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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 deep and durable responses, regardless of del(17p) and/or *TP53* mutational status (24-month PFS of 89% in patients without del[17p] and *TP53* mutation; 24-month PFS of 94% and 36-month PFS of 88% in patients with del[17p] and/or *TP53* mutation)
- The combination of zanubrutinib + venetoclax was tolerable with a favorable safety profile; no unexpected safety signals were identified including no cardiac or COVID-19-related deaths
- Zanubrutinib + venetoclax combination compares favorably to currently available fixed duration regimens for patients with TN CLL/SLL

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 that was designed to provide complete and sustained target inhibition and is the only BTKi to demonstrate superiority over ibrutinib in a head-to-head phase 3 trial, including high risk del(17p)[1-4]
- Fixed-duration therapies with BTK and BCL2 inhibitors are emerging as a new treatment option but there are limitations due to efficacy or safety concerns, especially in high-risk populations with del(17p)/*TP53* mutation
- Most previous studies either excluded or only included a small percentage of patients with del(17p)/*TP53* mutation[5-7]
- Furthermore, optimal duration of treatment to achieve deep and durable remission has yet to be determined
- SEQUOIA is a phase 3 study that evaluated zanubrutinib in a broad range of patients with treatment-naive CLL/SLL, including those with high-risk features[8,9]
- Here, results from SEQUOIA Arm D are presented for zanubrutinib + venetoclax in patients with del(17p) and/or *TP53* mutation or without both

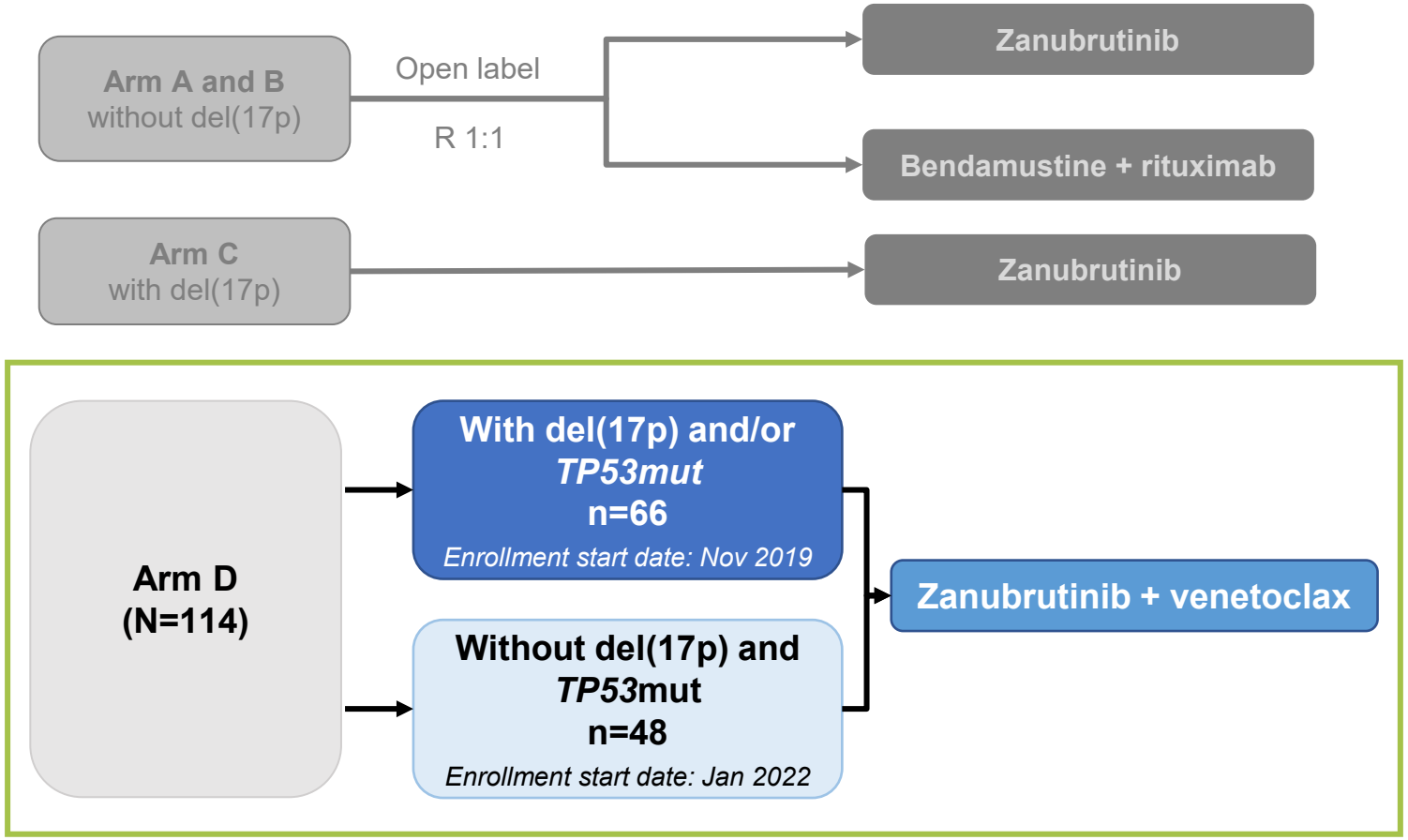
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R relapsed/refractory; TN, treatment naïve; uMRD, undetectable minimal residual disease.

