# Zanubrutinib and Venetoclax for Patients With 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 lymphocytic 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 intention-to-treat 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.



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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 (CLL)/small lymphocytic lymphoma (SLL). Many studies investigating combination treatment have enabled the adoption of fixed-duration (FD) or minimal residual disease (MRD)-guided treatment strategies.[1-6]

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.[2,7] 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

## CONTEXT

**Key Objective**

To determine whether patients with treatment-naïve chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma may benefit from continuous treatment with zanubrutinib monotherapy after 24 months of zanubrutinib + venetoclax (ZV) combination by driving deep and durable remission, especially in a population enriched for high-risk disease.

**Knowledge Generated**

Overall, this study enrolled over 50% (n = 66) of patients with *TP53*-aberrant disease. The initial data suggest that patients with *TP53*-aberrant disease may achieve similar clinical outcomes to those without *TP53*-aberrant disease when treated with or without continuous zanubrutinib monotherapy after ZV combination.

**Relevance *(J.W. Friedberg)***

These data provide valuable insights on treatment of high risk CLL, including *TP53* mutated disease, with a minimal residual disease (MRD)-guided doublet approach. Future randomized trials should determine whether anti-CD20 monoclonal antibody therapy increases the rate of MRD undetectable disease with this doublet.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.



+ obinutuzumab (AVO) study included 45 (62.5%) patients with *TP53*-aberrant disease.[4]

Data from these studies suggest that patients with *TP53*-aberrant disease may benefit from continued therapy. Both CAPTIVATE and CLL14 reported lower progression-free survival (PFS) rates for patients with *TP53*-aberrant disease compared with those without, despite similar uMRD rates.[2,9] Patients with *TP53*-aberrant disease treated with AVO in the phase II, MRD-guided study achieved similar PFS rates after a median of 25 cycles to lower risk patients treated in the FD AMPLIFY study (13 cycles).[4,6] These findings suggest that prolonged therapy may mitigate the prognostic impact of *TP53* aberrations on PFS outcomes, highlighting the importance of tailoring treatment duration on the basis of individual CLL risk profiles. Additionally, response to retreatment and time to a second PFS event or death (PFS2) are important considerations when determining the benefit of FD regimens.

Zanubrutinib is a highly potent and selective next-generation BTKi that is approved for CLL/SLL globally, including in the United States and European Union. The phase III SEQUOIA study (ClinicalTrials.gov identifier: NCT03336333; arms A-C) demonstrated that zanubrutinib is a favorable treatment option for patients with TN CLL/SLL, regardless of del(17p) or immunoglobulin heavy-chain variable region mutational status.[10-12]

SEQUOIA Arm D, which enrolled patients with *TP53*-aberrant disease and those without, was designed to investigate 24 months of zanubrutinib + venetoclax followed by continuous zanubrutinib monotherapy (ZV) to determine whether the combination improved long-term outcomes. Stringent uMRD-guided stopping criteria were included. In this article, we report the first efficacy and safety analysis from the total population of SEQUOIA Arm D.

## PATIENTS AND METHODS

### Study Design and Conduct

The SEQUOIA study design and inclusion criteria for Arms A-C have been previously reported.[10] In Arm D, patients with CLL/SLL with del(17p) and/or *TP53*mut (*TP53*-aberrant disease) or without *TP53*-aberrant disease received treatment with ZV (Data Supplement, Fig S1). After 60 patients with *TP53*-aberrant disease were enrolled, inclusion criteria were amended to include approximately 50 patients without *TP53*-aberrant disease who were considered unsuitable for treatment with fludarabine/cyclophosphamide/rituximab, as previously described.[10] Prospective del(17p) and retrospective *TP53* testing was performed through a central laboratory assessment for all patients.

### Treatment

Patients received zanubrutinib 160 mg twice daily starting at cycle 1 and venetoclax once daily from cycle 4-28 (including venetoclax ramp-up to 400 mg) followed by zanubrutinib monotherapy until progressive disease (PD), uMRD-guided stopping criteria were met, or unacceptable toxicity (Data Supplement, Fig S2). Patients meeting uMRD-guided stopping criteria (defined in Data Supplement, Fig S3) were eligible for early discontinuation of venetoclax after receiving a minimum of 12 cycles or for discontinuation of zanubrutinib after receiving a minimum of 27 cycles.

