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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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Key Takeaways

- With a median follow-up of 5-years, the estimated 60-month PFS with zanubrutinib was 72.2% in patients with TN CLL/SLL with del(17p)
- Zanubrutinib was well tolerated with no unexpected safety signals
- SEQUOIA Arm C is the largest cohort of uniformly treated patients (N=110) with del(17p) TN CLL/SLL

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

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 have achieved high overall response rates and PFS[5]
- Here, we present updated results from SEQUOIA Arm C after approximately 5 years of follow-up

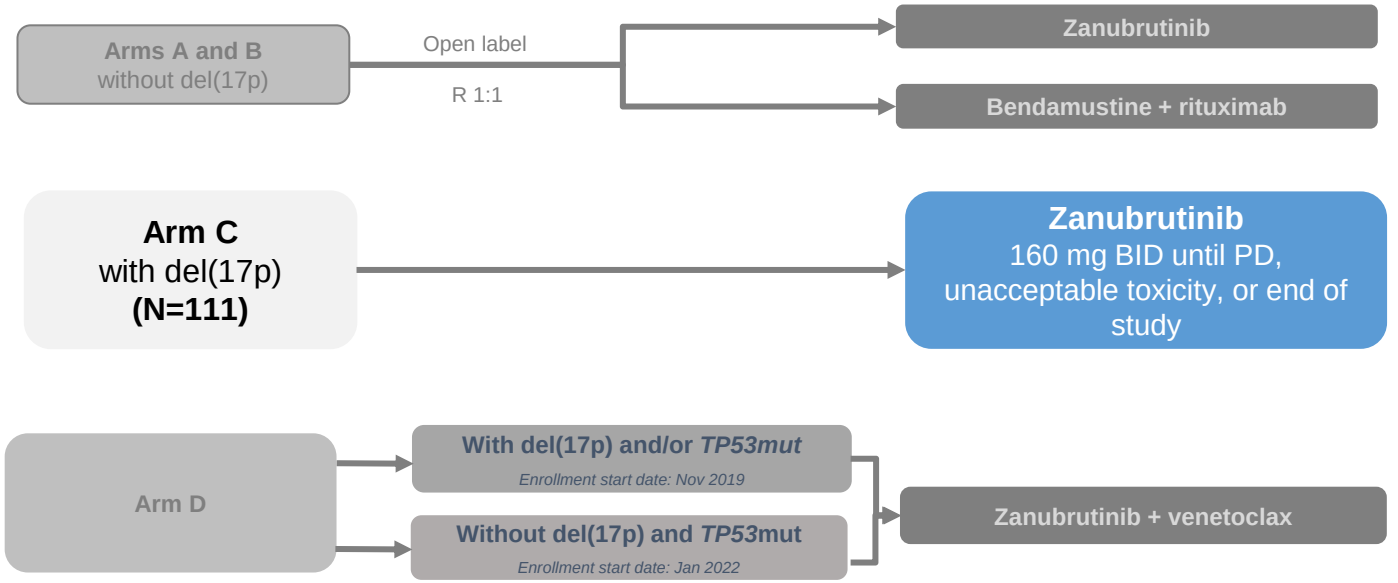
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive.

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.

SEQUOIA Study Design

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- Central confirmation of presence or absence of del(17p) by FISH
- Unsuitable for FCR



