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Combination of Zanubrutinib + Venetoclax for Treatment-naive CLL/SLL: Results in SEQUOIA Arm D

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Key Takeaways

- In SEQUOIA Arm D, treatment with zanubrutinib + venetoclax in TN CLL/SLL achieved a high 24-month PFS and best ORR, regardless of mutational status
- The safety profile of zanubrutinib + venetoclax was tolerable and no unexpected safety signals were identified
- Zanubrutinib + venetoclax, followed by continuous zanubrutinib appears to be a promising treatment option for patients with TN CLL/SLL regardless of del(17p)/*TP53*mut

CLL, chronic lymphocytic leukemia; ORR, overall response rate; mut, mutation; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TN, treatment-naive.

Introduction

- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor, approved in TN and R/R CLL[1-3]
- SEQUOIA (NCT03336333) is a registrational phase 3, open-label, randomized study with four treatment arms[4,5]
  - In Arms A and B, zanubrutinib monotherapy (Arm A) demonstrated superior PFS compared with bendamustine + rituximab (Arm B) in patients without del(17p) at 26.2-month follow-up and sustained PFS benefit at 5-year follow-up[4]
  - In Arm C, patients with del(17p) treated with zanubrutinib monotherapy (Arm C) have achieved high overall response rates and PFS[5]
- Several CLL studies have demonstrated promising efficacy with the combination of BCL2 + BTK inhibitors
  - Fixed-duration and uMRD-guided study designs have suggested that longer treatment duration may result in deeper remission[6,7]
  - However, patients with del(17p)/*TP53* mutation comprised a small percentage of study populations or were excluded entirely[8,9]
- Here, results from SEQUOIA Arm D are presented for zanubrutinib + venetoclax in patients with or without del(17p) and/or *TP53* mutation

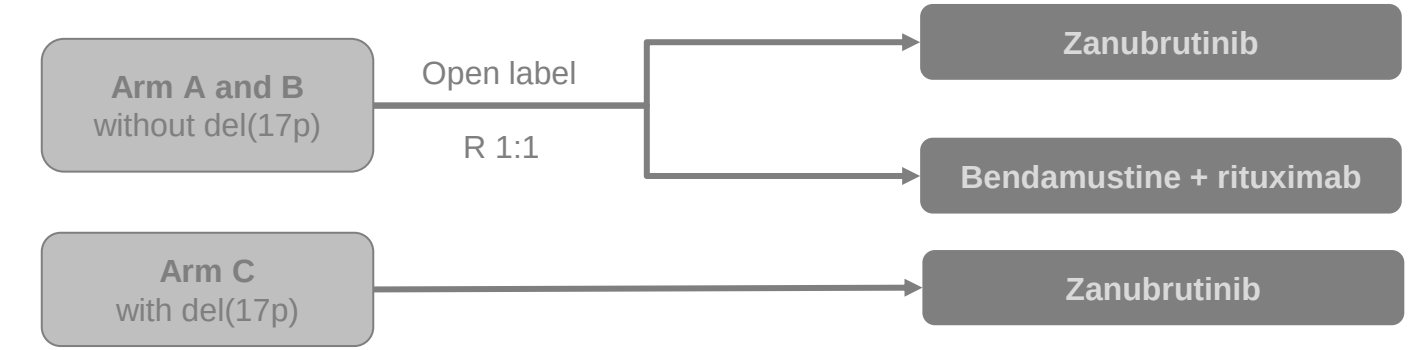
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R relapsed/refractory; TN, treatment naïve; uMRD, undetectable minimal residual disease.