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. Brown JR, et al. *Blood*. 2024;144(26):2706-2717 5. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363; 6. Brown JR et al. *N Engl J Med*. 2025. 392:748-762; 7. Tam CS, et al. *Blood*. 2022;139(22):3278-3289. 8. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787; 9. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.

# 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**

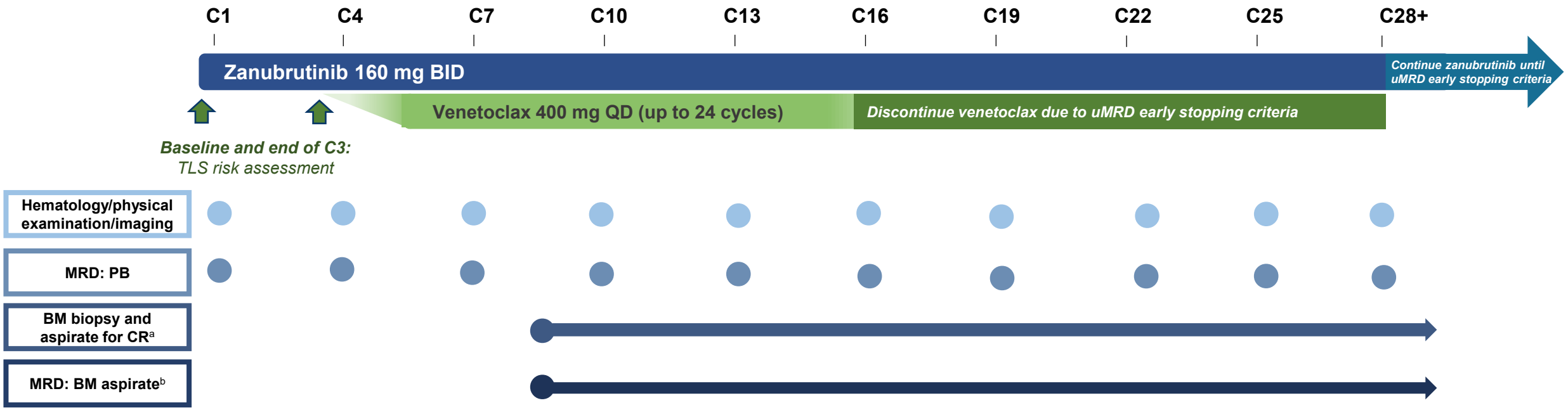
- PFS (INV)[a]
- ORR (INV)[b]
- OS[a]
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety per CTCAE

[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




**Stringent uMRD-guided stopping criteria**

**All conditions must be met:**

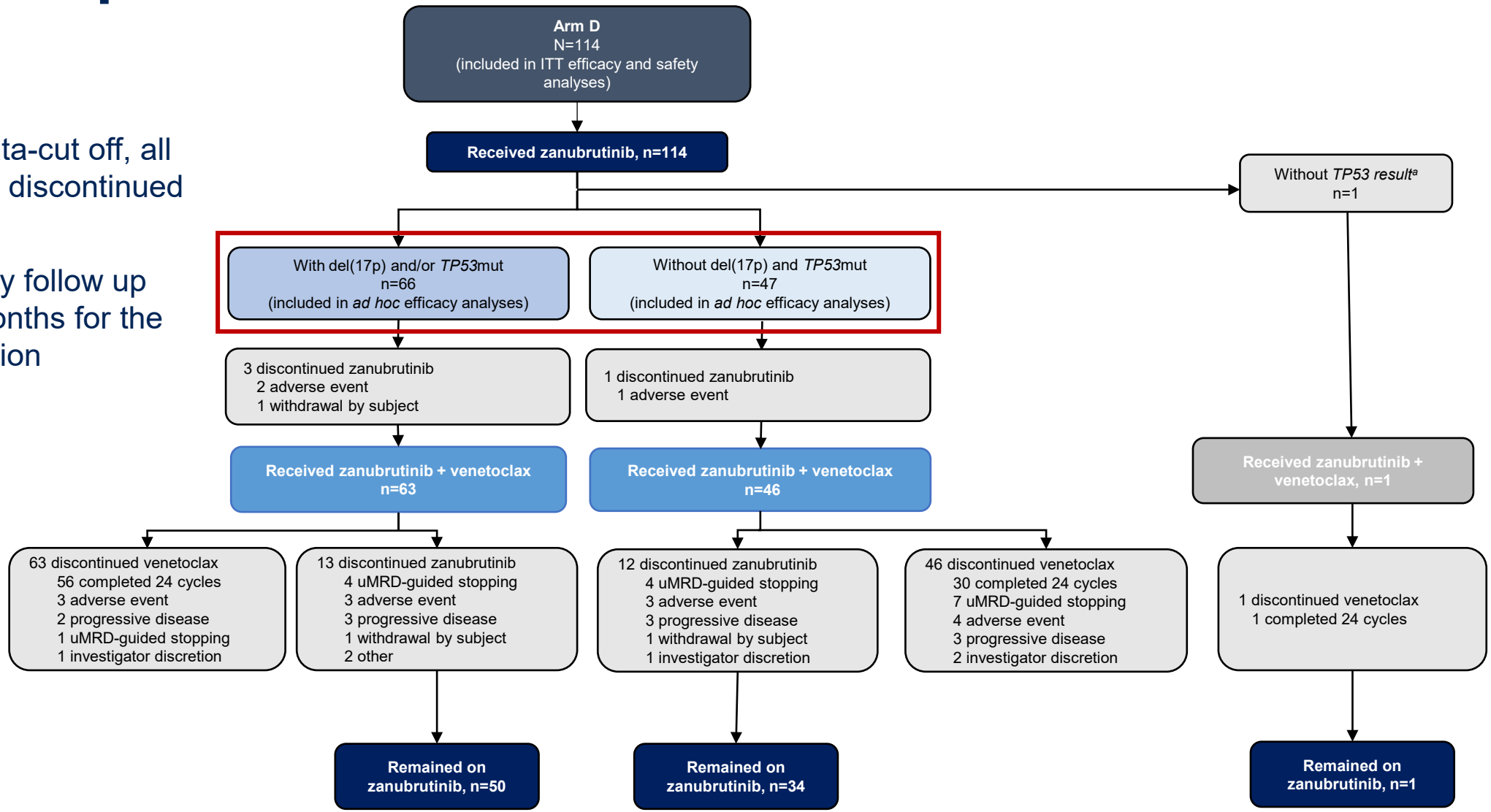
1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD <$1\times10^{-4}$ (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   - i) Minimum of 12 cycles of venetoclax (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).