Key endpoints for Arm C

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

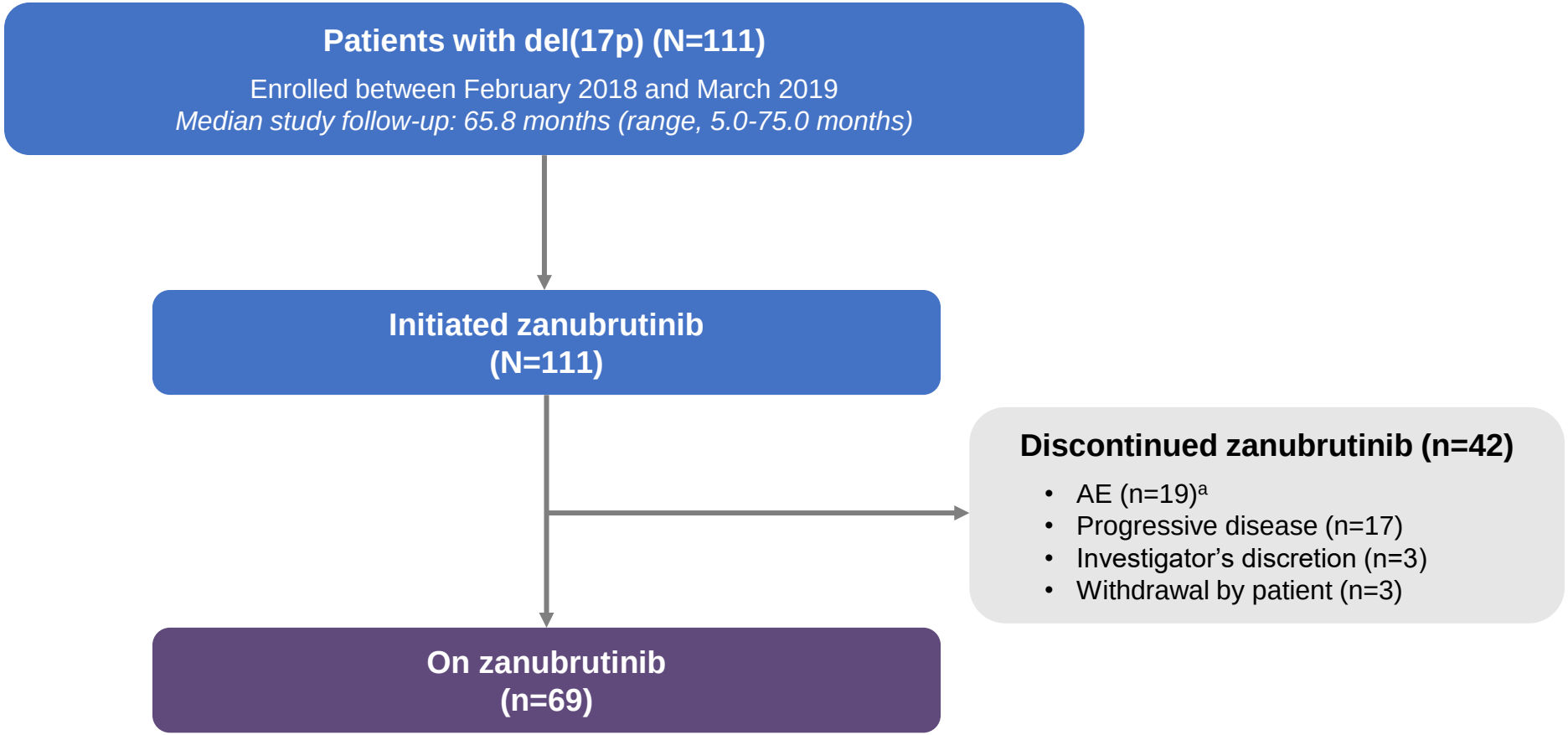
Assessments for Arm C:

- 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; Events; CLL, chronic lymphocytic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; 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):5446–56; 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.

Patient Disposition



Data cutoff: April 30, 2024.
[a]Two patients discontinued due to COVID-19-related AE.
AE, adverse event.

Baseline Demographics and Clinical Characteristics

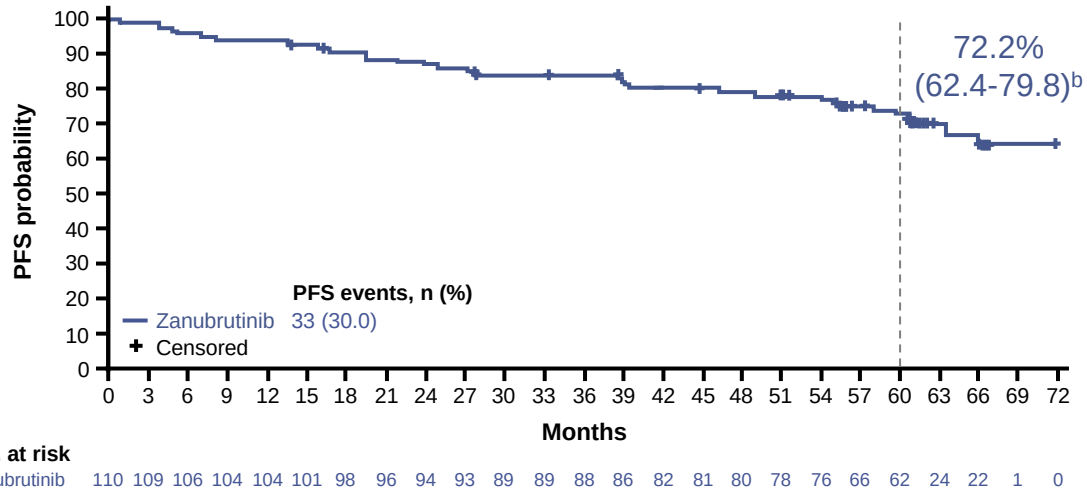
Baseline characteristics	All patients (N=111)
Age, median (range), years	71 (42-87)
≥65 years, n (%)	95 (85.6)
Male, n (%)	79 (71.2)
ECOG PS 0/1, n (%)	97 (87.3)
CLL, n (%)	100 (90.1)
SLL, n (%)	11 (9.9)
Binet stage C, n (%)[a]	37 (37.0)
Bulky disease, n (%)	
LDi ≥5 cm	44 (39.6)
LDi ≥10 cm	12 (10.8)
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.