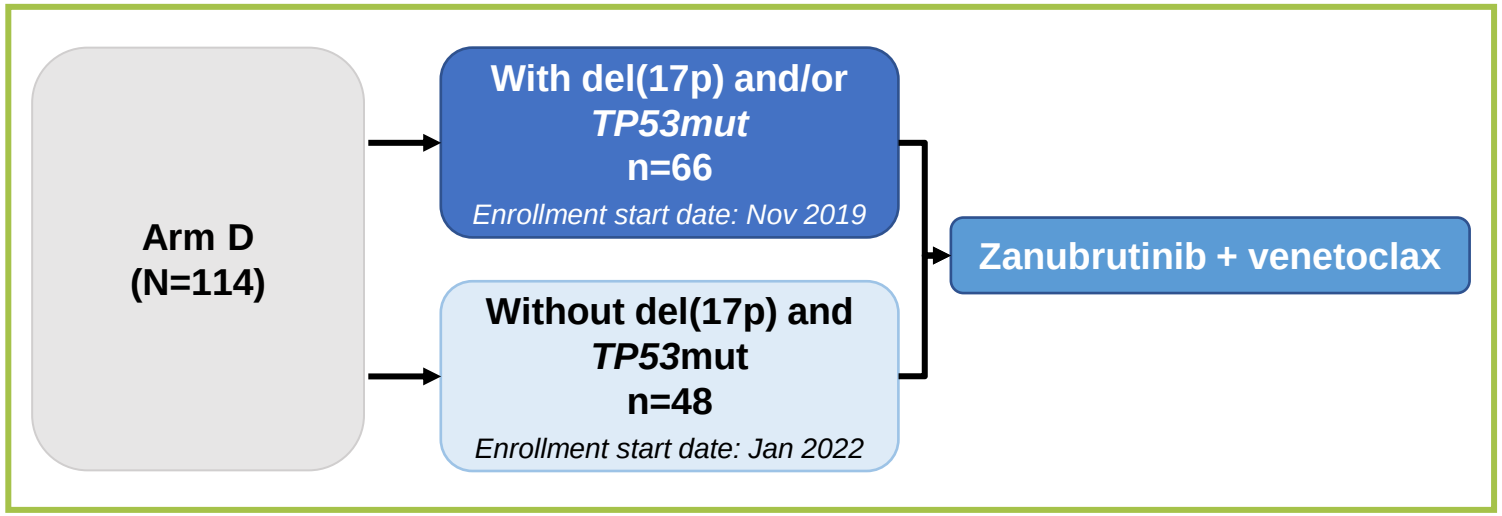
1. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 2. Brukinsa (zanubrutinib). Prescribing information. BeiGene USA; 2024; 3. Brukinsa (zanubrutinib). Summary of product characteristics. BeiGene Ireland Limited; 2024; 4. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787; 5. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363; 6. Davids et al. *J Clin Oncol*. 2025;43(7):788-799; 7. Munir T, et al. *N Engl J Med*. 2024;25;390(4):326-337; 8. Brown JR, et al. *Blood*. 2024;144(26):2706-2717; 9. Tam CS, et al. *Blood*. 2022;139(22):3278-3289.

SEQUOIA Study Design

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- Unsuitable for FCR





Endpoints for Arm D

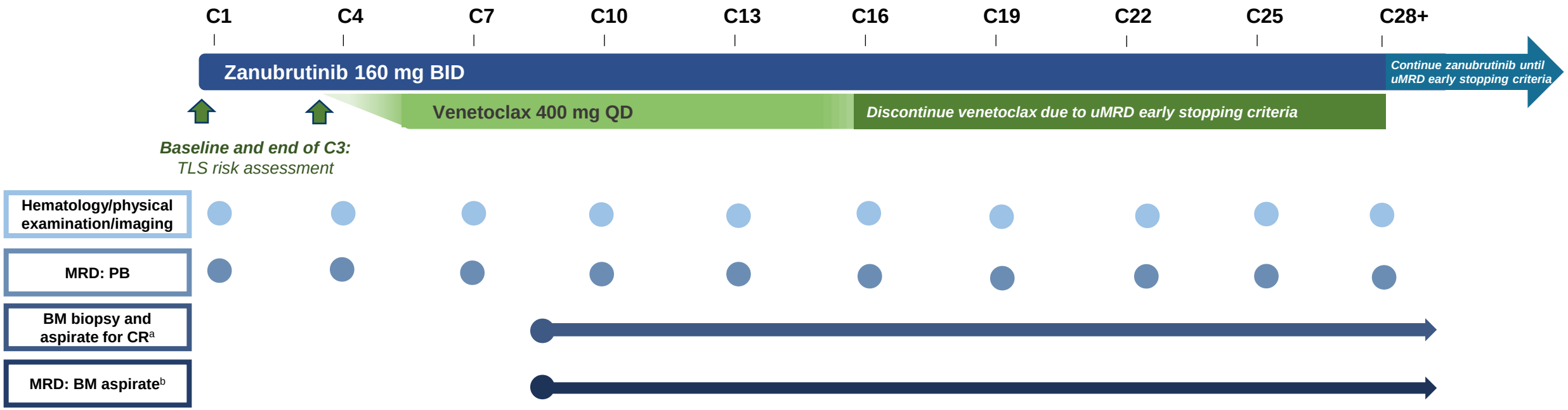
- PFS (INV)[a]
- ORR (INV)[b]
- OS[a]
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety per CTCAE

