Safety Analysis of Fixed-Duration Acalabrutinib-Venetoclax Combinations vs Chemo-immunotherapy: A Post Hoc Analysis From the Phase 3 AMPLIFY Trial

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Objective

- To assess the safety and tolerability profiles of fixed-duration AV and AVO versus FCR/BR in patients from the phase 3 AMPLIFY trial in a post hoc analysis

Conclusions

- Post hoc analysis showed no new safety signals with fixed-duration AV and AVO
  - Exposure-adjusted incidences of infections and cardiac events were similar in the AV and AVO arms versus FCR/BR
- Over 90% of patients at high TLS risk at baseline transitioned to low/medium risk with initial tumor debulking with 2 cycles of acalabrutinib lead-in

Plain language summary

Why did we perform this research?
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a blood cancer for which there is no definitive cure. A combination of two targeted therapies (acalabrutinib, a Bruton tyrosine kinase inhibitor, and venetoclax, a B-cell lymphoma-2 inhibitor [AV]) with or without an anti-CD20 antibody called obinutuzumab (O) has improved outcomes for many patients with CLL/SLL compared with standard chemoimmunotherapy regimens (fludarabine plus cyclophosphamide plus rituximab or bendamustine plus rituximab [FCR/BR]) in the large-scale AMPLIFY trial. AV and AVO have been well tolerated, but a closer look at the side effects is needed.

How did we perform this research?
Fit adult patients with CLL/SLL and without del(17p) or *TP53* mutations received either AV or AVO for 14 cycles of treatment or FCR/BR for 6 cycles of treatment. Patients were monitored for side effects for over 2 years after treatment.

What were the findings of this research and its implications?
This study found that the side effect profile was similar to previous reports. Although total rates of infections and heart-related side effects were similar in patients receiving AV and AVO and higher in those patients compared with patients receiving FCR/BR, the rates accounting for time on treatment were similar across all 3 regimens (AV, AVO, and FCR/BR). Most patients receiving AV and AVO at high risk for a blood disorder called tumor lysis syndrome became medium or low risk by the third cycle of treatment.

Where can I access more information?
Results on the effectiveness of AV and AVO from the AMPLIFY trial can be found in Brown JR, et al. *N Engl J Med*. 2025;392:748-62.

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Poster

Supplementary material

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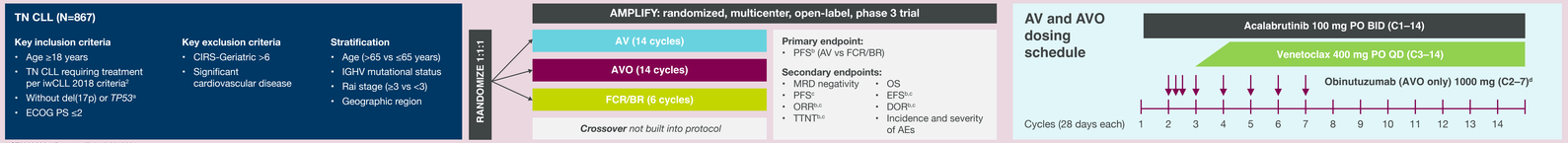
Introduction

- The phase 3 AMPLIFY trial (**Figure 1**) evaluated fixed-duration AV and AVO versus investigator's choice of chemoimmunotherapy (FCR/BR) in fit patients with TN CLL without del(17p) or *TP53* mutations[1]
- AV and AVO demonstrated significantly prolonged PFS versus FCR/BR and manageable safety profiles[1]
- This post hoc analysis from AMPLIFY assessed the safety and tolerability profiles of fixed-duration AV, AVO, and FCR/BR

Figure 1. AMPLIFY Study Design



NCT03836261. Data cutoff: April 30, 2024.
[a]Assayed by central lab. [b]IRC-assessed. [c]Investigator-assessed. [d]Each arrow represents 1000 mg. Patients received 3000 mg in C2.
EAERs (events/100 person-months) were calculated for ECIs, including cardiac events, neutropenia, hypertension, infections, and TLS. Cumulative incidences of cardiac events and infections were analyzed by Kaplan–Meier analysis. Descriptive statistics and *P*-values are given for key safety data. Time to early treatment discontinuation or death was analyzed by Kaplan–Meier analysis. Patients who completed treatment were censored. TLS risk at baseline and C3 (post-debulking/pre-venetoclax) was evaluated (high risk = LN ≥10 cm, or ALC ≥25×10⁹/L and LN ≥5 cm; medium risk = LN ≥5–<10 cm or ALC ≥25×10⁹/L; low risk = LN <5 cm and ALC <25×10⁹/L).