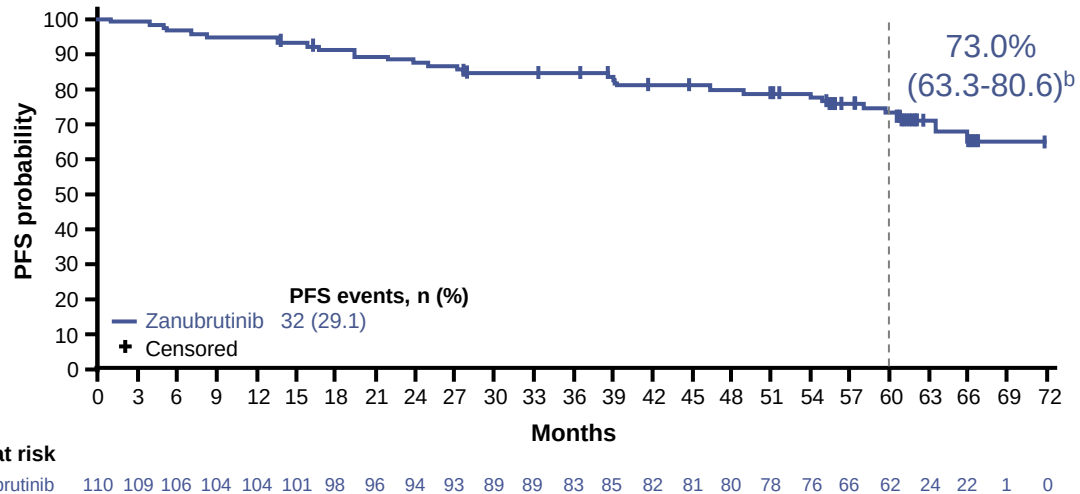
Progression-free Survival

- Median PFS was not reached with zanubrutinib

PFS[a]