[a]PFS and OS were assessed in the intention-to-treat population. [b]Responses were assessed by investigator per the 2008 iwCLL guidelines[1] with modification for treatment-related lymphocytosis[2] for patients with CLL and per Lugano criteria[3] for patients with SLL. ORR was defined as achievement of PR-L or better.

CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; INV, investigator-assessed; MRI, magnetic resonance imaging; mut, mutation; ORR, overall response rate; OS, overall survival; PR-L, partial response with lymphocytosis; PFS, progression-free survival; R, randomized; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease.

1. Hallek M, et al. *Blood.* 2008;111(12):5446–56; 2. Cheson BD, et al. *J Clin Oncol.* 2012;30(23):2820-2822; 3. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3967.

Treatment and Assessment Schedule



uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <1×10^{-4} (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

[a]BM biopsy and aspirate are required to confirm a suspected CR/CRi (BM biopsy 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 results at least 12 weeks apart. BID, twice daily; BM, bone marrow; C, cycle; CR, complete response; CRi, CR with incomplete bone marrow recovery; MRD, measurable residual disease; PB, peripheral blood; QD, once daily; TLS, tumor lysis syndrome; uMRD, undetectable measurable residual disease; uMRD4, undetectable measurable residual disease (<1 CLL cell in 10,000 leukocytes at 10^{-4} sensitivity by 8-color flow cytometry).

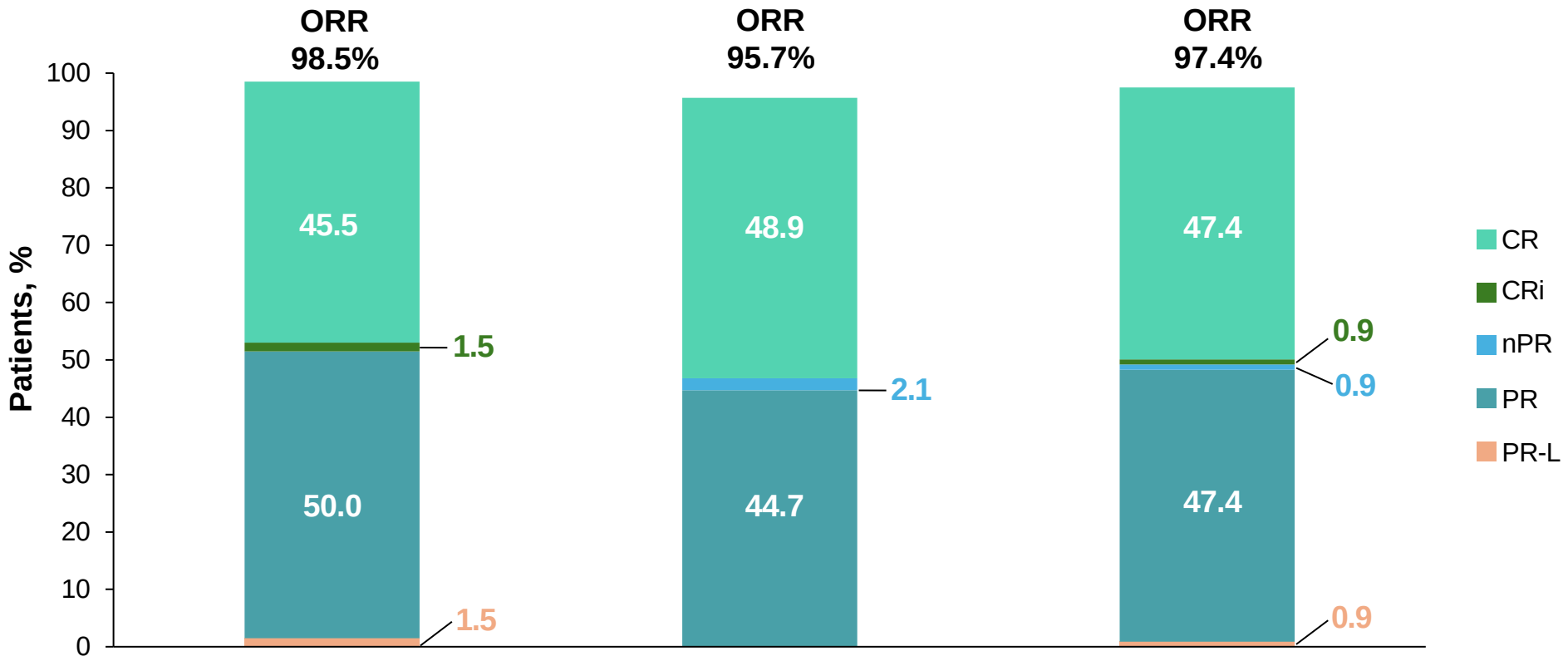
Baseline Demographics and Disease Characteristics

