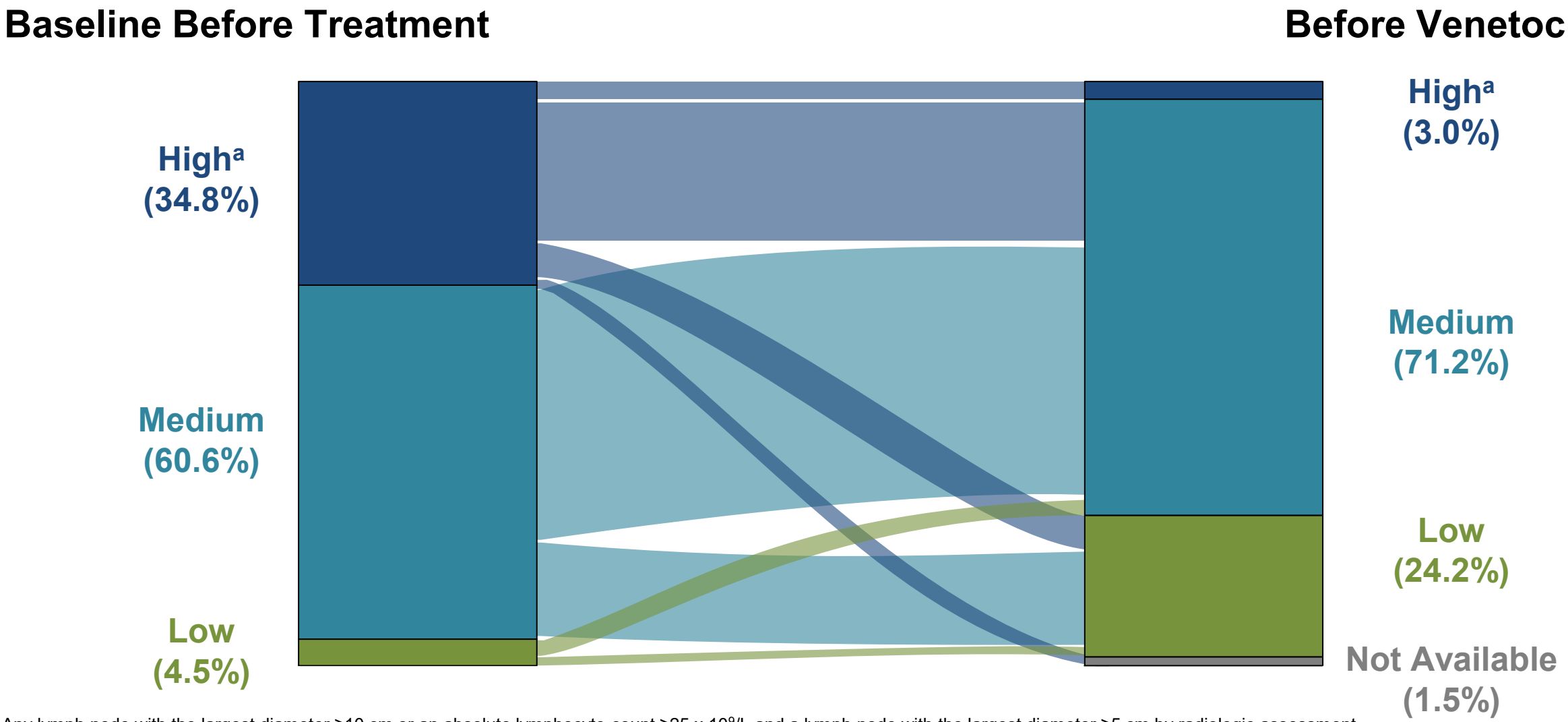
Patient, n (%)	Zanubrutinib + venetoclax (n=66)
Enrolled/dosed	66 (100)
Treated with zanubrutinib only	3 (5)
Discontinued from zanubrutinib	11 (17)
AE	5 (8)
PD	2 (3)
Completed treatment (uMRD early stopping)	3 (5)
Withdrawal by patient	1 (2)
Discontinued from venetoclax	55 (83)
Completed treatment	50 (76)
24 cycles per protocol	49 (74)
uMRD early stopping	1 (2)
AE	2 (3)
PD	2 (3)
Investigator decision	1 (2)