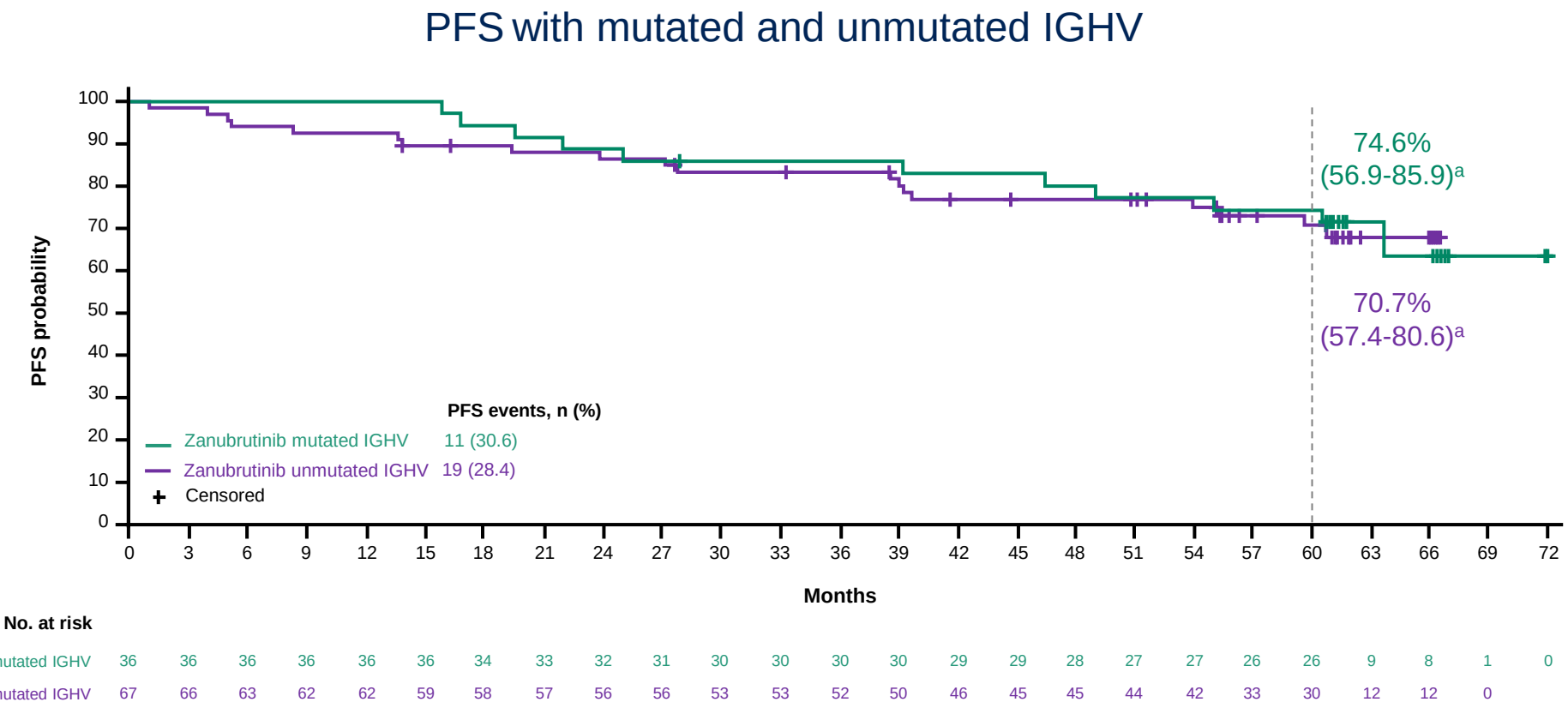


PFS with COVID-19 adjustment[a]



[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

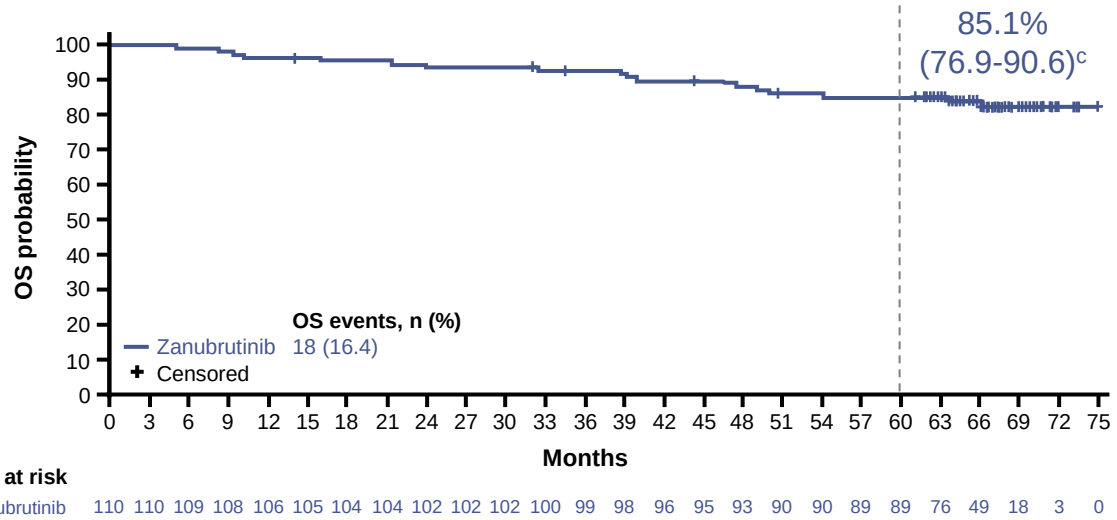


[a]95% CI values.
IGHV, immunoglobulin heavy-chain variable region; PFS, progression-free survival