Efficacy responses were assessed by the investigator every three cycles until cycle 28 and every six cycles thereafter

until disease progression. MRD in the peripheral blood (PB) was assessed at every scheduled efficacy response assessment. MRD in the bone marrow (BM) was assessed at the time of suspected complete response/complete response with incomplete hematopoietic recovery (CR/CRi) and every 12-24 weeks in patients with confirmed CR/CRi who demonstrated two consecutive peripheral blood–undetectable minimal residual diseases (PB-uMRDs), approximately 12 weeks apart. After completion of cycle 27, MRD analysis in the BM was optional for patients with detectable MRD in the BM. Dose modification guidelines can be found in the Supplement. Assessment of tumor lysis syndrome (TLS) risk category was required at baseline and before venetoclax initiation. TLS was graded per the Cairo-Bishop criteria.[13] Institutional review board/ethics committee approval and patients' written informed consent were obtained; study conduct was in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.

### Outcomes

Key outcomes included investigator-assessed PFS and overall response rate (ORR; defined as partial response with lymphocytosis or higher), overall survival (OS), uMRD, and safety (adverse events graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03).

### Statistical Analysis

Analyses were performed in two subgroups: patients with *TP53*-aberrant disease or without. Patients without a *TP53* result through central laboratory were not attributed to either subgroup but included in the intention-to-treat (ITT) analyses. Arm D was not powered to statistically compare ad hoc efficacy analyses between the subgroups. Efficacy end points were analyzed in the ITT population. MRD analyses were performed in both the ITT population and patients with an evaluable sample collected at the specified time point. Safety was assessed in the safety analysis set that included all patients who received at least 1 dose of zanubrutinib. Adverse events of special interest (AESIs) were previously defined.[10]

## RESULTS

### Patients

Between November 2019 and July 2022, 114 patients enrolled in Arm D; 114 initiated zanubrutinib and 110 initiated zanubrutinib and venetoclax. As of September 16, 2024, 110 discontinued venetoclax and 85 remained on zanubrutinib (Fig 1). Zanubrutinib was discontinued in 29 patients (25%) for adverse events (AEs; 9/114 [8%]), uMRD-guided stopping criteria (8/114 [7%]), PD (6/114 [5%]), withdrawal by patient (3/114 [3%]), investigator decision (1/114 [1%]), and other (2/114 [2%]). Venetoclax was discontinued because of completion of 24 cycles (87/114 [76%]), uMRD-guided stopping criteria (8/114 [7%]), AEs (7/114 [6%]), PD (5/114 [4%]), or investigator decision (3/114 [3%]). Eleven patients (10%) discontinued zanubrutinib and/or venetoclax early because of uMRD-guided stopping criteria. Five of the 11 patients discontinued both zanubrutinib and venetoclax early, three patients discontinued venetoclax early, and three patients discontinued zanubrutinib early.

Overall, 10 (9%) patients discontinued from the study. Three patients withdrew (1 before venetoclax initiation), and 1 patient was lost to follow-up. Six patients (5%) died (three before venetoclax initiation), five because of AEs, and 1 because of PD (Fig 1). Baseline demographic and disease characteristics are summarized in Table 1.

### Efficacy

With a median study follow-up of 31.2 months (range, 0.4-58.0 months), the median PFS was not reached for the ITT population; the 24-month PFS rate was 92% (95% CI, 85% to 96%; Fig 2A). For patients with *TP53*-aberrant disease and those without, the median (range) follow-up was 38.7 months (0.4-58.0 months) and 29.6 months (0.6-31.9 months), respectively. The 24-month PFS rate was 94% (95% CI, 85% to 98%) for patients with *TP53*-aberrant disease and 89% (95% CI, 76% to 95%) for patients without (Fig 2B). The 36-month PFS rate was 88% (95% CI, 75% to 94%) for patients with *TP53*-aberrant disease. Of the AEs leading to death, 3 deaths occurred in patients with *TP53*-aberrant disease and two deaths occurred in patients without (Data Supplement, Table S1). In the ITT population, median OS was not reached (Data Supplement, Fig S4) and the estimated 24-month OS was 96% (95% CI, 90% to 98%).

The ORR was 97% in the ITT population, 99% in patients with *TP53*-aberrant disease, and 96% in patients without *TP53*-aberrant disease (Fig 3A). Fifty-five (48%) patients achieved a best overall response of CR/CRi confirmed by BM biopsy. The rates of CR/CRi were 47% in patients with *TP53*-aberrant disease and 49% in patients without *TP53*-aberrant disease (Fig 3A). Among the 55 patients who achieved a best overall response of CR/CRi, 35 (64%) patients achieved PB-uMRD.