Baseline characteristics	With del(17p) and/or *TP53*mut (n=66)	Without del(17p) and *TP53*mut (n=47)	All patients (N=114)
Age, median (range), years	66 (26-87)	67 (36-80)	67 (26-87)
≥65 years, n (%)	36 (55)	32 (68)	68 (60)
Male, n (%)	34 (52)	29 (62)	64 (56)
ECOG PS 0-1, n (%)	64 (97)	47 (100)	112 (98)
CIRS >6	10 (15)	11 (23)	21 (18)
CrCl, mL/min, median (range)	73 (25-253)	82 (41-355)	76 (25-355)
SLL, n (%)	3 (5)	3 (6)	6 (5)
Binet stage C, n (%)[a]	30 (48)	16 (36)	46 (43)
Bulky disease, n (%)			
LDi ≥5 cm	29 (44)	19 (40)	49 (43)
LDi ≥10 cm	5 (8)	1 (2)	6 (5)
Median time from initial diagnosis, months	19.3	42.2	28.5
***TP53* mutated, n (%)**	49 (74)	0	49 (43)
del(17p), n (%)	59 (89)	0	59 (52)
del(17p) and *TP53* mutated, n (%)	42 (64)	0	42 (37)
***IGHV* unmutated, n (%)[b]**	56 (85)	30 (64)	86 (75)
Complex karyotype, n (%)			
≥3 abnormalities	33 (50)	14 (30)	47 (41)
≥5 abnormalities	24 (36)	2 (4)	26 (23)

[a]Binet stage was assessed at study entry for patients with CLL. [b]There were four patients with a missing IGHV result, 1 due to missed sample collection and 3 due to insufficient quantity of sample.
CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, immunoglobulin heavy-chain variable region; LDi, longest diameter; mut, mutation.

