Ibrutinib *versus* acalabrutinib in fixed-duration chronic lymphocytic leukemia therapy: a comparative analysis of efficacy

The phase III AMPLIFY trial (clinicaltrials.gov 03836261) provides important evidence on the efficacy of fixed-duration (FD) acalabrutinib-venetoclax (AV), with or without obinutuzumab, demonstrating improved progression-free survival (PFS) compared to standard chemoimmunotherapy in treatment-naïve chronic lymphocytic leukemia (CLL) patients without 17p deletion or *TP53* mutations.[1] These findings have informed recent updates to the National Comprehensive Cancer Network (NCCN) guidelines, resulting in a Category 1 recommendation for the FD AV regimen for previously untreated CLL patients requiring therapy.[2] Notably, comparable findings have been documented in the phase II CAPTIVATE trial (clinicaltrials.gov 02910583) and the phase III GLOW trial (clinicaltrials.gov 03462719), both of which investigated FD combinations of venetoclax with ibrutinib.[3,4]

Acalabrutinib is generally preferred over ibrutinib in continuous Bruton's tyrosine kinase inhibitor (BTKi)-based approaches, primarily due to its comparable efficacy and an improved safety profile.[5] However, it remains unclear whether acalabrutinib should be preferred over ibrutinib in FD combinations with venetoclax, as the degree of synergy between BTKi and venetoclax therapy may differ among different BTKi.

In the absence of direct comparative studies, we conducted an indirect analysis to assess the relative efficacy of FD venetoclax in combination with ibrutinib or acalabrutinib. Data from the FD cohort of the CAPTIVATE trial, which features a patient population closely aligned with that of the AMPLIFY trial, served as a benchmark for this indirect comparative analysis.[1,3]

To enable a rigorous yet indirect comparison, individual patient data (IPD) from the FD AV arm of the AMPLIFY trial and the FD ibrutinib-venetoclax (IV) cohort of the CAPTIVATE trial were reconstructed using the methodology outlined by Liu *et al*.[6] The IPD utilized for sensitivity analyses (specifically, those excluding COVID-19-related deaths in the AMPLIFY study and patients with *TP53* mutations in the CAPTIVATE study) were obtained from the IPD employed in the Kaplan-Meier subgroup plots presented in the original published reports.[1,3] The primary endpoint of this analysis, PFS, was evaluated through restricted mean survival time (RMST) analysis over a common 3-year follow-up period. Restricted mean survival time offers an alternative to hazard ratios and median survival times by directly quantifying the entire observed survival curve.[7] Specifically, RMST is calculated as the area under the Kaplan-Meier survival curve up to a pre-specified time point (t) which corresponds to the duration of follow-up in the study.[7] Unlike median survival, RMST summarizes the average survival experience and does not depend on the proportional hazards assumption, thereby capturing treatment benefits across the entire follow-up period.[8] In the present study, the difference (Δ) in RMST was used to quantify and compare the area between the PFS curves of the IV and AV treatment regimens, using the previously reported approach.[8] Baseline demographic and clinical characteristics of the patient cohorts were compared using χ^2 tests or Fisher exact tests, as appropriate. This indirect comparative analysis was conducted using publicly available, published data and did not involve the collection of new primary data from human participants. Therefore, ethical approval was not required in accordance with institutional guidelines and national regulations.[1,3]

In aggregate, 450 patients undergoing combination therapy with a BTKi in combination with venetoclax were included in the analysis. BTKi-venetoclax treated patients were divided into two groups: 159 patients treated with IV in the FD cohort of CAPTIVATE trial, and 291 patients treated with AV in the AMPLIFY trial. Baseline demographic and genetic features between groups were largely comparable, including age >65 years (P=0.437), sex distribution (P=0.146), immunoglobulin heavy-chain variable (IGHV) mutation status (P=0.424), complex karyotype (P=0.168), and 11q deletion (P=0.539). A higher proportion of AV-treated patients had advanced Rai stage 3-4 disease (P<0.001). Notably, due to differences in eligibility criteria, 17p deletion or *TP53* mutations (established predictors of response duration to BTKi and venetoclax-based therapies) were present in 17% of patients in the CAPTIVATE trial, but absent in the AMPLIFY trial cohort (Table 1).[1,3]