Of the ITT population, 112 (98%) patients had at least 1 MRD assessment in the PB: 65 patients with *TP53*-aberrant disease and 46 without. The rate of PB-uMRD increased over time throughout the combination treatment period in both subgroups (Data Supplement, Fig S5). Median time to first PB-uMRD was 19 months (range, 3-47 months) in patients with *TP53*-aberrant disease and 11 months (6-25 months) in patients without. In the ITT population, a total of 67 of 114 (59%) patients achieved PB-uMRD at any time. The best PB-uMRD rate (patients achieving PB-uMRD at least once) was similar between subgroups: 59% and 60% for patients with *TP53*-aberrant disease and without *TP53*-aberrant disease, respectively (Fig 3B). In patients with *TP53*-aberrant disease, the rate of PB-uMRD was 21% by cycle 16 and increased to

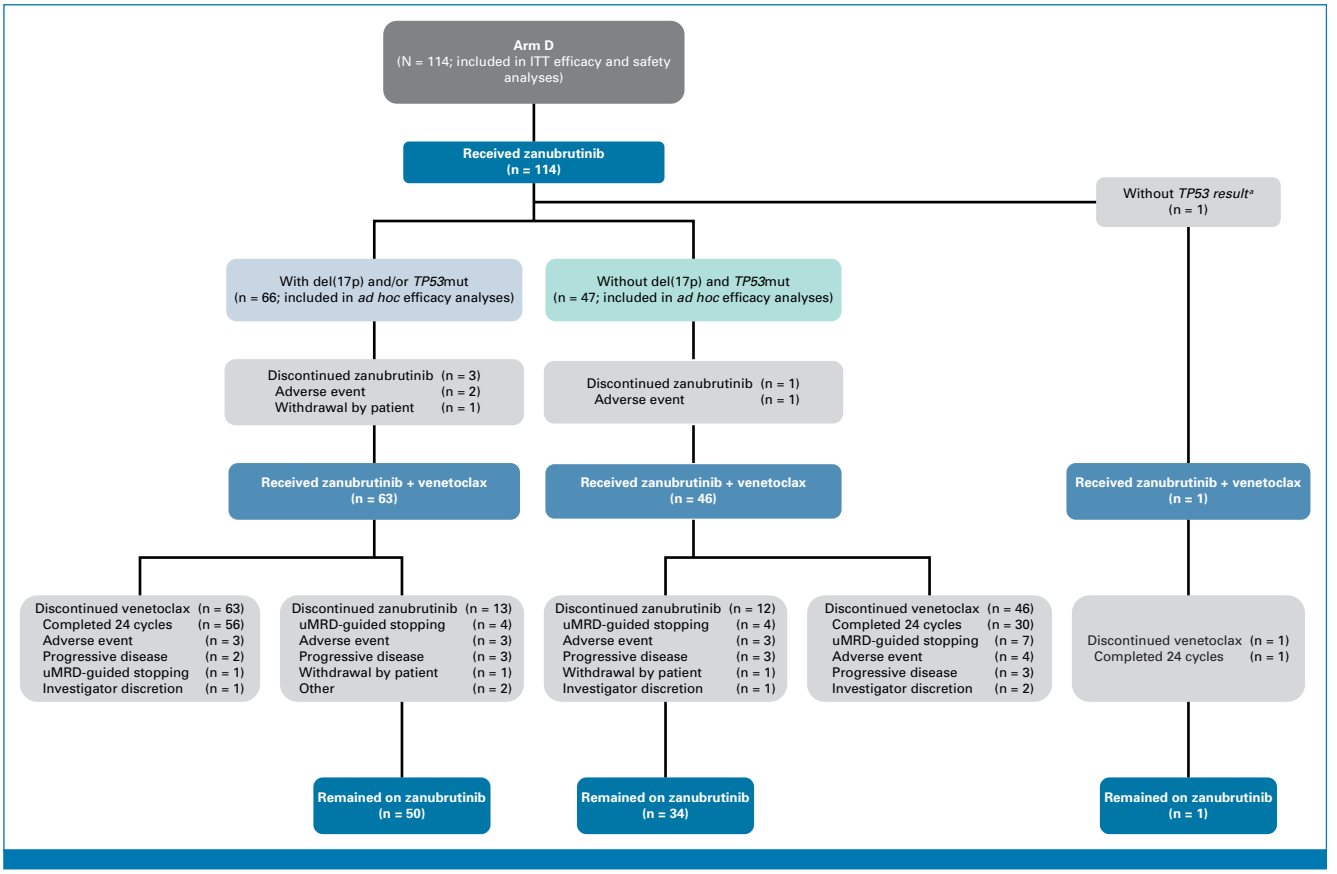


**FIG 1.** Flow diagram. [a]Via central laboratory. ITT, intention-to-treat; uMRD, undetectable minimal residual disease.

