SEQUOIA 5-year Follow-up in Arm C: Frontline Zanubrutinib Monotherapy in Patients with del(17p) and Treatment-naive CLL/SLL

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Disclosures for Mazyar Shadman

- **Consultant:** AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines Ltd, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck
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- **Employment:** BMS (spouse)

Key Takeaways

- Arm C from the pivotal SEQUOIA study is the largest prospective cohort (N=110) of uniformly treated patients with **del(17p)** TN CLL/SLL
- With a median follow-up of 5 years, zanubrutinib demonstrates durable efficacy in patients with del(17p)
  - The estimated 60-month PFS with zanubrutinib was 72.2%, similar to that observed in patients without del(17p) treated with zanubrutinib, highlighting robust efficacy across all types of patients with TN CLL/SLL
- Zanubrutinib was well tolerated with no unexpected safety signals

CLL, chronic lymphocytic leukemia; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TN, treatment-naïve.

Introduction

- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor that was designed to provide complete and sustained target inhibition and is the only BTK inhibitor to demonstrate superiority over ibrutinib in a head-to-head phase 3 trial[1-4]
- Zanubrutinib has continuous exposure coverage above its IC_{50} compared with ibrutinib and acalabrutinib which is expected to lead to more sustained and complete BTK inhibition to improve efficacy[5]

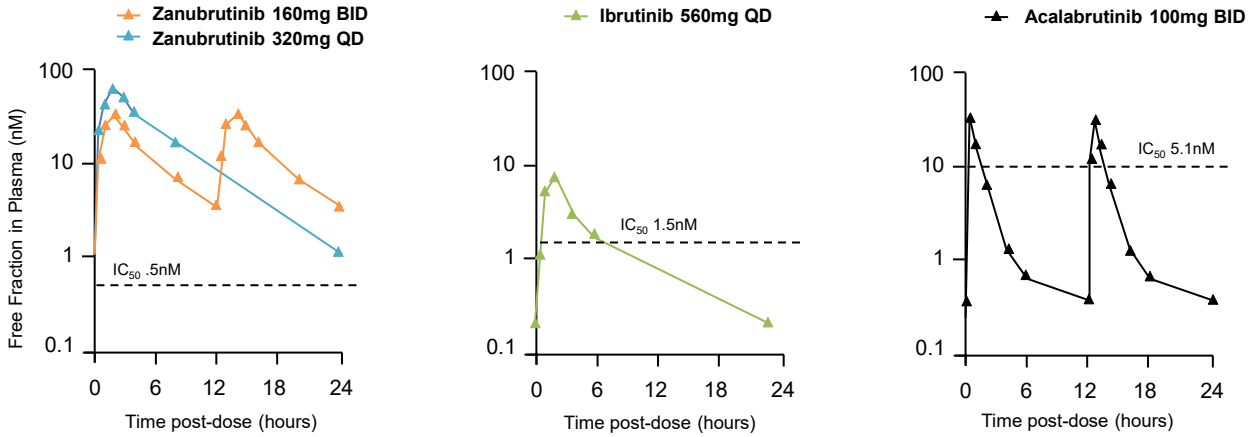


Figure adapted from: Tam CS et al. *Expert Rev Clin Pharmacol.* 2021;14(11):1329-1344

BID, twice daily; BTK, Bruton tyrosine kinase; C_{trough}, trough concentration; IC_{50}, half-maximal inhibitory concentration; QD, once daily.

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. Brown J. et al. *Blood.* 2024;144(26):2706-2717; 5. Tam CS et al. *Expert Rev Clin Pharmacol.* 2021;14(11):1329-1344.