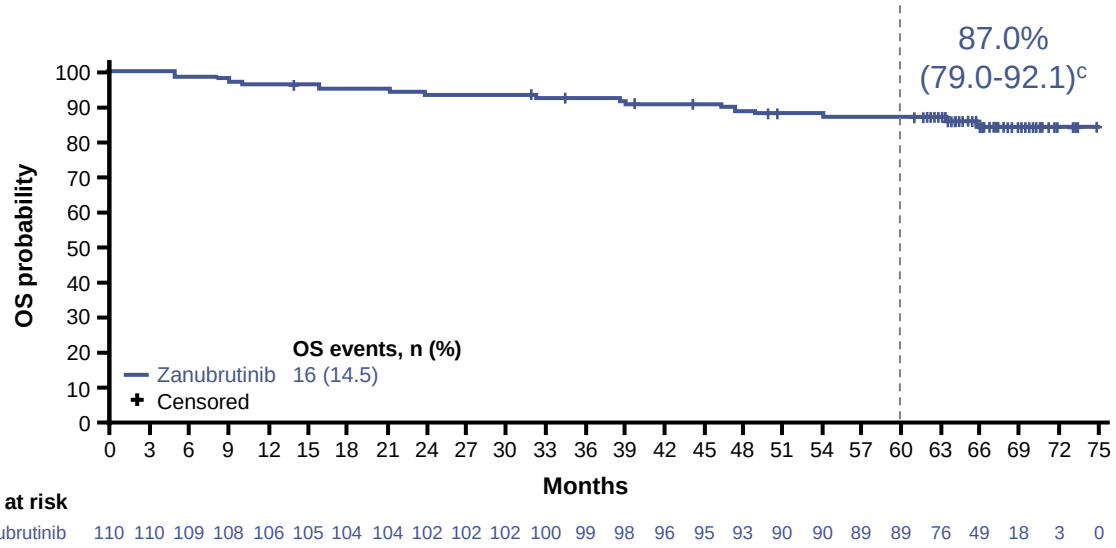
Overall Survival

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

OS[b]



OS with COVID-19 adjustment[b]



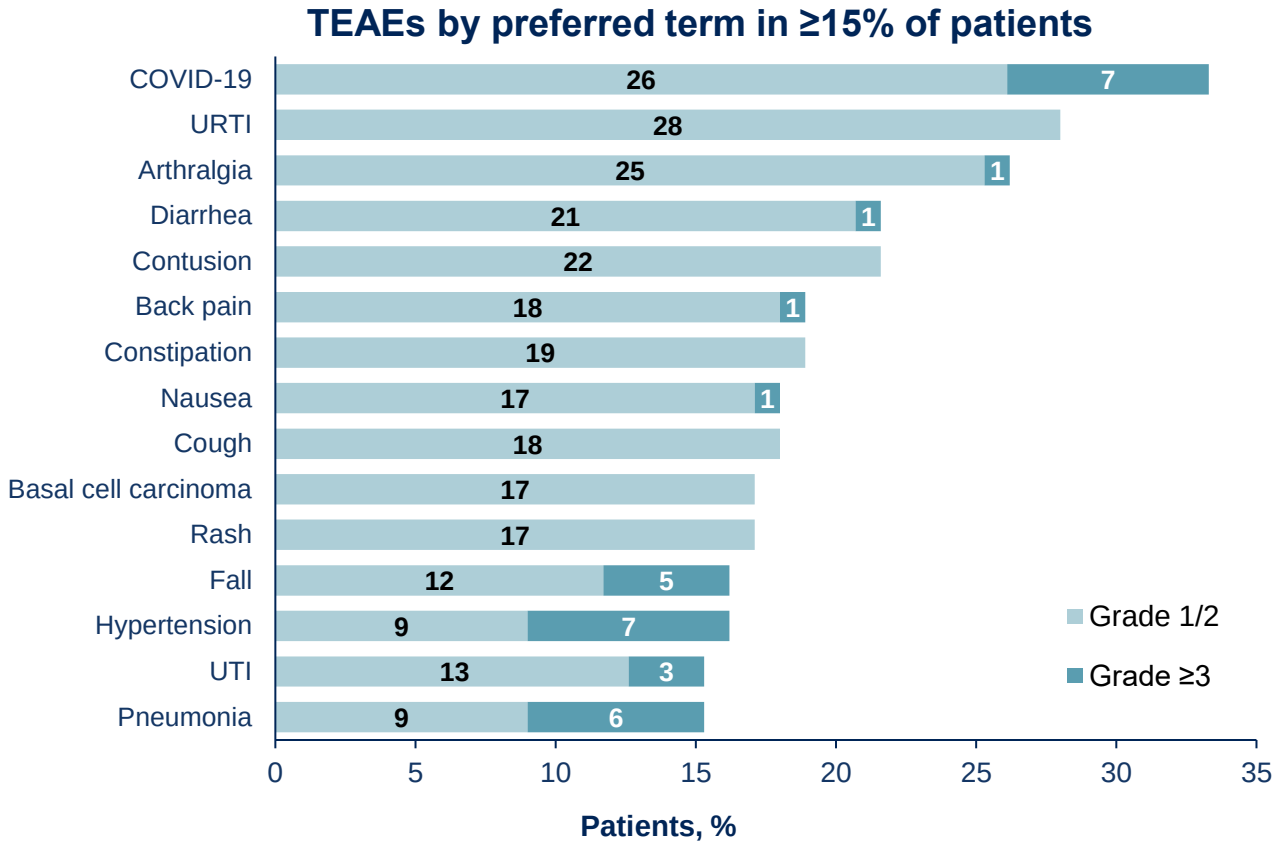
[a]Due to adverse event (n=6), progressive disease (n=5), other (n=3), or unknown (n=4). Reasons for death due to 'Other' included events of infections occurring outside of the adverse event report period. [b]Data is presented in patients with del(17p), confirmed by central laboratory (N=110). [c]95%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