49% by cycle 28. In patients without *TP53*-aberrant disease, the rate of PB-uMRD was 43% by cycle 16 and 60% by cycle 28 (Data Supplement, Table S2).

Of the 11 patients who discontinued treatment because of meeting uMRD-guided stopping criteria, nine remained in ongoing clinical remission with sustained PB-uMRD and 1 discontinued study while in clinical remission with PB-uMRD. One patient with *TP53*-aberrant disease discontinued zanubrutinib because of meeting uMRD-guided stopping criteria but progressed approximately 7 months after discontinuation (Data Supplement, Fig S6).

## Safety

There were no unexpected safety signals identified with ZV treatment. The median duration of exposure to the combination of ZV was 22 months (range, 0-30 months). After an initial three cycles of zanubrutinib lead-in, there was a 91% decrease in the number of patients considered to be at high risk of TLS from baseline (Data Supplement, Fig S7).

The most common treatment-emergent adverse events (TEAEs; occurring in >10% of patients) of any grade or grade 3 or higher are presented in Table 2. Overall, the most common TEAE of any grade was COVID-19, which occurred in 62 (54%) patients, and the most common TEAE of grade 3 or higher was neutropenia, which occurred in 19 (17%) patients. Two patients (2%) experienced grade 3 COVID-19. Serious adverse events occurred in 35 (31%) patients on study (Data Supplement, Table S3); serious COVID-19 adverse events occurred in four (4%). TEAEs leading to death occurred in five (4%) patients. Notably, there were no COVID-19–related deaths on study.

TLS occurred in 1 patient (Data Supplement, Table S4). Atrial fibrillation of any grade occurred in three (3%) patients and ventricular extrasystole occurred in two (2%) patients. TEAEs of ventricular extrasystole were low grade (grade 2), and no other ventricular tachyarrhythmia occurred. Major hemorrhage occurred in four (4%) patients (Data Supplement, Table S5) and led to death in two (2%) patients, one of which was an intracranial and intra-abdominal hemorrhage secondary to a road traffic accident and one intracranial hemorrhage in a patient with concomitant direct oral anticoagulant use and prior zanubrutinib discontinuation (Data Supplement, Table S1). Treatment-emergent AESI of infections and neutropenia of grade 3 or higher occurred in eight (7%) patients and 25 (22%) patients, respectively, after the first 15 cycles of treatment (Data Supplement, Table S6) and in 14 (12%) and 26 (23%) patients, respectively, at any time (Table 3). TEAE of non–COVID-19–related infection of any grade occurred in 64 (56%) patients. A summary of second primary malignancies is included in the Data Supplement (Table S7).

**TABLE 1.** Baseline Demographics and Clinical Characteristics

| Characteristic | With del(17p) and/or *TP53*mut (n = 66) | Without del(17p) and *TP53*mut (n = 47) | All Patients (N = 114) |
|---|---|---|---|
| Age, years, median (range) | 66 (26-87) | 67 (36-80) | 67 (26-87) |
| ≥65 years, No. (%) | 36 (55) | 32 (68) | 68 (60) |
| Male, No. (%) | 34 (52) | 29 (62) | 64 (56) |
| ECOG PS 0-1, No. (%) | 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, No. (%) | 3 (5) | 3 (6) | 6 (5) |
| Binet stage C, No. (%)[a] | 30 (48) | 16 (36) | 46 (43) |
| Bulky disease, No. (%) | | | |
| LDi ≥5 cm | 29 (44) | 19 (40) | 49 (43) |
| LDi ≥10 cm | 5 (8) | 1 (2) | 6 (5) |
| Time from initial diagnosis, months, median | 19.3 | 42.2 | 28.5 |
| *TP53* mutated, No. (%) | 49 (74) | 0 | 49 (43) |
| del(17p), No. (%) | 59 (89) | 0 | 59 (52) |
| del(17)p *and TP53* mutated, No. (%) | 42 (64) | 0 | 42 (37) |
| del(13q), No. (%) | 39 (59) | 27 (57) | 67 (59) |
| del(11q), No. (%) | 4 (6) | 14 (30) | 18 (16) |
| Trisomy 12, No. (%) | 13 (20) | 11 (23) | 24 (21) |
| IGHV unmutated, No. (%)[b] | 56 (85) | 30 (64) | 86 (75) |
| IGHV mutated, No. (%) | 9 (14) | 14 (30) | 24 (21) |
| Complex karyotype, No. (%) | | | |
| ≥3 abnormalities | 33 (50) | 14 (30) | 47 (41) |
| ≥5 abnormalities | 24 (36) | 2 (4) | 26 (23) |