SEQUOIA Arm D Included a High-risk Cohort

Characteristic	Zanubrutinib + venetoclax (n=66)
Age, median (range), years	66 (26-87)
≥65 years, n (%)	36 (55)
Male sex, n (%)	34 (52)
White race, n (%)	58 (88)
ECOG performance status, n (%)	
1	32 (48)
2	2 (3)
SLL, n (%)	3 (5)
Bulky disease, n (%)	
Any target lesion LDi ≥5 cm	29 (44)
Any target lesion LDi ≥10 cm	5 (8)
Genotype status, n (%)	
del(17p) positive and/or *TP53* mutated	66 (100)
del(17p) positive and *TP53* mutated	42 (64)
del(17p) positive and *TP53* wildtype	17 (26)
del(17p) negative and *TP53* mutated	7 (11)
Unmutated IGHV	56 (85)
Complex karyotype, n (%)	
≥3 abnormalities	33 (50)
≥5 abnormalities	24 (36)
del(17p) % of abnormal nuclei, median (range)	60.5 (1-98)

LDi, longest diameter.

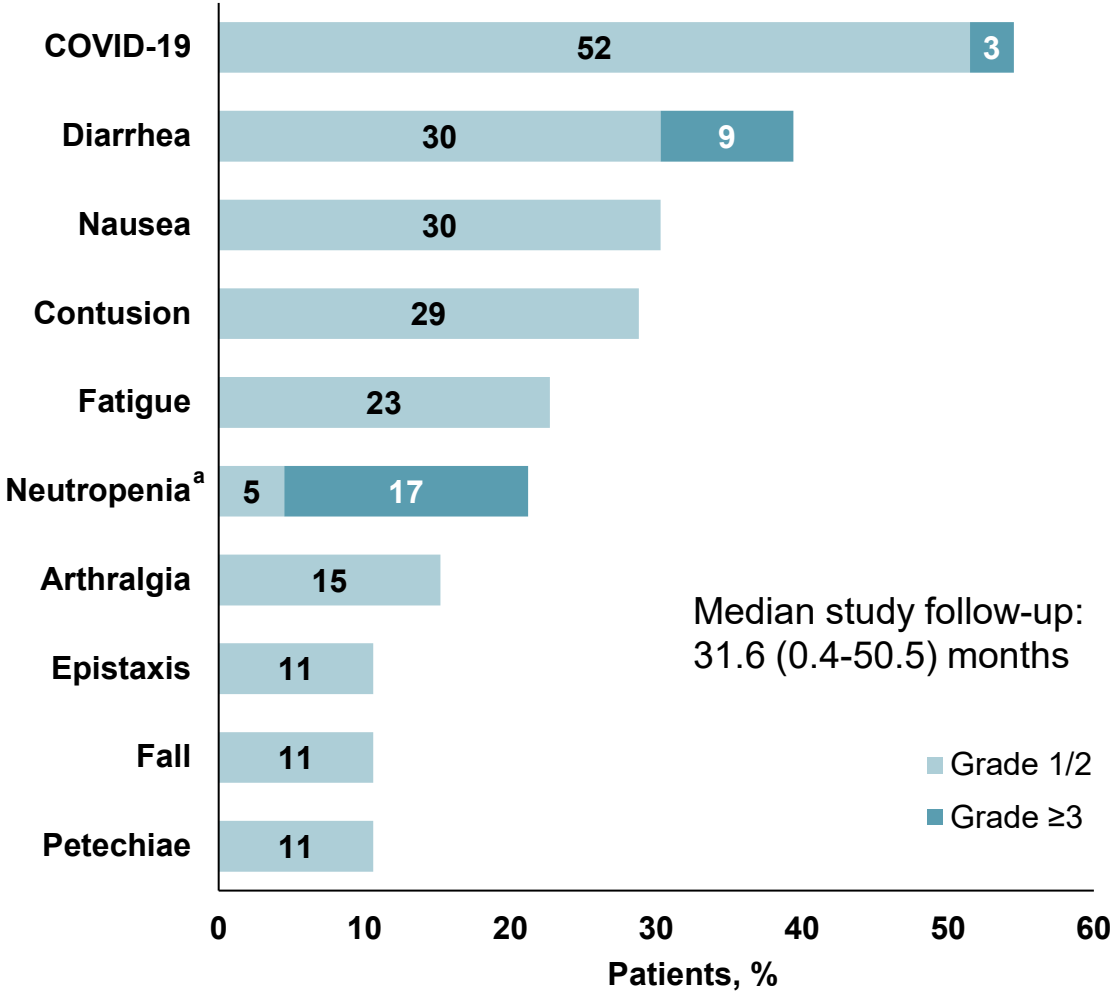
Proportion of Patients at High Risk for TLS Decreased by 91% After Zanubrutinib Lead-in