PRESENTED BY: Mazyar Shadman, MD, MPH

# Patient Disposition

- As of this data-cut off, all patients had discontinued venetoclax
- Median study follow up was 31.2 months for the total population



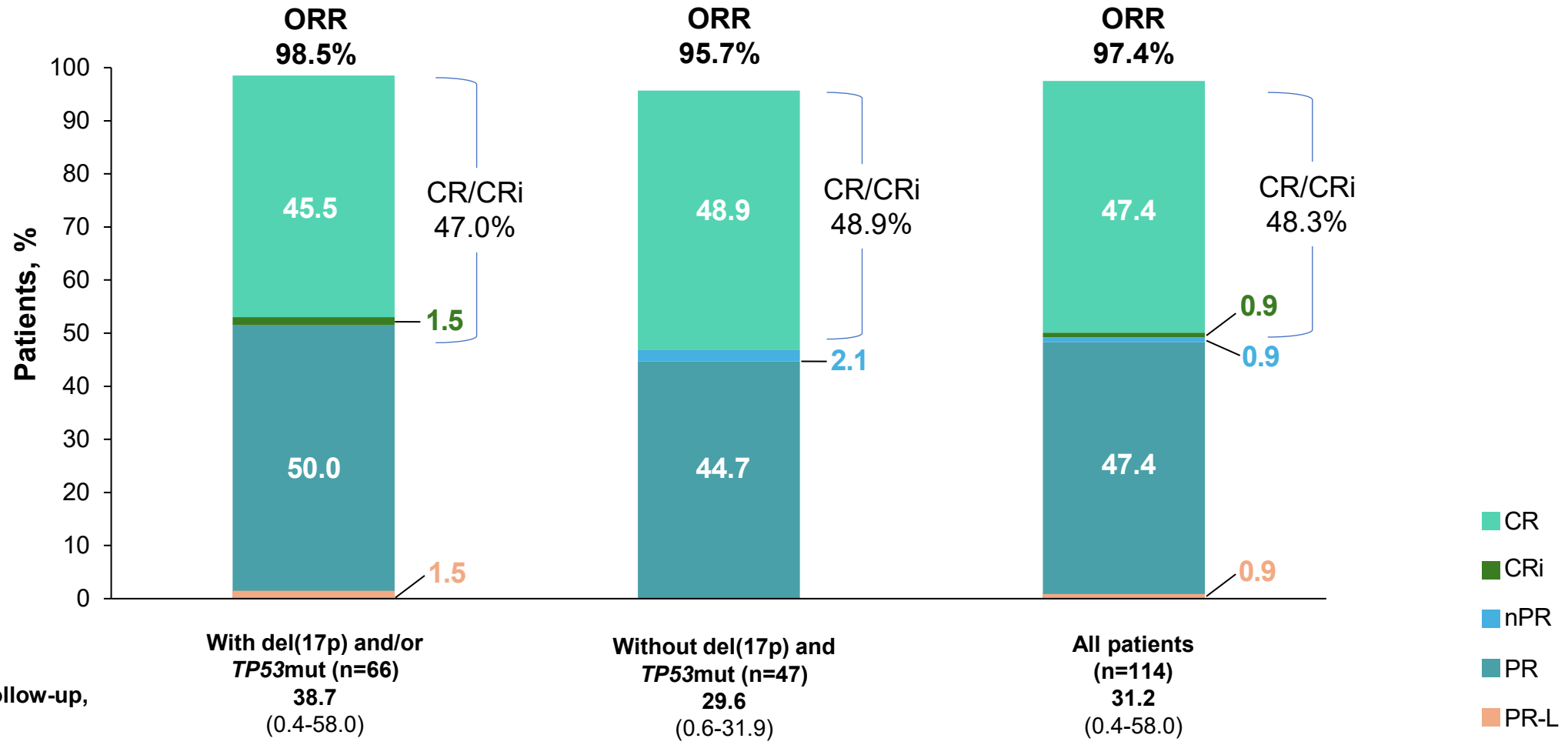

[a]Via central laboratory.
ITT, intention-to-treat; uMRD, undetectable minimal residual disease.