Introduction

- SEQUOIA (NCT03336333) is a registrational phase 3, open-label, randomized study that evaluated zanubrutinib in broad range of treatment naive (TN) CLL patients, including those with high-risk features[1-3]
  - 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 (Arm A: 75.8%)[1,2]
  - Recently published results for Arm D showed that zanubrutinib + venetoclax combination demonstrated robust efficacy with deep and durable responses, including a large subgroup with del(17p) and/or *TP53* mutation and another without del(17p) and *TP53* mutation[4]
- Here, we present updated results from SEQUOIA Arm C in patients with del(17p) after approximately 5 years of follow-up in this **historically difficult to treat patient population**

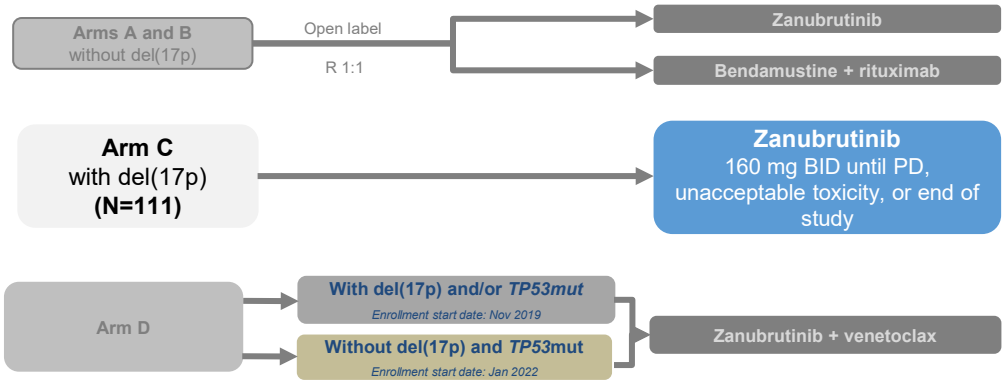
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive.

1. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043; 2. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787; 3. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363; 4. Shadman M, et al. *J Clin Oncol*. Published online May 31, 2025. doi: 10.1200/JCO-25-00758.

SEQUOIA Study Design

Key eligibility criteria

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



Key endpoints for Arm C

- PFS (INV)
- ORR (INV)[a]
- OS
- Safety per CTCAE

Assessments for Arm C:

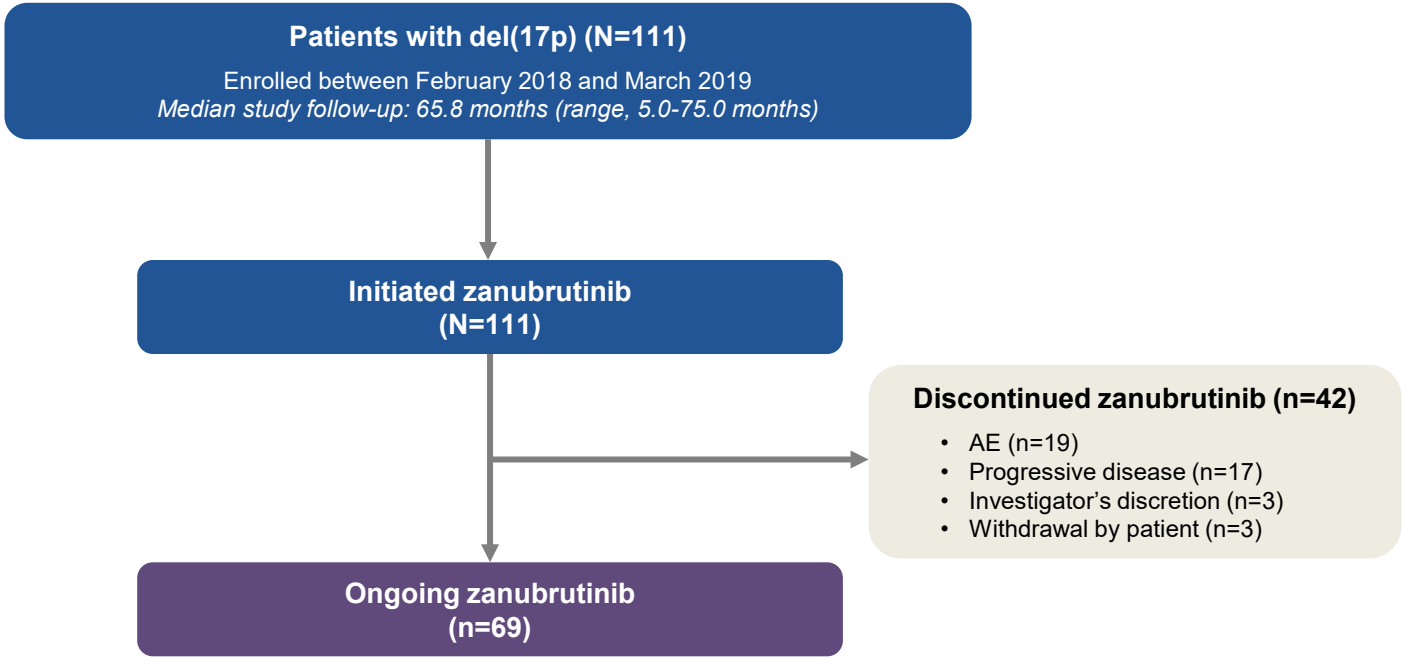
- Sensitivity analyses were performed for PFS and OS with deaths due to COVID infection, censored at the time of death if no prior progression was observed
- Response assessments were performed every 12 weeks after the first dose of study drug for 96 weeks, then every 24 weeks until PD
- Adverse events were graded by CTCAE version 4.03 and documented from the time of first dose of study drug, until 30 days after the last dose of study drug, or until PD (whichever occurred later), or until the first day of a new CLL/SLL treatment