Best Overall Response Rates

- ORR and rates of CR/CRi were high regardless of mutational status

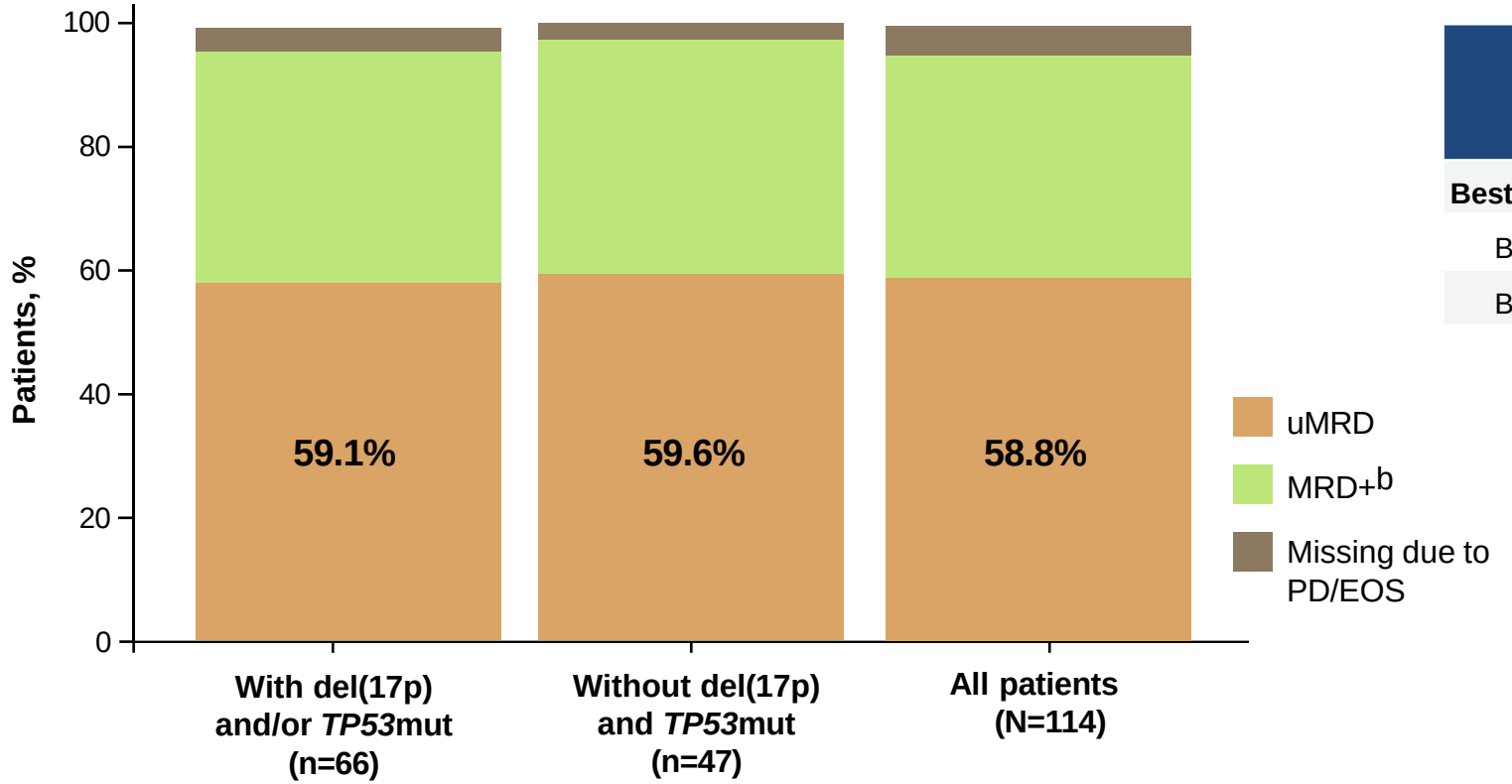


	With del(17p) and/or *TP53*mut (n=66)	Without del(17p) and *TP53*mut (n=47)	All patients (n=114)
Median study follow-up, months (range)	**38.7** (0.4-58.0)	**29.6** (0.6-31.9)	**31.2** (0.4-58.0)

CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ORR, overall response rate; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis.

Best uMRD in the Peripheral Blood[a]

- Best PB-uMRD was similar regardless of mutational status
- Median time to first PB-uMRD was 19 months (range, 3-47 months) in patients with del(17p) and/or *TP53*mut and 11 months (range, 6-25 months) in patients without del(17p) and *TP53*mut