# 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.

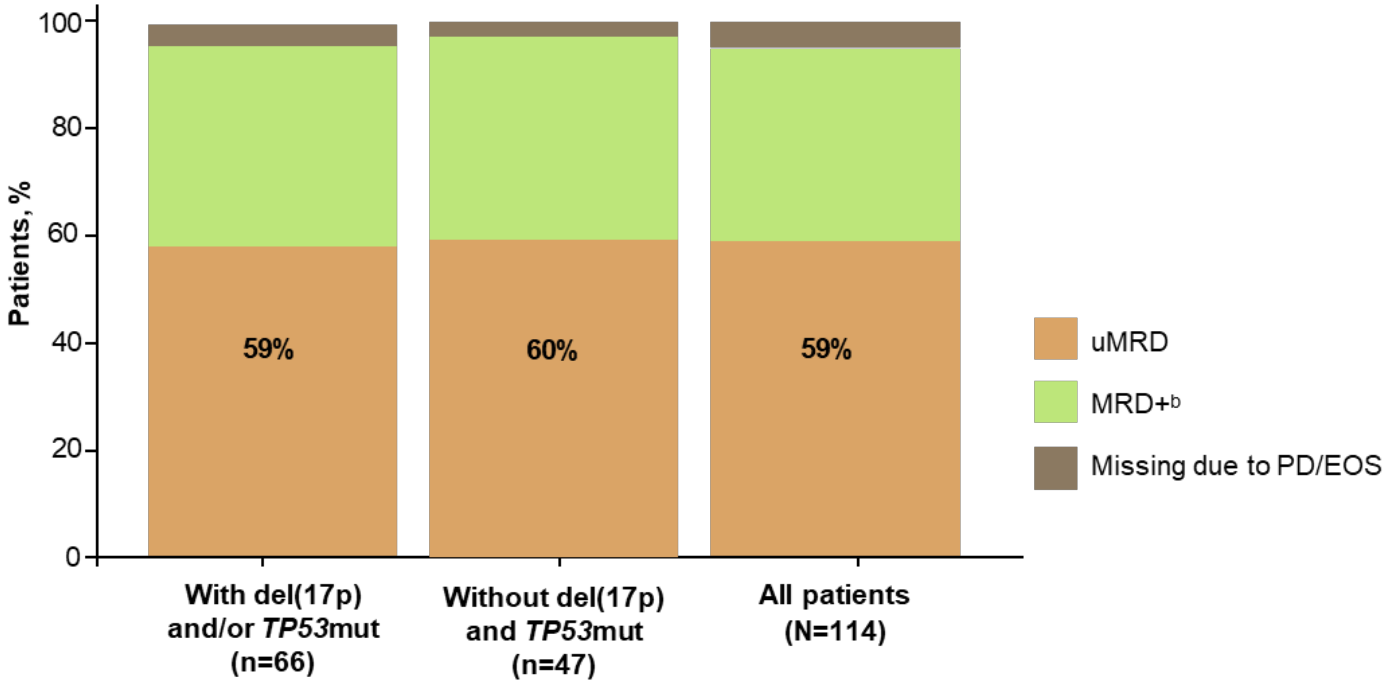
# ORR and CR/CRi Rates Were High Regardless of Mutational Status




**Median study follow-up,** months (range)

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 PB-uMRD[a] Was Similar Regardless of Mutational Status



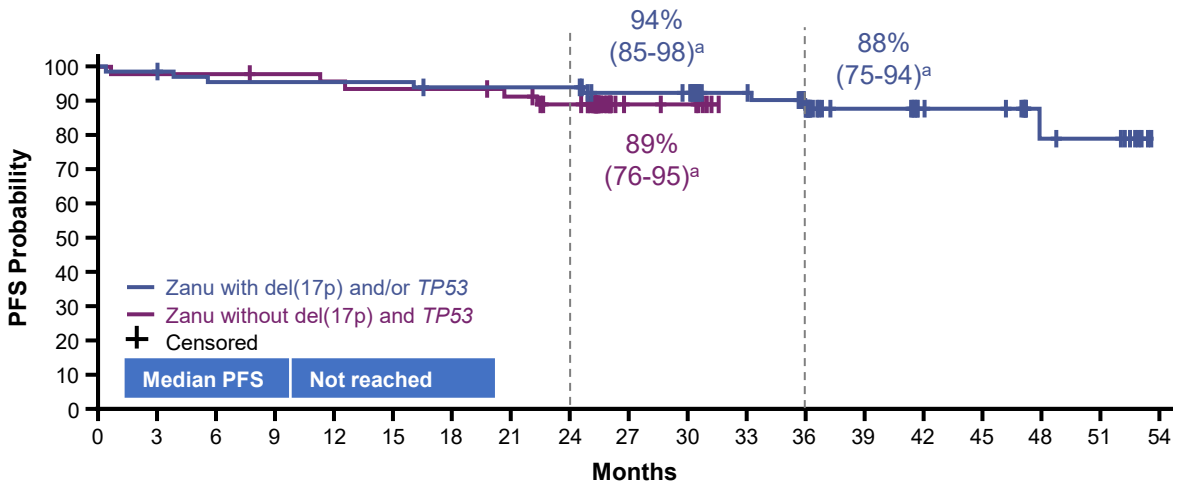

| | Without del(17p) and *TP53*mut (n=47) | With del(17p) and/or *TP53*mut (n=66) |
|---|---|---|
| **Best PB-uMRD, n (%)** | | |
| By cycle 16 | **20 (43)** | 14 (21) |
| By cycle 28 | **28 (60)** | 32 (49) |