[a]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] in patients with SLL. ORR was defined as achievement of PR-L or better.

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

1. Hallek M, et al. *Blood.* 2008;111(12):5446–5456; 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.

Patient Disposition



Data cutoff: April 30, 2024.
AE, adverse event.

Baseline Demographics and Clinical Characteristics

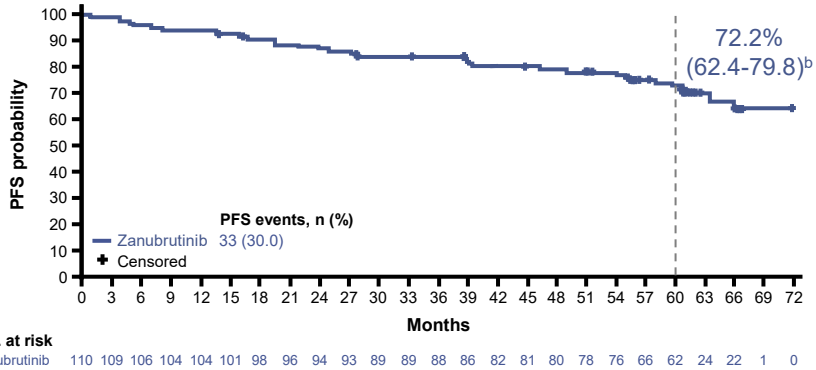
Baseline characteristics	All patients (N=111)
Age, median (range), years	71 (42-87)
≥65 years, n (%)	95 (85.6)
Male, n (%)	79 (71.2)
ECOG PS 0/1, n (%)	97 (87.3)
CLL, n (%)	100 (90.1)
SLL, n (%)	11 (9.9)
Binet stage C, n (%)[a]	37 (37.0)
Bulky disease, n (%)	
LDi ≥5 cm	44 (39.6)
LDi ≥10 cm	12 (10.8)
Median time from initial diagnosis, months	21.39
***TP53* mutated, n (%)**	47 (42.3)
del(17p), n (%)	110 (99.1)
del(17p) and *TP53* mutated, n (%)	47 (42.3)
IGHV mutated, n (%)	36 (32.4)
IGHV unmutated, n (%)	67 (60.4)
Complex karyotype, n (%)	
≥3 abnormalities	31 (27.9)
≥5 abnormalities	21 (18.9)

[a]Binet stage was assessed at study entry for patients with CLL.
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.