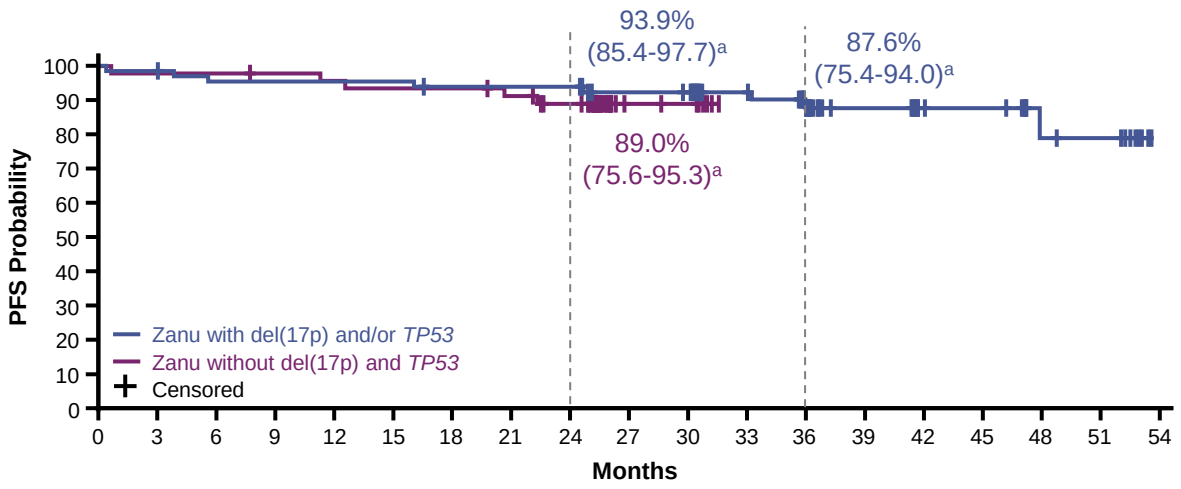
	With del(17p) and/or *TP53*mut (n=66)	Without del(17p) and *TP53*mut (n=47)
Best PB-uMRD, n (%)		
By cycle 16	14 (21)	20 (43)
By cycle 28	32 (49)	28 (60)

[a]Best uMRD in the peripheral blood is defined as achieving uMRD in the peripheral blood at ≥1 timepoint. [b]MRD ≥1 x 10^{-4}.
EOS, end of study; mut, mutation; PB-uMRD, peripheral blood-undetectable minimal residual disease; PD, progressive disease; uMRD, undetectable minimal residual disease.

Progression-free Survival

- Median PFS was not reached
- Estimated 24-month PFS rates were high, regardless of mutational status

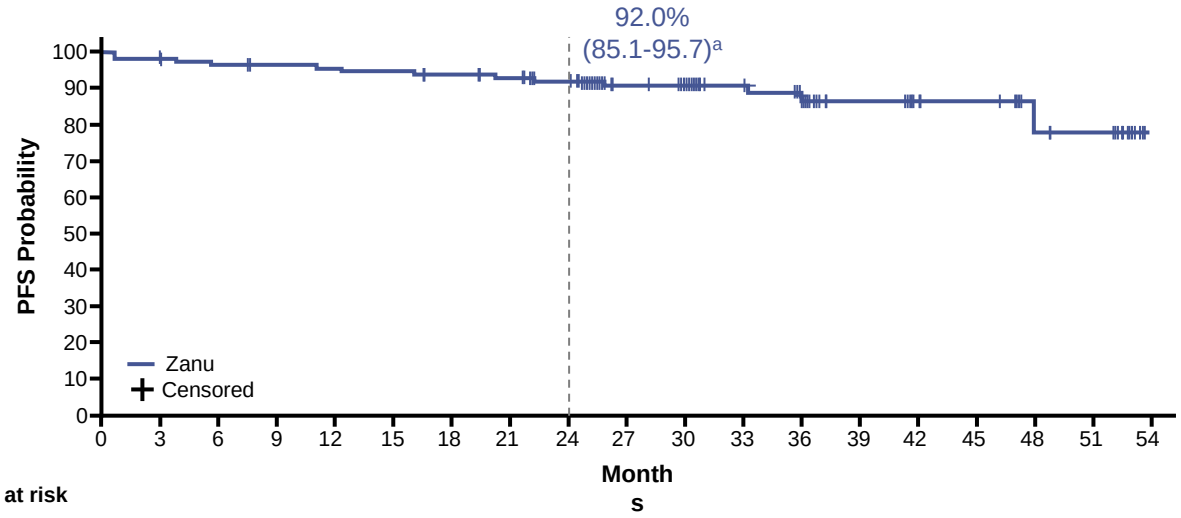
With and without del(17p) and/or *TP53* mutation



No. at risk																			
Zanu with del(17p)/*TP53*	66	65	62	62	62	62	60	60	60	55	54	45	35	23	17	16	9	8	0
Zanu w/o del(17p)/*TP53*	47	46	46	45	44	43	43	41	37	7	4	0							

- Median study follow-up:
  - With del(17p) and/or *TP53*mut: 38.7 months
  - Without del(17p) and *TP53*mut: 29.6 months