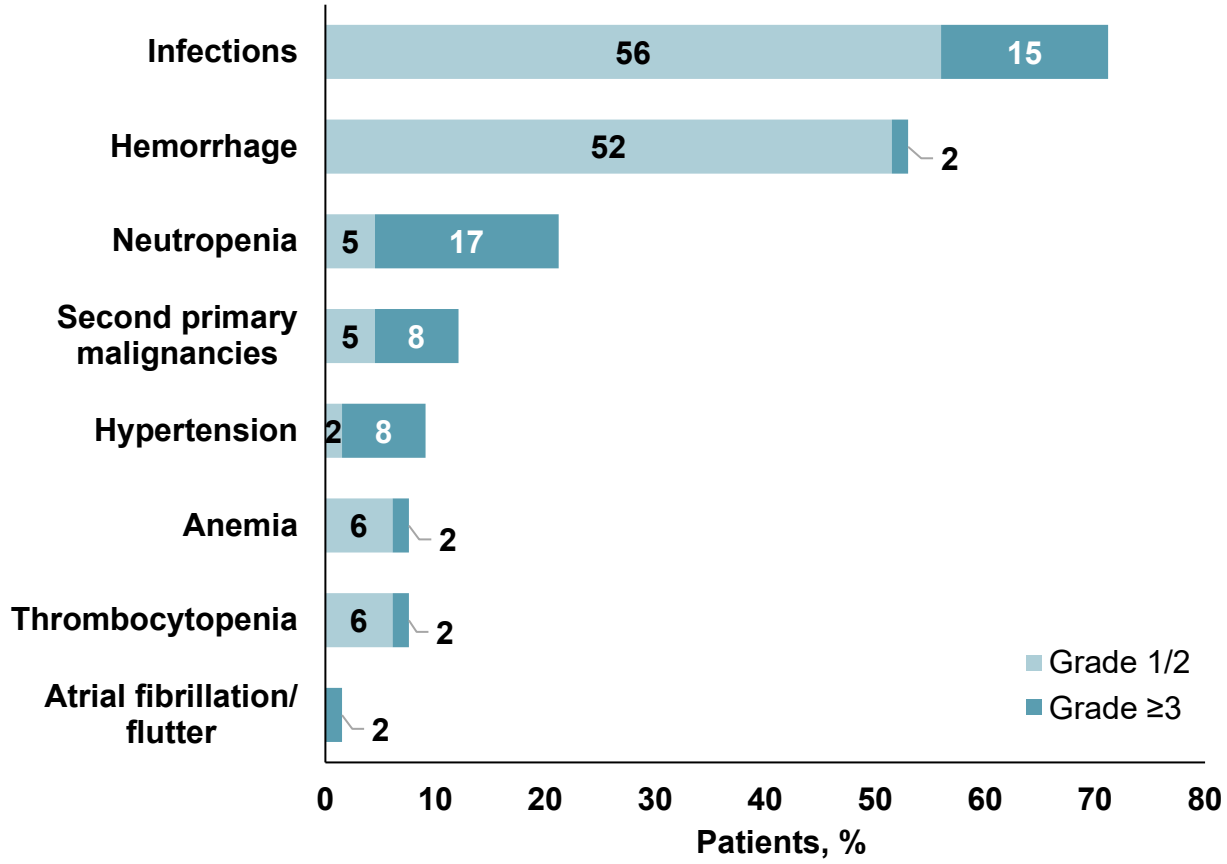
[a] Any lymph node with the largest diameter ≥10 cm or an absolute lymphocyte count ≥25 x 10^9/L and a lymph node with the largest diameter ≥5 cm by radiologic assessment.
TLS, tumor lysis syndrome.