Results

- Any-grade TEAEs ≥10% and grade 3 TEAEs ≥5% were previously published[1]

Treatment Exposure

- A total of 867 patients were randomized, and 834 received ≥1 dose of study drug (AV, n=291; AVO, n=284; FCR/BR, n=259)
- Median duration of acalabrutinib exposure was 12.9 months in the AV and AVO arms, and median treatment exposure was 5.6 months in the FCR/BR arm

ECIs

- Incidence of any-grade ECIs for each treatment arm's treatment-emergent period was 76.3%, 85.2%, and 71.4% for the AV, AVO, and FCR/BR arms, respectively
  - EAERs of ECIs (**Table 1**) were 25.3, 36.1, and 57.8 events/100 person-months in the AV, AVO, and FCR/BR arms, respectively
- Incidence of any-grade cardiac events (cumulative incidence, **Figure 2**) was higher with AV (9.3%) and AVO (12.0%) versus FCR/BR (3.5%) (AV vs FCR/BR, *P*=0.0063; AVO vs FCR/BR, *P*=0.0003)
  - EAERs of cardiac events were similar across arms (0.83, 1.11, and 0.86, respectively)
- Incidence of any-grade infections (**Table 2**; cumulative incidence, **Figure 3**) was higher with AV (50.9%) and AVO (53.9%) versus FCR/BR (31.7%; *P*<0.0001, both comparisons)
  - EAERs of infections were similar across arms (6.47, 8.38, and 8.77, respectively)
  - With baseline IgG ≥ lower limit of normal (600 mg/dL), incidence of grade ≥3 infections appears to be increased with AVO but not AV; with baseline IgG ≤400 mg/dL, incidence was similar across all arms (**Supplemental Table 1**)
- Incidence of any-grade treatment-emergent SPMs (cumulative incidence, **Supplemental Figure 1A**) was higher with AV (5.2%) and AVO (4.2%) versus FCR/BR (0.8%) (AV vs FCR/BR, *P*=0.0031; AVO vs FCR/BR, *P*=0.0113)
  - EAERs of SPMs were higher with AV (0.45) and AVO (0.32) versus FCR/BR (0.14)
  - No specific SPM was predominant in any treatment arm when non-melanoma skin malignancies were included or excluded (basal cell carcinoma was the most frequently reported SPM across all 3 arms)
  - Cumulative incidence of grade ≥3 SPMs is shown in **Supplemental Figure 1B**

Discontinuation

- Premature discontinuation of all study treatment or death (**Figure 4** and **Table 3**) occurred in 8.4% (AV), 5.1% (AVO), and 18.6% (FCR/BR) of patients
  - Time to premature discontinuation of any study treatment is shown in **Supplemental Figure 2**
- Time-to-event (premature discontinuation or death) analysis favored AV and AVO versus FCR/BR (AV vs FCR/BR: HR 0.07, 95% CI 0.03, 0.15, *P*<0.0001; AVO vs FCR/BR: HR 0.16, 95% CI 0.07, 0.30, *P*<0.0001)
- AEs were the most common reason for all study treatment discontinuation (AV, 5.9%; AVO, 4.3%; FCR/BR, 10.5%)
  - Other reasons include disease progression, investigator or patient decision, or lost to follow-up
  - AEs were the most common reason for any study treatment discontinuation, reported in 7.0%, 19.6%, and 10.5% of patients in the AV, AVO, and FCR/BR arms, respectively
  - TEAEs led to discontinuation of study treatment (AV, 7.9%; AVO, 20.1%; FCR/BR, 10.8%), mainly related to COVID-19 for AV and AVO, and cytopenias for FCR/BR (**Supplemental Tables 2** and **3**)

TLS

- Most patients with high TLS risk at baseline (AV, n=93; AVO, n=75; FCR/BR, n=86) had medium (60.2% [n=56], 21.3% [n=16], 8.1% [n=7]) or low (19.4% [n=18], 61.3% [n=46], 77.9% [n=67]) TLS risk at C3 (**Figure 5**)
- TLS observed in AV (n=1; during venetoclax ramp-up) and AVO (n=1; during acalabrutinib lead-in) was limited to laboratory TLS only; no clinical TLS was observed

G-CSF

- G-CSF use (**Table 4**) was lower in the AV (30.9%) and AVO (42.6%) arms compared with the FCR/BR arm (57.1%)