All patients



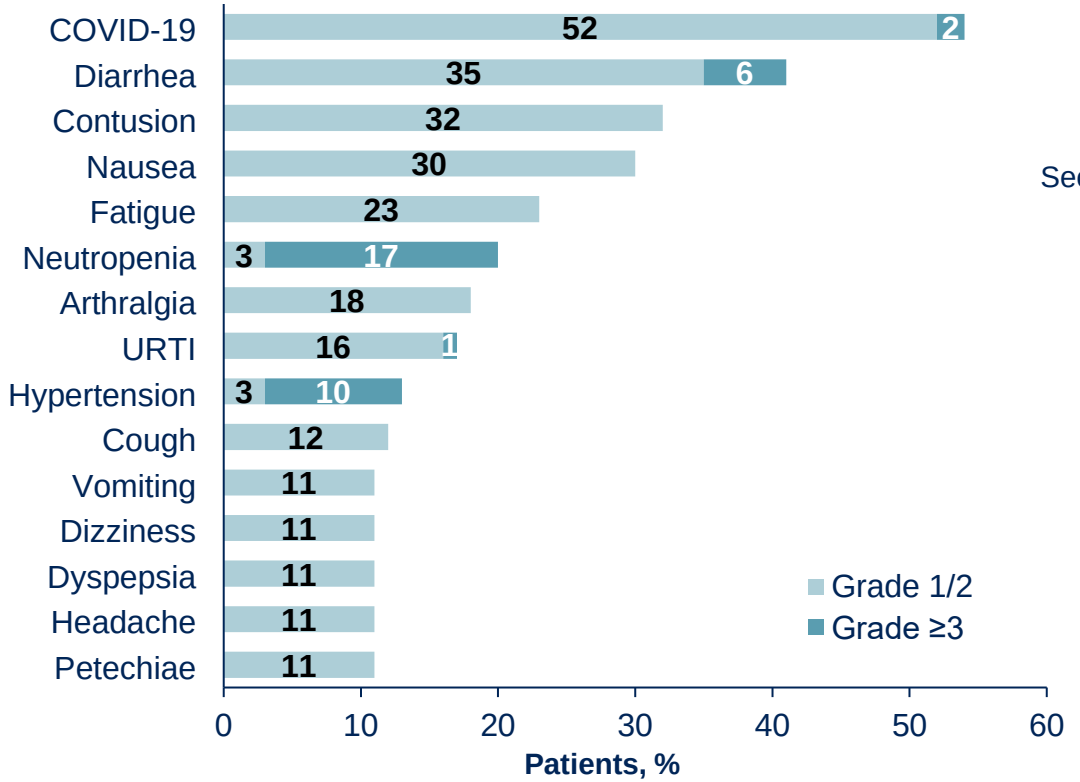
No. at risk																			
Zanu	114	112	109	108	107	106	104	102	98	62	58	45	35	23	17	16	9	8	0