Safety Summary

TEAEs in >10% of patients



Treatment-emergent adverse events of special interest



- Of all infections, 36 patients (55%) had COVID-19, 2 (3%) of whom experienced a grade ≥3 event

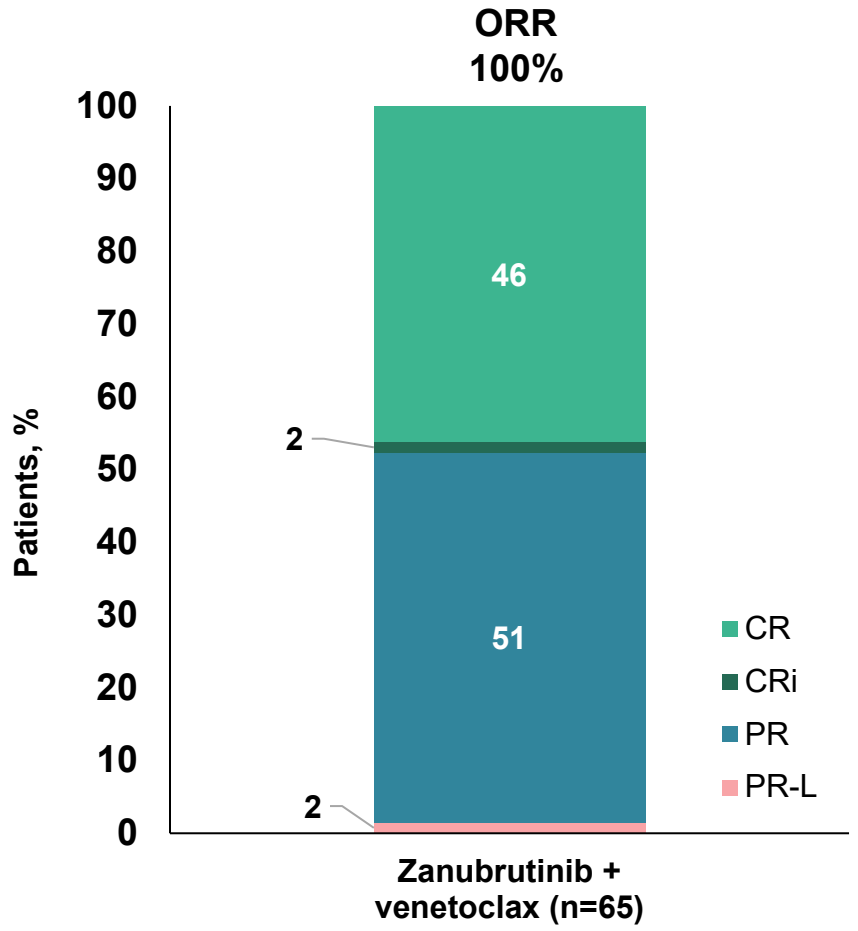
[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.

TEAEs Leading to Discontinuation and Death

Patients, n (%)			Zanubrutinib + venetoclax (n=66)	
TEAE leading to zanubrutinib discontinuation			5 (8)	
TEAE leading to venetoclax discontinuation			2 (3)	
TEAE leading to death			3 (5)	
Patient	**TEAE(s)**	**Led to zanubrutinib discontinuation**	**Led to venetoclax discontinuation**	**Led to death**
1	Motor vehicular accident, intra-abdominal hemorrhage, and intracranial hemorrhage	X	X	X
2	Pneumonitis	X	N/A[a]	
3	Lung carcinoma	X	N/A[b]	X
4	Pneumonia	X	X	
5	Pneumonia (*S. aureus*) Septic shock (*S. aureus*)	X	N/A[b]	X X

[a] Patient completed venetoclax treatment. [b] Patient did not start venetoclax.