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

# Similar PFS Rates Were Achieved Across Subgroups

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

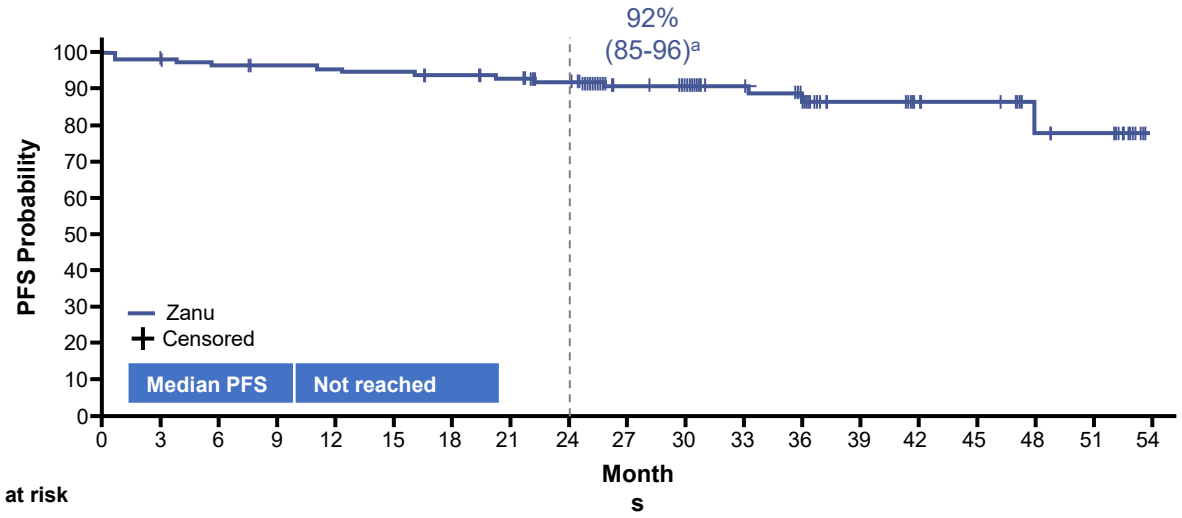
- Median study follow-up for patients with del(17p) and/or *TP53*mut was 38.7 mo (0.4-58.0) and 29.6 mo (0.6-31.9) for patients without del(17p) and *TP53*mut




| 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 | | | | | | | |

## All patients

- Median study follow-up for all patients was 31.2 mo (0.4-58.0)