Abbreviations: CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.
[a]Binet stage was assessed at study entry for patients with CLL.
[b]There were four patients with a missing IGHV result, one because of missed sample collection and three because of insufficient quantity of the sample.



## DISCUSSION

This analysis demonstrated favorable safety and clinically meaningful responses in patients treated with ZV. Regardless of del(17p)/*TP53* mutational status, similar 24-month PFS rates were observed (94% in patients with *TP53*-aberrant disease and 89% in patients without *TP53*-aberrant disease), indicating the effectiveness of ZV across these genetic risk factors.

In the context of BTKi + BCL2i therapy, ZV demonstrated comparable efficacy outcomes to FD. Rates of CR/CRi in patients treated with ZV are comparable with the rates observed with IV and numerically higher than 14-month FD acalabrutinib + venetoclax (AV), suggesting that longer treatment duration with ZV may result in deeper clinical remissions.[1,2,6] Despite enrichment for *TP53*-aberrant disease, the overall 24-month PFS rate observed with ZV was similar to FD IV.[2] Among patients with *TP53*-aberrant disease treated with ZV, an impressive 36-month PFS estimate was observed suggesting ZV lessens the prognostic impact of *TP53* aberrations. However, this requires confirmation through additional clinical studies.

With the addition of αCD20ab to BTKi + BCL2i therapy such as AVO and IV + obinutuzumab (IVO), a clear increase in uMRD rates was observed.[6,14] Treatment with ZV resulted in a best PB-uMRD rate of 59% in the ITT population and 59% in patients with *TP53*-aberrant disease, which was expectedly lower than that achieved with AVO or IVO in patients without *TP53*-aberrant disease and lower than that of AVO in the phase II study that enriched for patients with *TP53* aberration.[4,6,14] Despite this difference in PB-uMRD rates, the 24-month PFS with ZV was comparable with the 24-month PFS in the obinutuzumab-containing triplet regimens.[9,14] The 36-month PFS estimate for patients with *TP53*-aberrant disease treated with ZV was comparable with the 36-month PFS demonstrated in the FD triplet combinations, even across studies that excluded patients with *TP53* aberrations.[9,14,15] In the phase II, MRD-guided AVO study, the 4-year PFS was 96% in patients without *TP53* aberration and was 70% among patients with *TP53*-