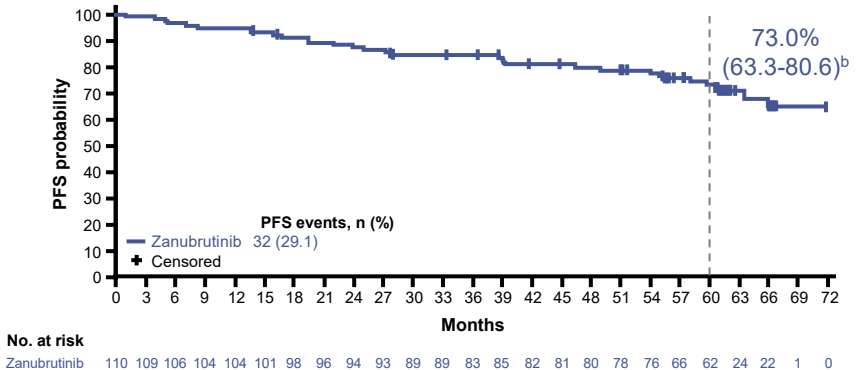
Progression-free Survival

- Median PFS was not reached with zanubrutinib

PFS[a]

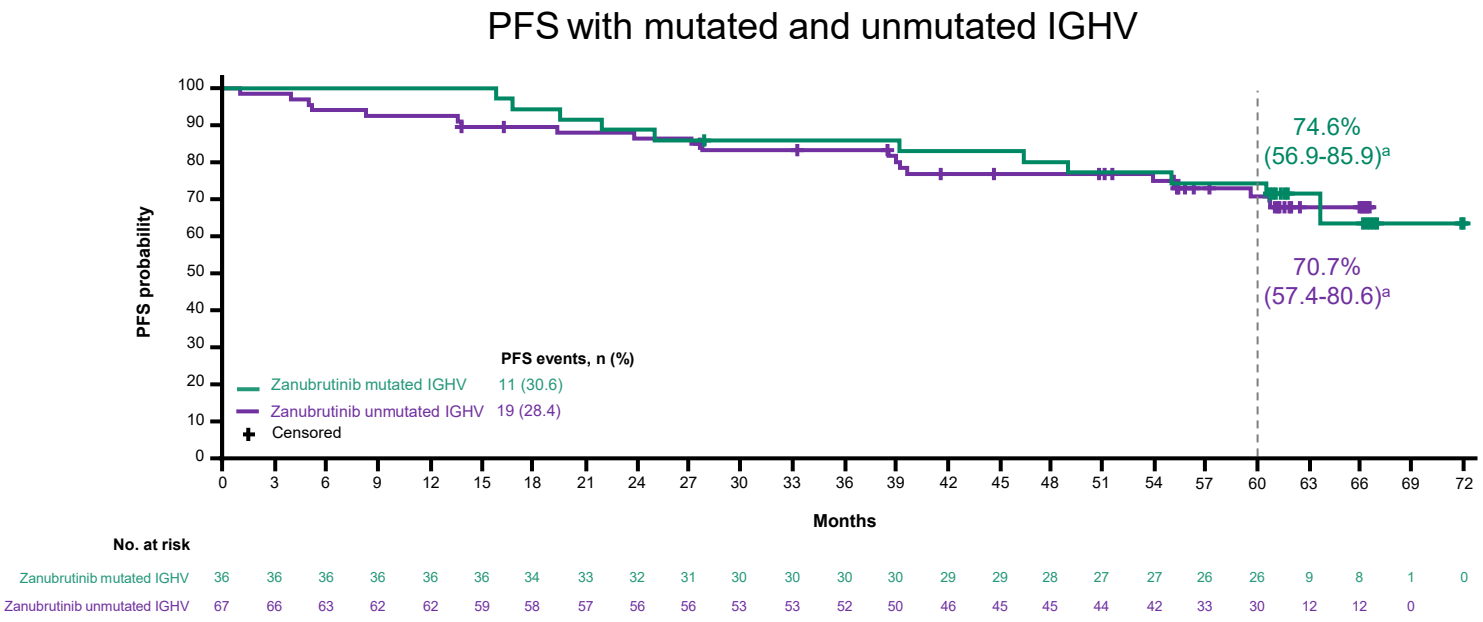


PFS with COVID-19 adjustment[a]



[a]Data are presented in patients with del(17p), confirmed by central laboratory (N=110). [b]95% CI values.
PFS, progression-free survival.