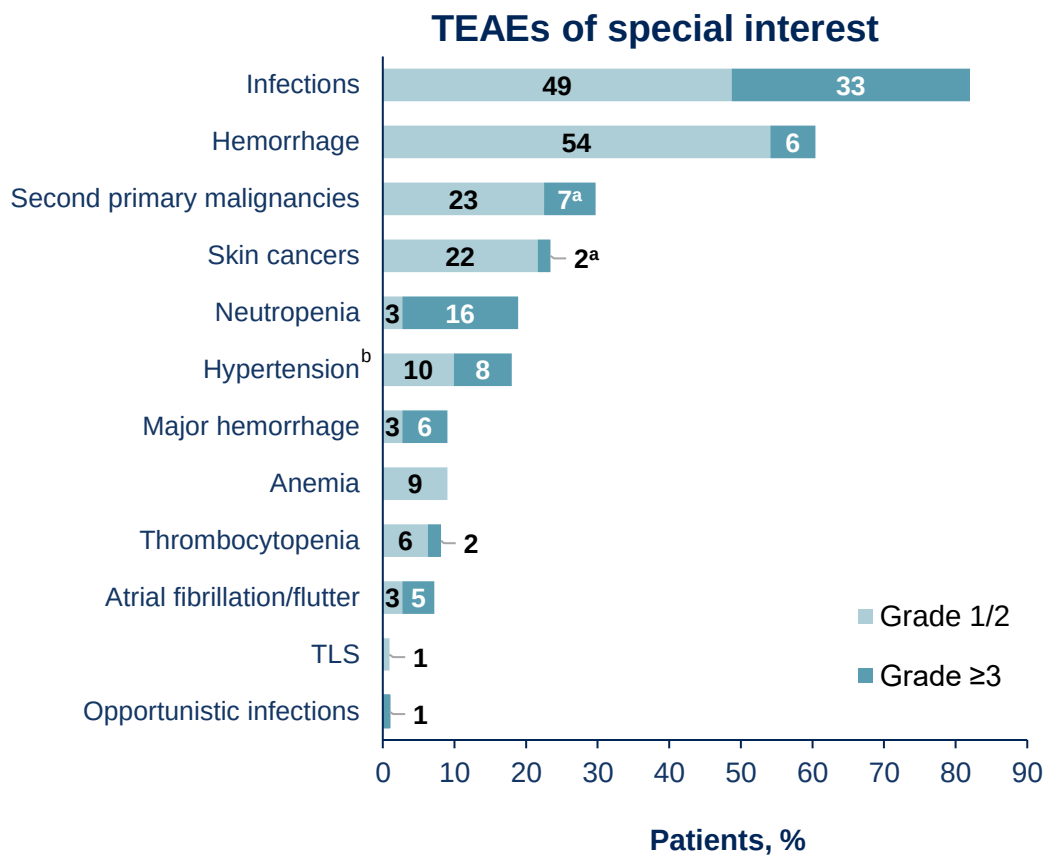
ORR and CR+CRi Rates

	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.

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 cohort of uniformly treated patients with del(17p) TN CLL/SLL
- With this 5-year median study follow-up in SEQUOIA Arm C, the efficacy of zanubrutinib in patients with TN CLL/SLL with del(17p) was maintained with a 60-month PFS of 72.2%
  - These higher-risk patients with del(17p) demonstrated a similar PFS to that of patients with TN CLL/SLL without del(17p)[1]
- Zanubrutinib was well tolerated over this extended treatment period with no unexpected safety signals identified
- Zanubrutinib remains a valuable frontline treatment option for patients with CLL/SLL regardless of del(17p) status

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

1. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787.

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