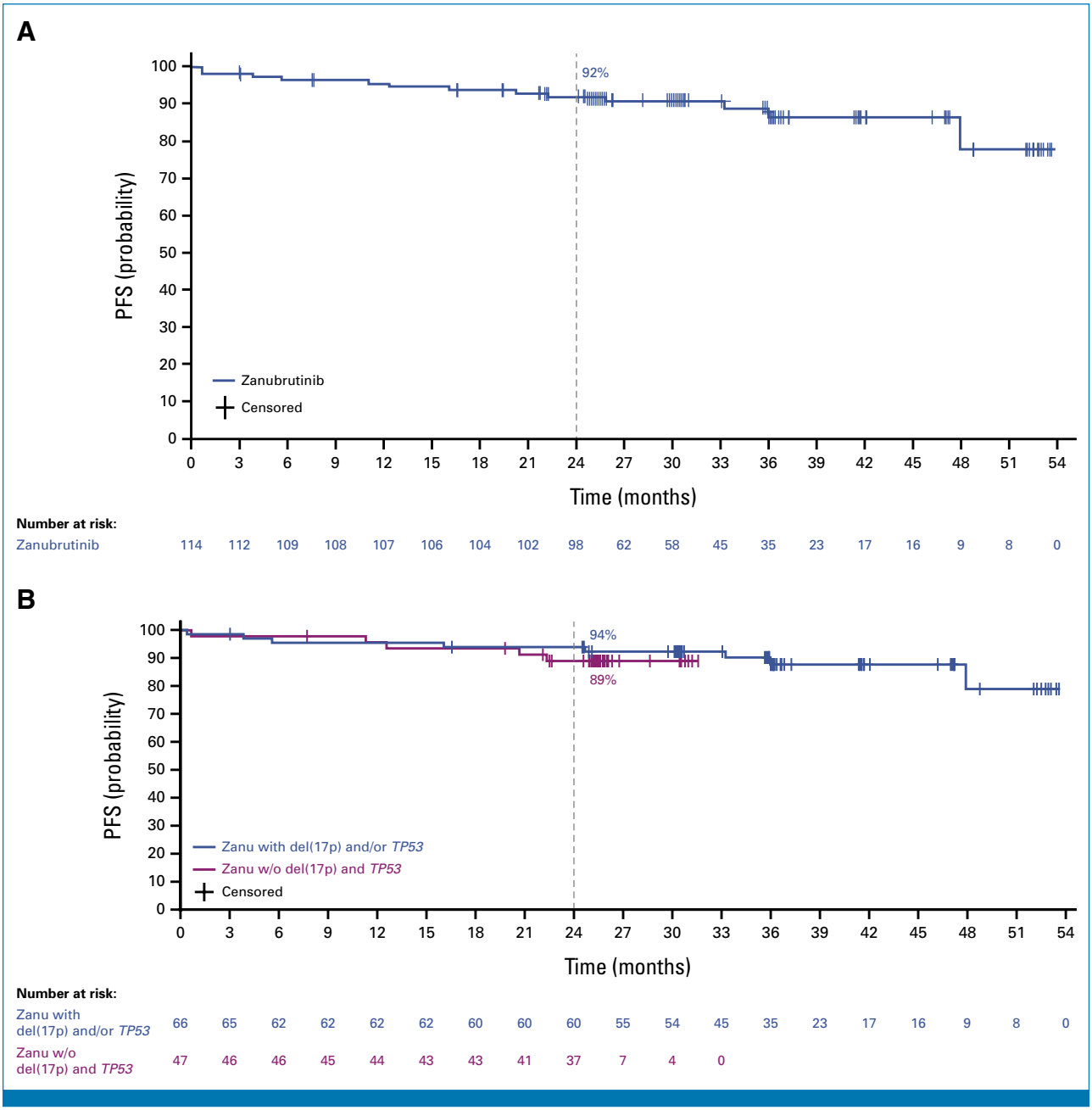


**FIG 2.** PFS. (A) All patients. (B) Patients with del(17p) and/or *TP53*mut, and without del(17p) and *TP53*mut. PFS, progression-free survival; Zanu, zanubrutinib.



aberrant disease.[4] By contrast, Arm D patients with *TP53*-aberrant disease achieved similar PFS rates as patients without *TP53*-aberrant disease, albeit at differing follow-up times, suggesting a benefit of continuous zanubrutinib after 24 months of combination in Arm D.

There are ongoing studies exploring zanubrutinib + BCL2i ± αCD20ab. The MRD-guided BOVen study exploring zanubrutinib + VO demonstrated high rates of PB-uMRD as expected, but PFS estimates have not yet been reported.[16] With a median study follow-up of 19.4 months, phase I data of zanubrutinib combined with the second-generation BCL2i sonrotoclax demonstrated high rates of uMRD by week 48 (91%) at the target dose with no patients experiencing PD. This suggests that patients may be able to achieve deep responses in the absence of an αCD20ab, although more data are needed to assess long-term outcomes.[17]

Although most FD BTKi + BCL2i regimens in TN CLL/SLL are 15 cycles, this may be suboptimal for patients with *TP53* aberrations.[1,2,6] The differing median time to first PB-uMRD observed in patients treated with ZV suggests that the MRD