In 65 Response-evaluable Patients[a] with del(17p) and/or *TP53* Mutation, ORR[b,c] was 100% and the CR+CRi rate was 48%

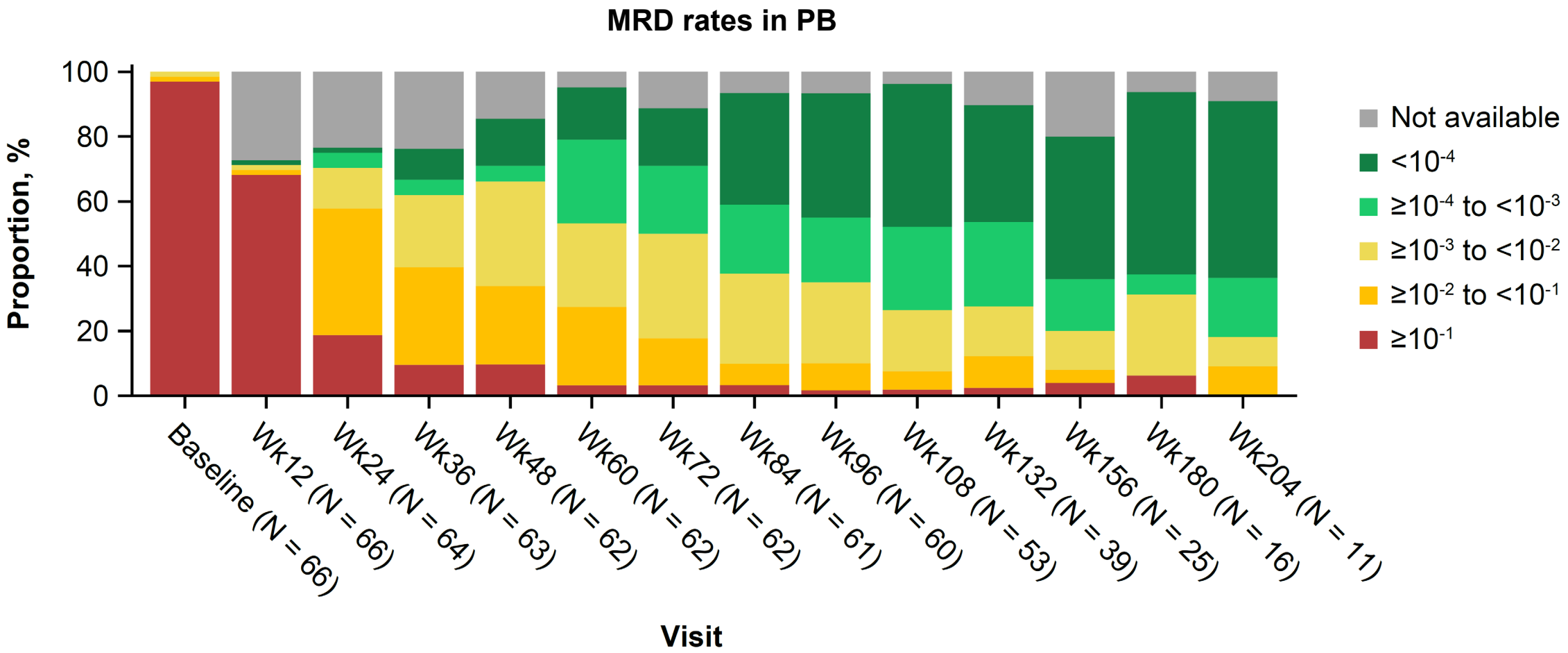


Median study follow-up: 31.6 (0.4-50.5) months

[a] Received ≥1 dose of zanubrutinib with ≥1 post-baseline disease assessment. The 1 patient that was not response-evaluable died during cycle 1. [b] Responses assessed by investigator per modified iwCLL criteria for CLL and Lugano criteria for SLL. [c] ORR was defined as PR-L or better.