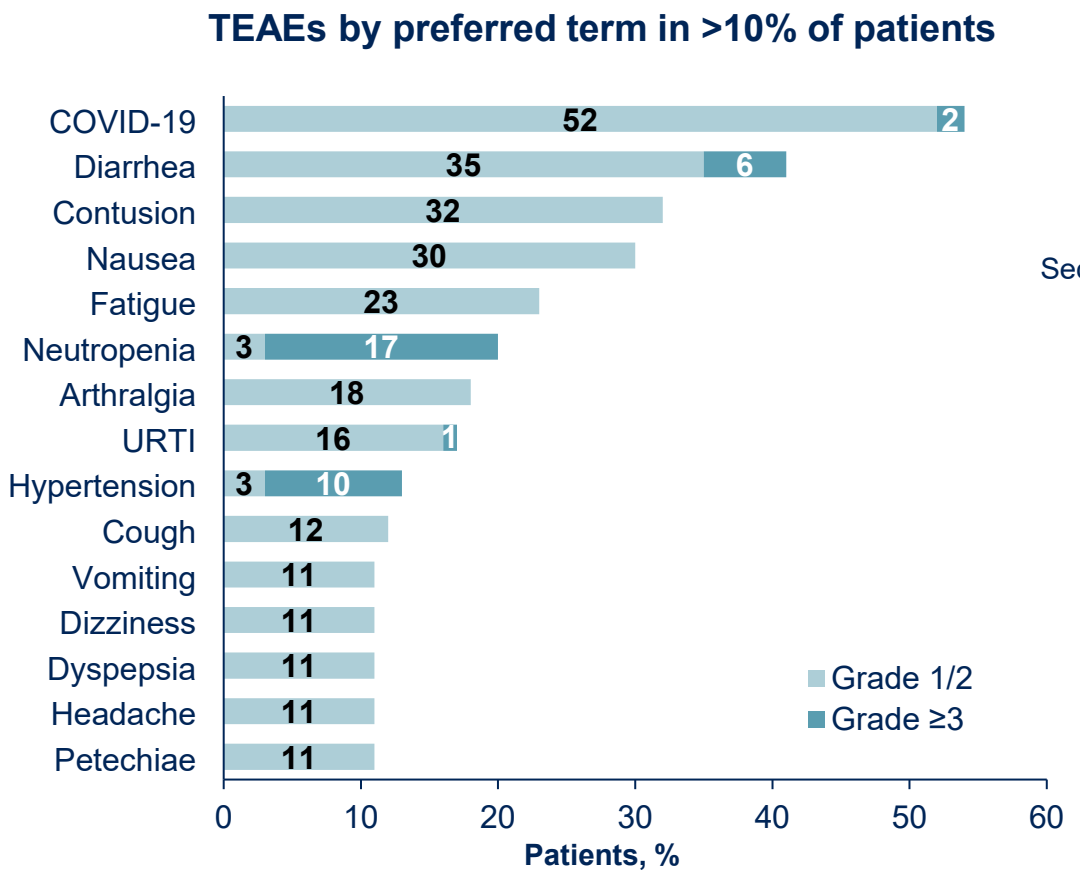


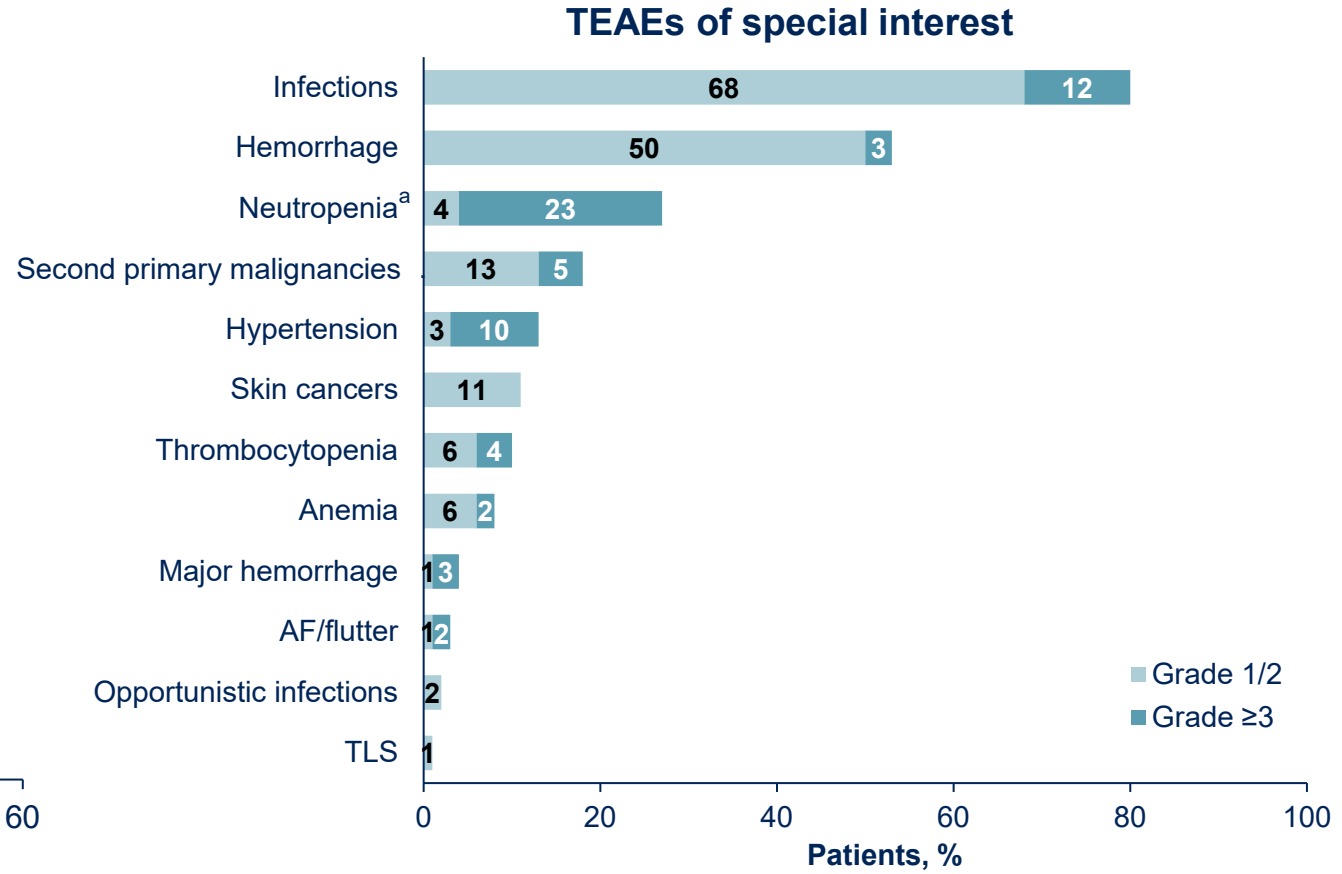

| No. at risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zanu | 114 | 112 | 109 | 108 | 107 | 106 | 104 | 102 | 98 | 62 | 58 | 45 | 35 | 23 | 17 | 16 | 9 | 8 | 0 |

- Of the 11 patients who discontinued after meeting stringent uMRD-guided stopping criteria, only one patient with del(17p) has progressed

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

# Safety Profile for All Patients




- Zanubrutinib + venetoclax had a favorable 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 showed robust efficacy with deep and durable responses in patients with TN CLL/SLL, including large subgroups with del(17p) and/or *TP53* mutation and without del(17p) and *TP53* mutation**
  - In patients without del(17p) and *TP53* mutation, the 24-month PFS was 89%
  - In patients with del(17p) and/or *TP53* mutation, the 24-month PFS was 94% and maintained at 36-months (88%)
- **Best uMRD in the peripheral blood was achieved in 59% of patients regardless of mutational status**
  - uMRD was achieved in 43% by Cycle 16 and 60% by Cycle 28 for patients without del(17p) and *TP53* mutation
- **The safety profile of zanubrutinib + venetoclax was tolerable and no unexpected safety signals were identified**
  - Rates of atrial fibrillation/flutter were low, and no cardiac-related or COVID-19-related deaths were observed
- **Zanubrutinib + venetoclax combination compares favorably with currently available fixed-duration regimens for patients with TN CLL/SLL**
- **These data highlight the potential for an all oral, time-limited therapy, with zanubrutinib as a backbone, to drive meaningful disease control regardless of del(17p) and/or *TP53* mutation status**

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; ORR, overall response rate; mut, mutation; PFS, progression-free survival; TN, treatment-naive; uMRD, undetectable minimal residual disease.