Progression-free Survival by IGHV Mutation Status

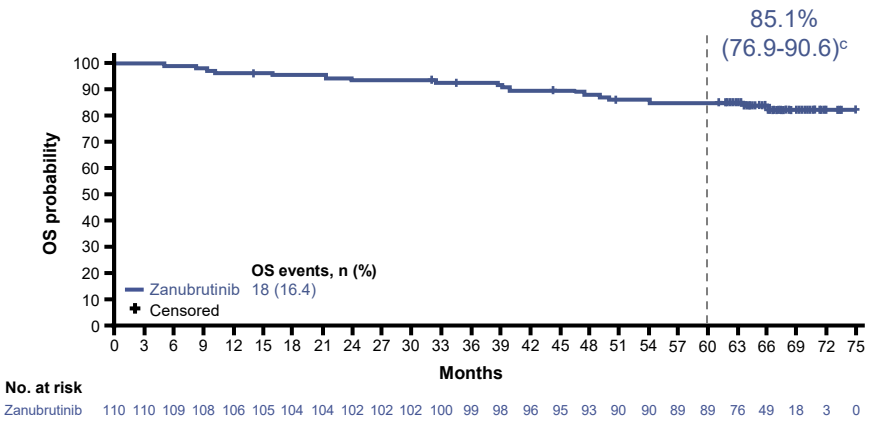


[a]95% CI values.
IGHV, immunoglobulin heavy-chain variable region; PFS, progression-free survival.

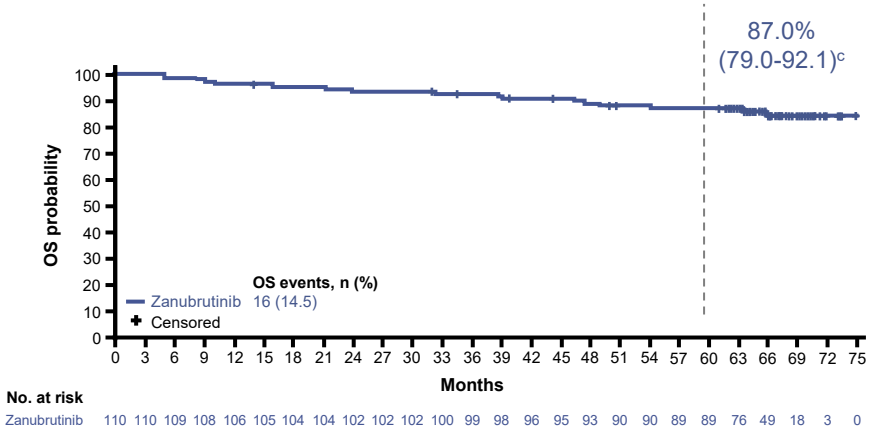
Overall Survival

- Median OS was not reached with zanubrutinib and 18 deaths occurred during the study[a]

OS[b]



OS with COVID-19 adjustment[b]



[a]Due to adverse event (n=6), progressive disease (n=5), other (n=3), or unknown (n=4). Reasons for death due to 'Other' included events of infections occurring outside of the adverse event report period. [b]Data is presented in patients with del(17p), confirmed by central laboratory (N=110). [c]95% CI values.
OS, overall survival.

ORR and CR+CRi Rates

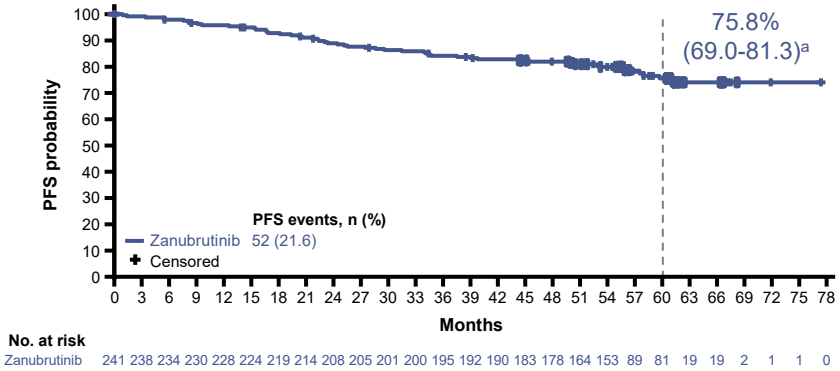
	Zanubrutinib (N=110)[a]
ORR, n (%)	107 (97.3)
Best overall response, n (%)	
CR/CRi rate	20 (18.2)
nPR	3 (2.7)
PR	84 (76.4)
PR-L	0
SD	2 (1.8)
PD	1 (0.9)