Grade 5 TEAEs

- Grade 5 TEAEs occurred in 3.4% of patients receiving AV, 6.0% receiving AVO, and 3.5% receiving FCR/BR (**Table 5**)
  - Most grade 5 events were COVID-19 related across all 3 arms

Table 1. Exposure-Adjusted Event Rates of ECIs

Events per 100 Person-Months	AV (N=291) Any Grade	AV (N=291) Grade ≥3	AVO (N=284) Any Grade	AVO (N=284) Grade ≥3	FCR/BR (N=259) Any Grade	FCR/BR (N=259) Grade ≥3
Any TEAE of clinical interest	25.275	11.706	36.098	18.895	57.791	38.123
Cardiac events	0.831	0.126	1.110	0.211	0.855	0.285
Atrial fibrillation	0.050	0.025	0.159	0.053	0.143	0.143
Ventricular tachyarrhythmias	0.050	0	0.079	0	0	0
Anemia	0.680	0.378	0.396	0.159	1.853	1.283
Leukopenia	5.790	4.531	8.826	7.029	19.382	15.392
Neutropenia	5.387	4.330	7.981	6.554	17.245	13.967
Other leukopenia	0.403	0.201	0.846	0.476	2.138	1.425
Thrombocytopenia	0.529	0.151	1.691	1.163	3.563	2.280
Hemorrhage	3.323	0.076	4.704	0.185	0.926	0.071
Major hemorrhage	0.076	0.076	0.238	0.185	0.143	0.071
Hepatotoxicity	0.705	0.302	0.714	0.238	1.354	0.285
Hypertension	0.302	0.201	0.317	0.185	0.570	0.143
Infections	6.470	1.032	8.377	2.193	8.765	2.138
Interstitial lung disease/ pneumonitis	0	0	0.132	0	0.071	0.071
Second primary malignancies	0.453	0.126	0.317	0.132	0.143	0
Excluding non-melanoma skin cancer	0.201	0.126	0.185	0.106	0.071	0
Tumor lysis syndrome	0.025	0.025	0.026	0.026	0.570	0.570

Exposure-adjusted event rate was calculated as the total number of TEAEs for each ECI by treatment multiplied by 100 and divided by the sum of the treatment-emergent period of all patients in the respective treatment arm in months.

Table 2. Infections in More Than 1 Patient

n (%)	AV (N=291) Any Grade	AV (N=291) Grade ≥3	AVO (N=284) Any Grade	AVO (N=284) Grade ≥3	FCR/BR (N=259) Any Grade	FCR/BR (N=259) Grade ≥3
Any infection	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Viral	82 (28.2)	24 (8.2)	84 (29.6)	47 (16.5)	26 (10.0)	11 (4.2)
COVID-19 grouped term	64 (22.0)	23 (7.9)	69 (24.3)	47 (16.5)	10 (3.9)	9 (3.5)
COVID-19	55 (18.9)	8 (2.7)	58 (20.4)	19 (6.7)	6 (2.3)	4 (1.5)
COVID-19 pneumonia	21 (7.2)	16 (5.5)	35 (12.3)	33 (11.6)	7 (2.7)	7 (2.7)
Post-acute COVID-19 syndrome	1 (0.3)	0	4 (1.4)	0	0	0
SARS-CoV-2 test positive	2 (0.7)	0	1 (0.4)	0	0	0
Suspected COVID-19	3 (1.0)	0	3 (1.1)	0	1 (0.4)	1 (0.4)
Herpes zoster	5 (1.7)	0	4 (1.4)	1 (0.4)	4 (1.5)	1 (0.4)
Oral herpes	3 (1.0)	0	4 (1.4)	0	3 (1.2)	0
Herpes simplex	3 (1.0)	0	1 (0.4)	0	3 (1.2)	0
Influenza	3 (1.0)	0	3 (1.1)	0	0	0
Viral infection	0	0	3 (1.1)	0	1 (0.4)	0
Viral upper respiratory tract infection	0	0	1 (0.4)	0	2 (0.8)	0
Gastroenteritis viral	1 (0.3)	0	1 (0.4)	0	0	0
Herpes virus infection	1 (0.3)	0	1 (0.4)	0	0	0
Cytomegalovirus infection reactivation	0	0	0	0	2 (0.8)	1 (0.4)
Conjunctivitis viral	0	0	2 (0.7)	0	0	0
Respiratory syncytial virus infection	0	0	2 (0.7)	0	0	0
Herpes simplex reactivation	2 (0.7)	0	0	0	0	0
Bacterial	25 (8.6)	3 (1.0)	23 (8.1)	4 (1.4)	8 (3.1)	3 (1.2)
Cellulitis	2 (0.7)	0	5 (1.8)	0	1 (0.4)	0
Folliculitis	2 (0.7)	0	3 (1.1)	1 (0.4)	1 (0.4)	0
Paronychia	4 (1.4)	0	0	0	0	0
Haemophilus infection	0	0	3 (1.1)	0	0	0
Clostridium difficile infection	2 (0.7)	0	1 (0.4)	1 (0.4)	0	0
Lyme disease	3 (1.0)	0	0	0	0	0
Bacterial infection	1 (0.3)	0	2 (0.7)	0	0	0
Campylobacter infection	0	0	2 (0.7)	0	0	0
Pneumonia staphylococcal	0	0	0	0	2 (0.8)	1 (0.4)
Tuberculosis	2 (0.7)	1 (0.3)	0	0	0	0
Fungal	7 (2.4)	1 (0.3)	13 (4.6)	4 (1.4)	11 (4.2)	0
Oral candidiasis	0	0	2 (0.7)	0	3 (1.2)	0
Tinea versicolor	0	0	2 (0.7)	0	2 (0.8)	0
Tinea pedis	1 (0.3)	0	1 (0.4)	0	1 (0.4)	0
Vulvovaginal candidiasis	1 (0.3)	0	0	0	2 (0.8)	0
Meningitis cryptococcal	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	0	0
Candida infection	0	0	1 (0.4)	0	1 (0.4)	0
Fungal skin infection	0	0	0	0	2 (0.8)	0