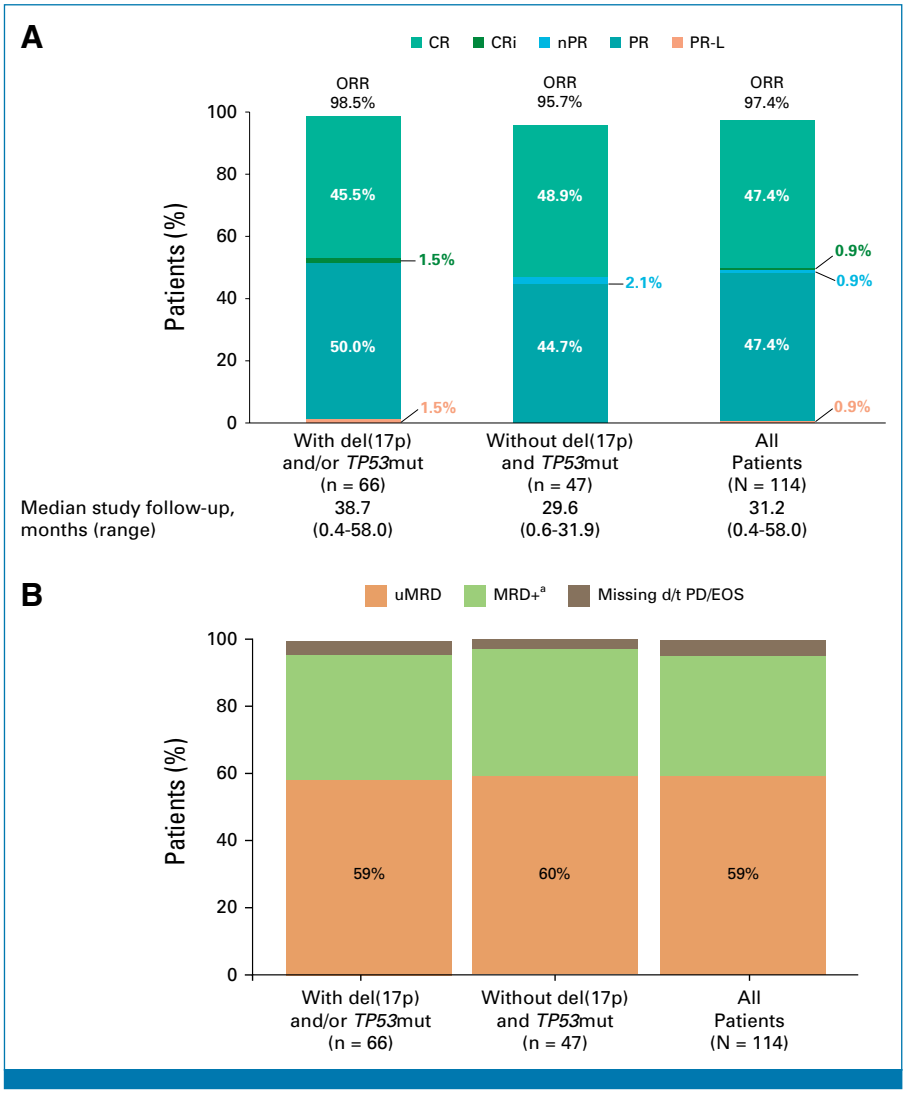


**FIG 3.** Efficacy. (A) Best ORRs. Responses were assessed by an investigator per the 2008 iwCLL guidelines with modification for treatment-related lymphocytosis for patients with CLL and per Lugano criteria for patients with SLL. ORR was defined as achievement of PR-L or better. (B) Best uMRD rate in peripheral blood, defined as patients achieving PB-uMRD at least once. [a]MRD ≥1 × $10^{-4}$. CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete hematopoietic recovery; d/t, due to; EOS, end of study; iwCLL, International Workshop on CLL; MRD, minimal residual disease; nPR, nodular PR; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SLL, small lymphocytic lymphoma; uMRD, undetectable MRD.



kinetics may vary dependent on the presence of *TP53* aberrations. In Arm D, while the rates of PB-uMRD by cycle 16 were much lower in patients with *TP53*-aberrant disease than in patients without, this difference was reduced by cycle 28 and the best PB-uMRD rates were the same. This suggests that patients with *TP53*-aberrant disease may require a longer treatment period to achieve similar rates of PB-uMRD as patients without.

At the time of initial Arm D design, limited data existed on the durability of response to FD regimens in patients harboring high-risk features such *TP53* aberrations. To address this, Arm D implemented stringent uMRD-guided stopping criteria: Patients were required to achieve CR/CRi confirmed by BM biopsy and two consecutive uMRD in the PB and BM. This design is significantly stricter than the phase II CAPTIVATE-uMRD and phase III FLAIR study, which required PB-uMRD and only 1 confirmatory BM uMRD result.[3,7] Despite these rigorous criteria, 10% of patients discontinued treatment because of meeting the uMRD-guided stopping criteria, most of whom without *TP53*-aberrant disease. Notably, most of the patients who discontinued treatment have remained in remission and sustained PB-uMRD, regardless of mutational status. However, longer follow-up is needed to assess the durability of uMRD response.