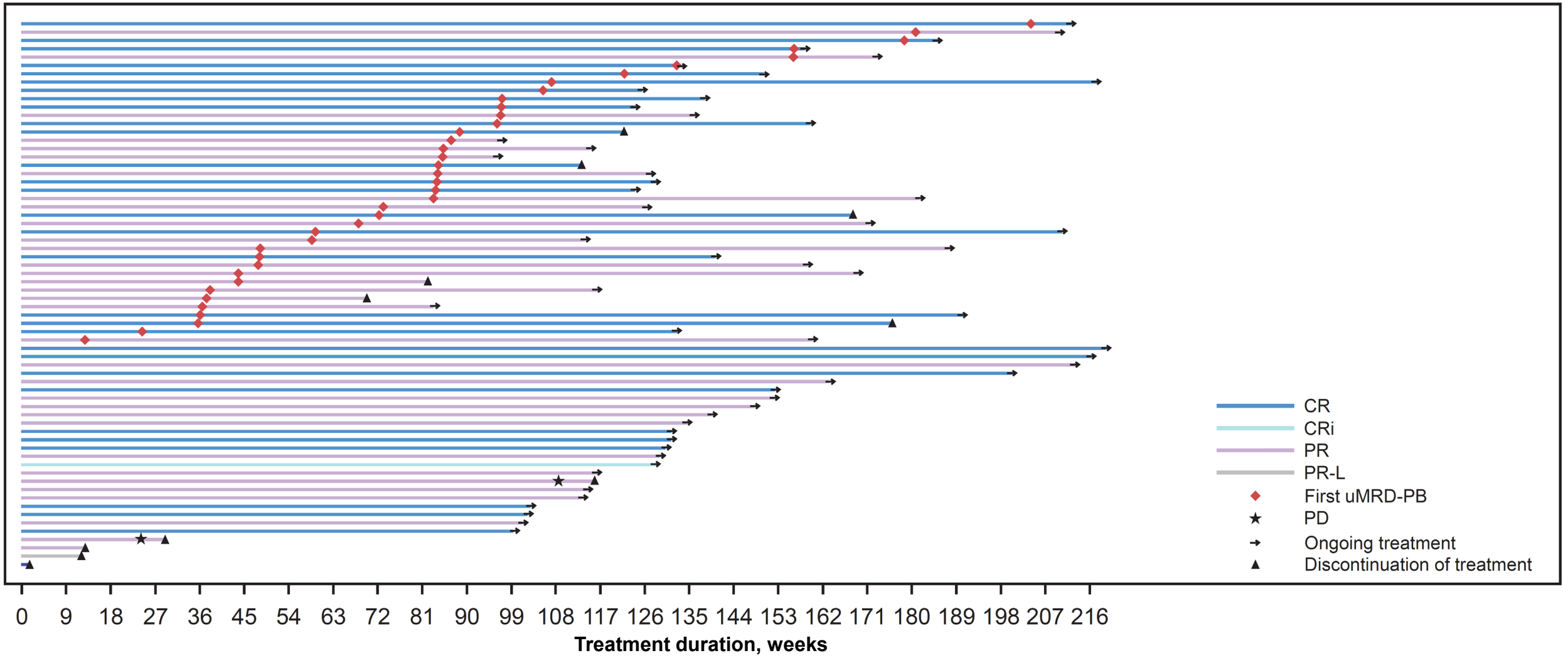
Rates of uMRD in PB Increased with Longer Treatment Duration

- Best uMRD rate: 59% (39/66) in ≥1 PB sample; 37% (13/35) in ≥1 BM sample[a]