Journal of Clinical Oncology®

# Zanubrutinib and Venetoclax for Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del (17p)/TP53 Mutation: SEQUOIA Arm D Results

Original Reports | Hematologic Malignancy

Zanubrutinib and Venetoclax for Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma With and Without Del (17p)/TP53 Mutation: SEQUOIA Arm D Results

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ABSTRACT

PURPOSE Several chronic lymphatic leukemia (CLL) studies have demonstrated promising efficacy with the combination of BCL2 and Bruton tyrosine kinase inhibitors; however, patients with CLL with del(17p) and/or *TP53* mutation (*TP53*mut) comprised a small percentage of study populations or were excluded entirely. The purpose of the SEQUOIA Arm D cohort was to evaluate the combination of zanubrutinib + venetoclax in treatment-naïve (TN) patients with CLL/small lymphocytic lymphoma (SLL), in a large population of patients with *TP53*-aberrant disease.

PATIENTS AND METHODS Arm D is a nonrandomized cohort of patients aged 65 years and older (or 18-64 years with comorbidities). Patients received zanubrutinib from cycle 1 and venetoclax from cycle 4 (ramp-up) to cycle 28, followed by continuous zanubrutinib monotherapy until progressive disease (PD), unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)-guided stopping criteria.

RESULTS Between November 2019 and July 2022, 114 patients were enrolled: 66 (58%) with *TP53*-aberrant disease, 47 (41%) without *TP53*-aberrant disease, and 1 with missing *TP53* results. At a median follow-up of 31.2 months, 85 patients (75%) remained on zanubrutinib monotherapy; 29 patients (25%) discontinued zanubrutinib because of adverse event, uMRD-guided stopping criteria, PD, or other. In the ITT population, 59% of patients achieved peripheral blood uMRD. The 24-month progression-free survival estimate was 92% (95% CI, 85% to 96%). The most common any-grade treatment-emergent AEs (TEAEs) were COVID-19 (54%), diarrhea (41%), contusion (32%), and nausea (30%). The most common grade ≥3 TEAEs were neutropenia (17%), hypertension (10%), diarrhea (6%), and decreased neutrophil count (6%).

CONCLUSION Zanubrutinib + venetoclax demonstrated impressive efficacy and a favorable safety profile in patients with TN CLL/SLL, regardless of the presence of *TP53*-aberrant disease.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Combination regimens of a BCL2 inhibitor (BCL2i) with a Bruton tyrosine kinase inhibitor (BTKi) and/or an anti-CD20 monoclonal antibody (αCD20ab) have emerged as effective therapies for treatment-naïve (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Many studies investigating combination treatment have enabled the adoption of fixed-duration (FD) or minimal residual disease (MRD)-guided treatment strategies.[1-5]

However, these FD studies often did not include a large number of patients with *TP53*-aberrant disease, creating a gap in the data. The CAPTIVATE study that investigated ibrutinib + venetoclax (IV) FD treatment included 17 (17%; FD cohort) and 32 (20%; undetectable minimal residual disease [uMRD] cohort) patients with *TP53*-aberrant disease.[3,7] The CLL14 trial included 49 (11.8%) patients with *TP53*-aberrant disease treated in venetoclax + obinutuzumab (VO) and chlorambucil + obinutuzumab arms.[8,9] By contrast, a phase II, MRD-guided acalabrutinib + venetoclax



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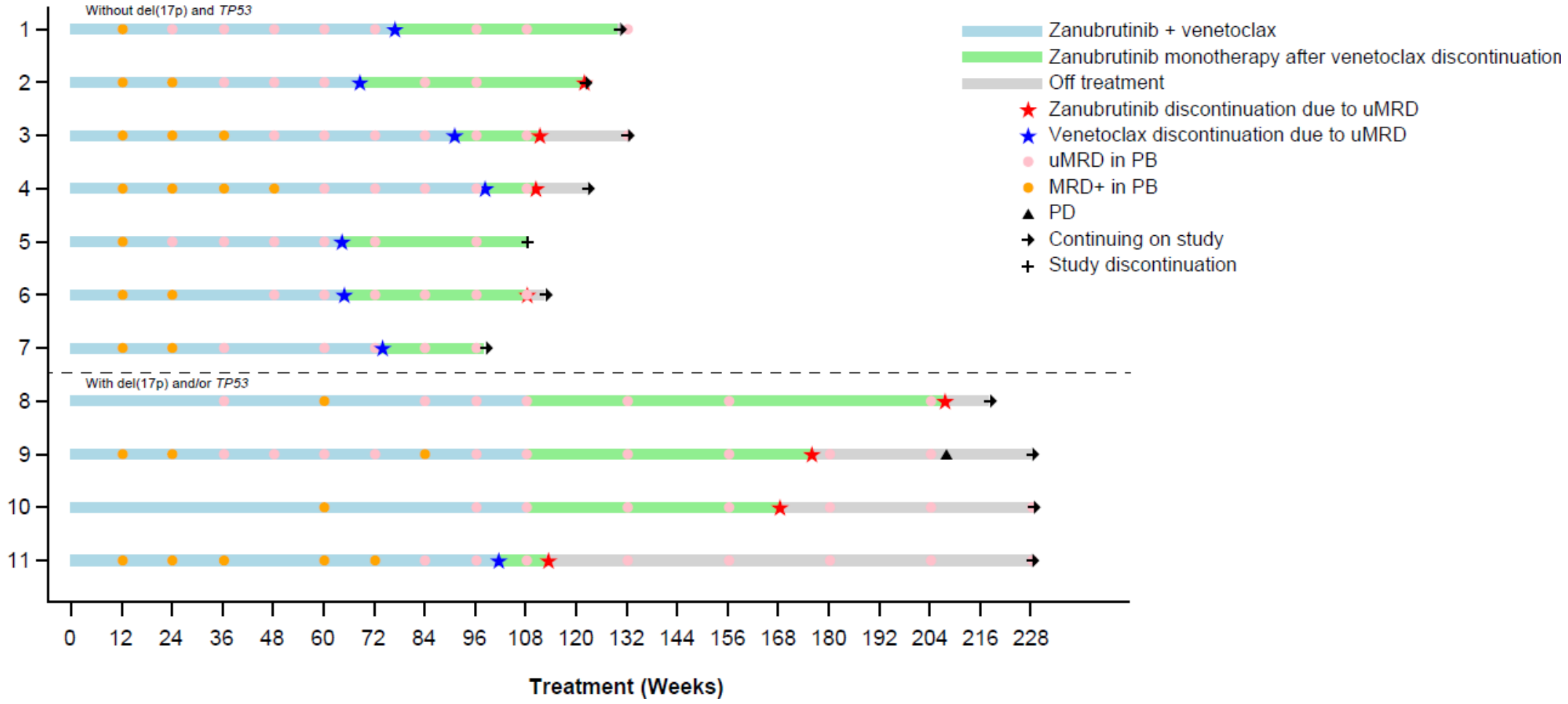
# BACK UP