**TABLE 2.** TEAEs in >10% of Patients

| | All Patients (N = 114) | |
|---|---|---|
| TEAE | Any Grade, No. (%) | Grade ≥3, No. (%) |
| Any TEAE | 112 (98) | 62 (54) |
| Common TEAEs (>10%) | | |
| COVID-19 | 62 (54) | 2 (2) |
| Diarrhea | 47 (41) | 7 (6) |
| Contusion | 36 (32) | 0 |
| Nausea | 34 (30) | 0 |
| Fatigue | 26 (23) | 0 |
| Neutropenia | 23 (20) | 19 (17) |
| Arthralgia | 21 (18) | 0 |
| Upper respiratory tract infection | 19 (17) | 1 (1) |
| Hypertension | 15 (13) | 11 (10) |
| Cough | 14 (12) | 0 |
| Vomiting | 13 (11) | 0 |
| Dizziness | 12 (11) | 0 |
| Dyspepsia | 12 (11) | 0 |
| Headache | 12 (11) | 0 |
| Petechiae | 12 (11) | 0 |

Abbreviation: TEAE, treatment-emergent adverse event.

**TABLE 3.** TEAEs of Special Interest

| | All Patients (N = 114) | |
|---|---|---|
| TEAE of Special Interest | Any Grade, No. (%) | Grade ≥3, No. (%) |
| Any TEAE of special interest | 109 (96) | 49 (43) |
| Infections | 91 (80) | 14 (12) |
| Hemorrhage | 60 (53) | 3 (3) |
| Neutropenia | 30 (26) | 26 (23) |
| Second primary malignancies | 20 (18) | 6 (5) |
| Hypertension | 15 (13) | 11 (10) |
| Skin cancers | 13 (11) | 0 |
| Thrombocytopenia | 11 (10) | 4 (4) |
| Anemia | 9 (8) | 2 (2) |
| Major hemorrhage | 4 (4) | 3 (3) |
| Atrial fibrillation and flutter | 3 (3) | 2 (2) |
| Opportunistic infections[a] | 2 (2) | 0 |
| Tumor lysis syndrome | 1 (1) | 0 |

Abbreviation: TEAE, treatment-emergent adverse event.
[a]Bronchopulmonary aspergillosis (n = 1), herpes zoster reactivation (n = 1).

Treatment with ZV demonstrated a similar AE profile to AV and a more tolerable profile compared with IV, despite selection of a more unfit patient population and longer treatment exposure.[1,2,6] Treatment with ZV demonstrated promising cardiac tolerability with low rates of cardiac toxicities and no cardiac-related deaths, while the GLOW study, which included an unfit patient population, reported four patients (3.8%) with sudden and cardiac deaths.[1] Additionally, the rates of any-grade atrial fibrillation/flutter and hypertension with ZV were similar to the rates observed in patients receiving zanubrutinib monotherapy on SEQUOIA Arm C suggesting that the addition of venetoclax did not exacerbate cardiac toxicity associated with BTKi.

Given the absence of an αCD20ab in Arm D, the lower rates of any-grade neutropenia and grade 3 or higher infection with ZV compared with AVO and IVO regimens were expected.[4,14] The SEQUOIA study was conducted during the pandemic, with the majority of Arm D enrollment occurring between 2020 and 2022. Patients with COVID-19 in Arm D were primarily of low grade, and no COVID-19–related deaths were reported. Not accounting for potential geographic impact and vaccine accessibility over time between study populations, the impact of COVID-19 on patients in the AMPLIFY study was particularly evident during this similar time period, with 10 (3.4%) and 25 (8.7%) deaths due to COVID-19 in the AV and AVO arms, respectively.[6]

An important consideration of FD compared with treat-to-progression regimens is the potential for patients to respond to re-treatment.[18-20] Recent studies have shown that patients exposed to FD IV develop few resistance mutations to BCL2i and BTKi and retain sensitivity to therapy with response rates of up to 86% after retreatment. To our knowledge, with very few progression events observed in Arm D to date, response to second-line therapy or re-exposure to BTKi and/or BCL2i remains unknown. Additionally, the benefit of continuous therapy in Arm D compared with FD therapies may be challenging to interpret when only considering time to first PFS event. Rather, assessment of OS and PFS2 may be more optimal in comparing these regimens but requires longer follow-up.

To our knowledge, this is the first publication of all-comers from SEQUOIA Arm D. In summary, these analyses demonstrate that patients achieved similar PFS, best overall response, and PB-uMRD regardless of the presence of *TP53* aberrations.



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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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