- Median study follow-up: 31.2 months

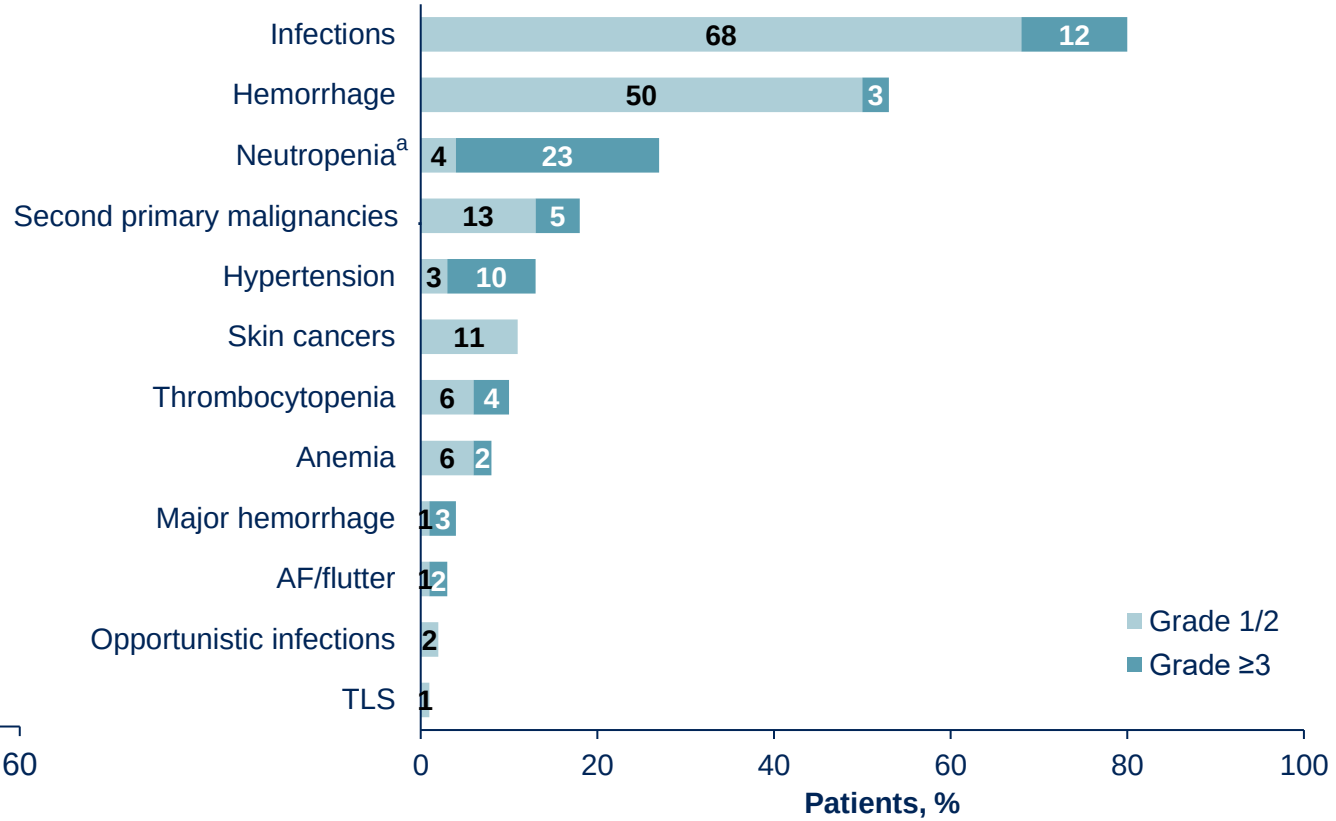
[a]95% CI values.
ITT, intention-to-treat; mut, mutation; PFS, progression-free survival; w/o, without.

Safety Profile

TEAEs by preferred term in >10% of patients



TEAEs of special interest



- Zanubrutinib + venetoclax had a favourable safety profile
- Five deaths occurred in this study due to AEs[b]; No COVID-19-related deaths occurred

[a]Included neutropenia, neutrophil count decreased and agranulocytosis. [b]One patient experienced a fatal road traffic accident leading to intracranial hemorrhage and intra-abdominal hemorrhage. One patient experienced death due to pneumonia and septic shock. Other TEAEs leading to death included lung carcinoma, gallbladder carcinoma, and intracranial hemorrhage in a patient with concomitant direct oral anticoagulant use and prior zanubrutinib discontinuation.
AEs, adverse event; AF, atrial fibrillation; TEAE, treatment-emergent AEs; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection.

Conclusions

- In SEQUOIA Arm D, zanubrutinib + venetoclax in patients with TN CLL/SLL showed promising efficacy with deep and durable responses regardless of del(17p)/*TP53* mutational status
  - Patients achieved a 24-month PFS of 92%; In patients with del(17p) and/or *TP53*mut, efficacy was maintained with a 36-month PFS of 88%
- Best uMRD in the peripheral blood was achieved in 59% of patients
  - Despite differences in time to first uMRD in the peripheral blood, the best uMRD was similar regardless of mutational status, suggesting continuous therapy may be beneficial for patients with high-risk features
- The safety profile of zanubrutinib + venetoclax was tolerable and no unexpected safety signals were identified
  - Rates of atrial fibrillation/flutter were low
  - There were no cardiac-related or COVID-related deaths on study
- Zanubrutinib + venetoclax, followed by continuous zanubrutinib appears to be a promising treatment option for patients with TN CLL/SLL regardless of del(17p)/*TP53*mut

ORR, overall response rate; mut, mutation; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable minimal residual disease.

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