[a]Patients with del(17p), confirmed by central laboratory.
CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ORR, overall response rate; nPR, nodular partial response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

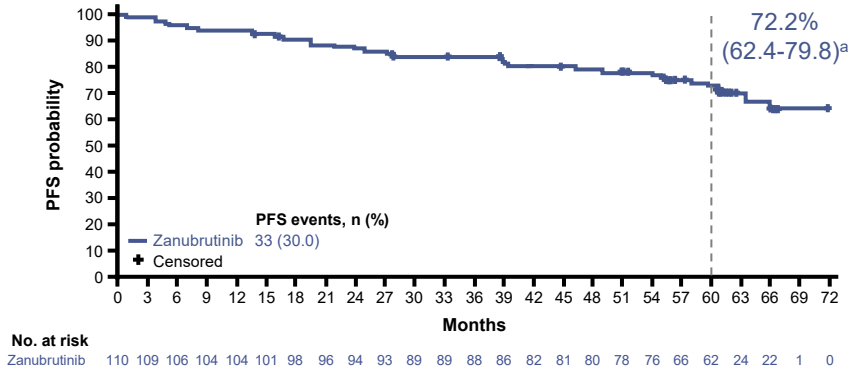
Consistent Outcomes Regardless of Del(17p) Status

- The estimated 60-month PFS rate was similar to that seen in patients without del(17p)[1]

PFS (Arm A)



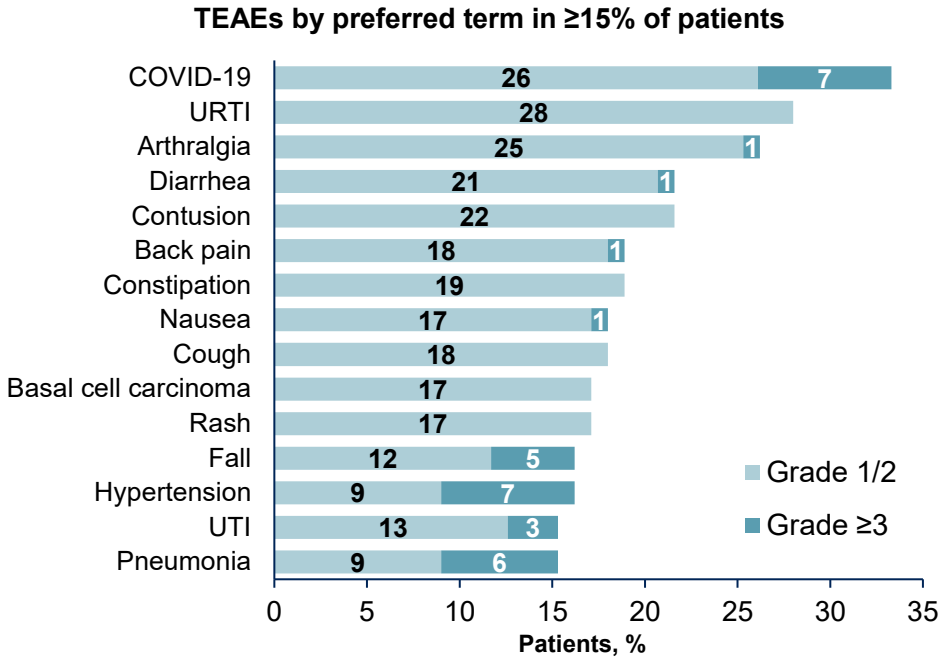
PFS[b] (Arm C)