Table 3. Discontinuation of All Study Treatment

	AV (N=286)	AVO (N=276)	FCR/BR (N=258)
Event, n (%)	24 (8.4)	14 (5.1)	48 (18.6)
Discontinuation of all study treatment	23 (8.0)	14 (5.1)	42 (16.3)
Progression	2 (0.7)	0	3 (1.2)
AE	17 (5.9)	12 (4.3)	27 (10.5)
Investigator decision	2 (0.7)	1 (0.4)	9 (3.5)
Patient decision	2 (0.7)	0	2 (0.8)
Lost to follow-up	0	1 (0.4)	0
Other	0	0	1 (0.4)
Death	1 (0.3)	0	6 (2.3)
Censored observations, n (%)	262 (91.6)	262 (94.9)	210 (81.4)
Completed treatment	262 (91.6)	262 (94.9)	210 (81.4)
Comparison of treatment groups, HR (95% CI)	0.07 (0.03, 0.15)	0.16 (0.07, 0.30)	Reference

Patients who did not start the full combination therapy were excluded from this analysis.

Table 4. Summary of G-CSF Use

n (%)	AV (N=291)	AVO (N=284)	FCR/BR (N=259)
Any G-CSF	90 (30.9)	121 (42.6)	148 (57.1)
Prophylactic[a]	29 (10.0)	38 (13.4)	87 (33.6)
Therapeutic[b]	84 (28.9)	112 (39.4)	106 (40.9)

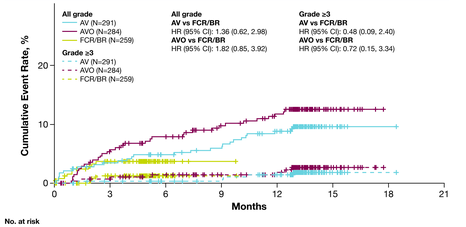
[a]Primary prophylaxis: preventive use of G-CSF for patients with an estimated 20% or higher risk of febrile neutropenia based on patient, disease, and treatment-related factors (per ASCO guidelines); secondary prophylaxis: preventive use for patients who have experienced a neutropenic complication from a previous chemotherapy/treatment cycle (without prior primary prophylaxis), where a reduced dose or treatment delay may compromise disease-free survival or overall survival. [b]Administration of G-CSF following a neutropenic event.