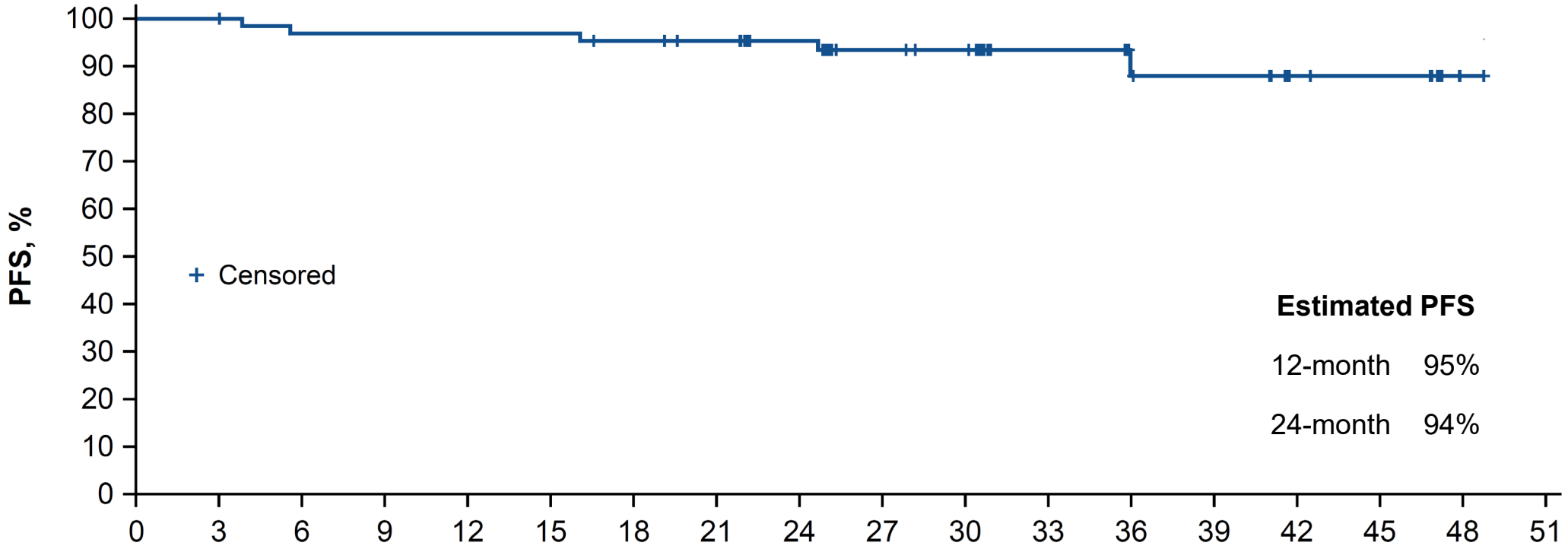


[a] BM biopsy and aspirate were required to confirm a suspected CR/CRi and additional BM aspirate uMRD sample collection was dependent on PB uMRD status; BM collection timing varied by patient. On treatment BM aspirate samples have been collected in 35 patients to date.

Treatment Duration With Time to First uMRD



With Median Study Follow-up of 31.6 Months, Median PFS was Not Reached



No. of patients at risk

Zanubrutinib	65	65	62	62	62	62	60	58	51	37	35	22	16	15	10	9	1	0

Conclusions

- Preliminary results for treatment with zanubrutinib + venetoclax in patients with high-risk TN CLL/SLL with del(17p) and/or *TP53* mutation showed favorable safety and tolerability
  - Rates of atrial fibrillation/flutter and hypertension were low (2% and 9%, respectively)
- Promising efficacy was seen in this high-risk population with deep and durable responses
  - An ORR of 100% and a high rate of uMRD were achieved
  - With a median follow-up of 31.6 months, high 12- and 24-month PFS estimates were seen (95% and 94%, respectively)
- The study is ongoing and results in patients who meet MRD-guided early stopping rules will be reported as data mature
- The ongoing phase 3 CELESTIAL-TNCLL trial (BGB-11417-301) is evaluating zanubrutinib in combination with sonrotoclax, a next-generation and potent BCL2 inhibitor, as fixed duration therapy in patients with TN CLL

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Corresponding Author: Richard Greil, r.greil@salk.at