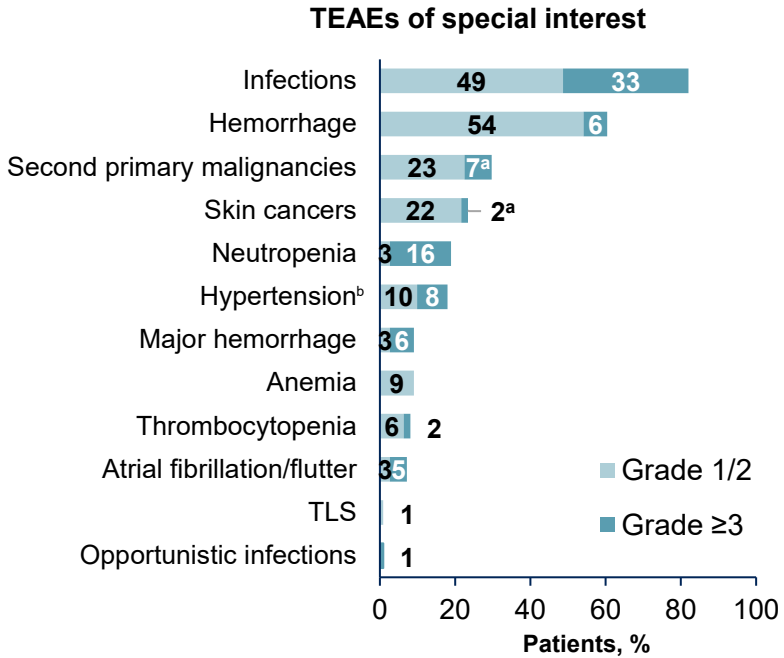


- The CR/CRi rate with zanubrutinib was 18.2%, similar to that seen in patients without del(17p) at 20.7%[1]

[a]95% CI values. [b]Data are presented in patients with del(17p), confirmed by central laboratory (N=110).
CR, complete response; CRi, complete response with incomplete hematopoietic recovery; PFS, progression-free survival.
1. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787.

No New Safety Signals were Identified with Zanubrutinib



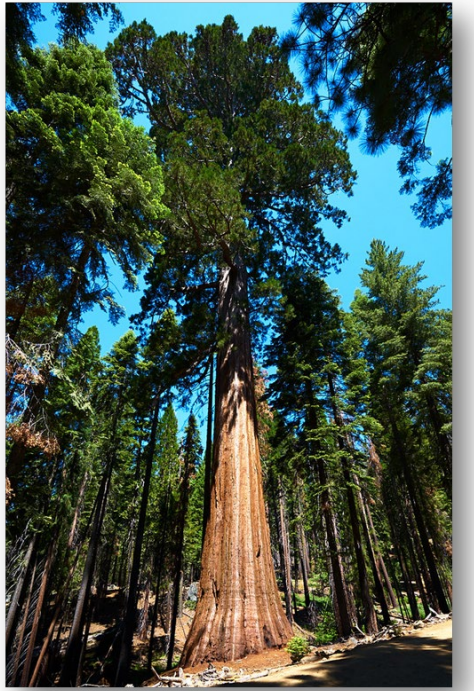


- AEs led to death in 6 patients (5.4%)

[a]Includes two patients with malignant melanoma. [b]Includes hypertension, increased blood pressure, hypertensive crisis and hypertensive heart disease.
AE, adverse event; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Conclusions

- SEQUOIA Arm C reports on the largest prospective cohort of uniformly treated patients with del(17p) TN CLL/SLL
- With a median follow-up of 5-years, zanubrutinib demonstrates durable efficacy in patients with del(17p)
  - The estimated 60-month PFS with zanubrutinib was 72.2%, similar to that observed in patients without del(17p)[1], highlighting that zanubrutinib overcomes the negative prognostic impact of del(17p)
  - The CR/CRi rate with zanubrutinib was 18.2%, similar to that seen in patients without del(17p)[1]
- The benefit of zanubrutinib in patients with del(17p) was also demonstrated in the phase 3 ALPINE study, which demonstrated PFS superiority of zanubrutinib over ibrutinib[2]
- Zanubrutinib remains a valuable frontline treatment option for patients with CLL/SLL with or without del(17p)



CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; PFS, progression-free survival; SLL, small lymphocytic lymphoma; TN, treatment-naive.

1. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787. 2. Brown J. et al. *Blood*. 2024;144(26):2706-2717. 3. szeke. Sequoia Tree. Retrieved from https://www.flickr.com/photos/43355249@N00/41563931240 on May 28, 2025. Creative Commons Attribution 2.0 International License.

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