Table 5. Grade 5 TEAEs

n (%)	AV (N=291)	AVO (N=284)	FCR/BR (N=259)
Grade 5 TEAE	10 (3.4)	17 (6.0)	9 (3.5)
COVID-19 pneumonia[a]	6 (2.1)	10 (3.5)	4 (1.5)
COVID-19[a]	2 (0.7)	5 (1.8)	3 (1.2)
Cardiac arrest	1 (0.3)[b]	0	1 (0.4)[b]
Infection	1 (0.3)	0	0
Acute kidney injury	0	0	1 (0.4)
Pneumonia	0	1 (0.4)	0
Sudden death	0	1 (0.4)[c]	0

[a]Death due to COVID-19 at any time during the trial occurred in 10 (3.4%), 25 (8.7%), and 21 (7.2%) patients in the AV, AVO, and FCR/BR arms. Of these, 0/10 (0%, AV), 6/25 (24%, AVO), and 2/21 (10%, FCR/BR) received ≥1 COVID-19 vaccination. [b]Not related to study treatment. [c]Not related to acalabrutinib treatment.

Figure 2. Cumulative Incidence of Cardiac Events and Grade ≥3 Cardiac Events



No. at risk								
All grade								
AV	291	277	266	260	245	8	1	0
AVO	284	263	249	230	219	16	0	
FCR/BR	259	222	10	1	0			
Grade ≥3								
AV	291	286	279	276	265	8	1	0
AVO	284	275	265	249	242	17	0	
FCR/BR	259	228	10	1	0			

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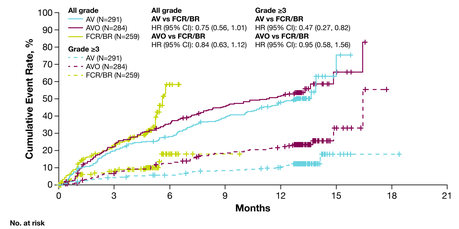
References

1. Brown JR, et al. *N Engl J Med*. 2025;392:748-62. 2. Hallek M, et al. *Blood*. 2018;131:2745-60.

Abbreviations

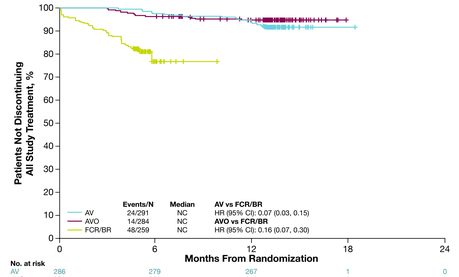
AE, adverse event; ALC, absolute lymphocyte count; ASCO, American Society of Clinical Oncology; AV, acalabrutinib plus venetoclax; AVO, acalabrutinib plus venetoclax and obinutuzumab; BID, twice daily; BR, bendamustine plus rituximab; C, cycle; CI, confidence interval; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; DOR, duration of response; EAER, exposure-adjusted event rate; ECI, event of clinical interest; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FCR, fludarabine plus cyclophosphamide plus rituximab; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IgG, immunoglobulin G; IGHV, immunoglobulin heavy chain variable region genes; IRC, independent review committee; IV, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LLN, lower limit of normal; LN, lymph node; MRD, measurable residual disease; NC, not calculable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, oral; QD, once daily; SLL, small lymphocytic lymphoma; SPM, second primary malignancy; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; TN, treatment naive; TTNT, time to next treatment

Figure 3. Cumulative Incidence of Infections and Grade ≥3 Infections



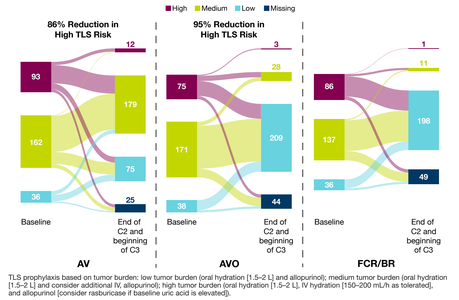
No. at risk								
All grade								
AV	291	232	205	172	144	2	0	
AVO	284	215	178	147	131	5	0	
FCR/BR	259	181	3	0				
Grade ≥3								
AV	291	277	269	259	247	5	1	0
AVO	284	259	243	222	213	8	0	
FCR/BR	259	218	9	1	0			

Figure 4. Time to Discontinuation of All Study Treatment



No. at risk					
AV	286	279	267	1	0
AVO	276	266	243	0	
FCR/BR	258	13	0		

Figure 5. TLS Risk at Baseline vs End of Cycle 2 and Beginning of Cycle 3



TLS prophylaxis based on tumor burden: low tumor burden (oral hydration [1.5–2 L] and allopurinol); medium tumor burden (oral hydration [1.5–2 L] and consider additional IV allopurinol); high tumor burden (oral hydration [1.5–2 L], IV hydration [150–200 mL/h as tolerated], and allopurinol [consider rasburicase if baseline uric acid is elevated]).