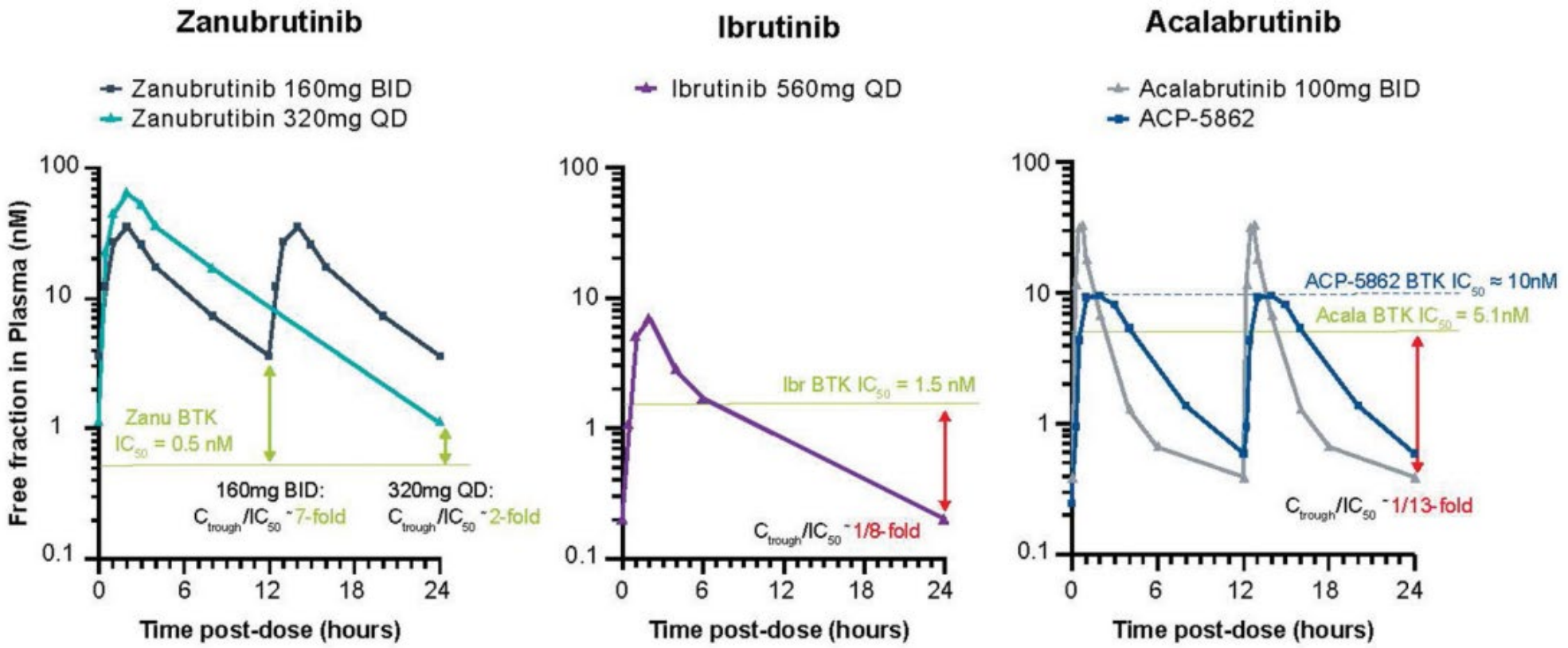
# MRD Status of Patients After Treatment Discontinuation Due to uMRD Early Stopping Criteria




MRD, minimal residual disease; PB, peripheral blood; PD, progressive disease; uMRD, undetectable minimal residual disease.

# Approved BTKis for TN CLL: Concentration Time Profiles

Concentration time profiles relative to $IC_{50}$




The daily unbound plasma exposure (AUC) for zanubrutinib is estimated to be ~6- to 8-fold higher than that of ibrutinib and 2- to 3-fold higher than that of acalabrutinib[1]

1. Tam CS et al. 2021. Expert Review of Clinical Pharmacology.14:11.1329-1344