A comparative analysis of 3-year PFS between the IV and AV regimens, assessed using RMST, was conducted by excluding *TP53*-mutated patients from the CAPTIVATE cohort to ensure homogeneity. This analysis demonstrated a significant advantage for ibrutinib-based therapy (P=0.001) (Table 2). Given the higher prevalence of COVID-19-related deaths in the AV arm of the AMPLIFY trial (10 of 291 patients; 3.4%) relative to the IV FD cohort of the CAPTIVATE trial (1 of 159 patients; 0.6%), a sensitivity analysis was conducted excluding COVID-19-related deaths. While COVID-19-related mortality had minimal impact on PFS in the CAPTIVATE cohort, censoring patients in the AV arm of AMPLIFY at the time of COVID-19-related death led to an increase in the RMST. However, this RMST remained statistically shorter

than that observed with IV therapy (*P*=0.006) (Table 2). Notably, the PFS advantage of IV over AV appeared to be primarily driven by its relative benefit among patients with unmutated IGHV status (*P*=0.02) (Table 2).

The PFS benefit of IV relative to AV was further evaluated using RMST difference (Δ) analysis. At the 3-year mark, IV demonstrated a statistically significant RMST Δ of 2.7 months (95% CI: 1.3-4.1; *P*=0.01) relative to AV. Sensitivity analyses excluding COVID-19-related deaths yielded a slightly attenuated but still significant RMST Δ of 1.9 months (95% CI: 0.7-3.2; *P*=0.04) (Figure 1). Subgroup analyses revealed that this benefit was again most pronounced among patients with unmutated *IGHV*, with an RMST Δ of 3.4 months (95% CI: 1.1-5.6; *P*=0.03). Conversely, in patients with mutated *IGHV*, the difference in RMST Δ was not statistically significant (RMST Δ of 2.2 months; 95% CI: −0.2 to 4.2; *P*=0.16) (Figure 1).

Finally, we evaluated the prognostic significance of depth of response, defined by the achievement of undetectable measurable residual disease (uMRD), on 3-year PFS among patients receiving various FD BTKi-based regimens. Using flow cytometry with a sensitivity threshold of 10^{-4}, the rates of reported uMRD at the end of therapy were 77% among patients treated with IV, compared to 45% among those receiving AV.[1,3] Among patients who achieved uMRD, the 3-year RMST was 35.1 months (95% CI: 34.2-36.0) in the IV arm and 33.3 months (95% CI: 31.7-35.0) in the AV arm. While this trend favored the IV regimen, the RMST Δ among uMRD patients receiving IV *versus* AV was 1.8 months (95% CI: −0.1 to 3.6), which did not reach statistical significance (*P*=0.09) (Figure 1). Accordingly, it appears the benefits of IV relative to AV may relate to the higher proportion of patients achieving uMRD rather than a difference in outcome once a uMRD state is reached.

In aggregate, the present RMST analysis indicates that FD IV may provide superior PFS compared to FD AV in TN, fit patients with CLL who do not harbor *TP53* aberrations. Notably, the efficacy advantage was apparent primarily in *IGHV* unmutated patients. Among the subset of patients who achieved uMRD, no statistically significant differences in PFS were identified between the IV and AV regimens.

The differences in efficacy between IV and AV observed in our study likely reflect underlying pharmacological distinctions between ibrutinib and acalabrutinib.[9] Despite these pharmacological differences, consistent with the effects observed with ibrutinib, acalabrutinib elicited a significant increase in BCL-2 dependence in CLL cells, both *ex vivo* and *in vivo*.[10] However, while pharmacokinetic interactions between ibrutinib and venetoclax are well documented, pharmacokinetic interactions involving acalabrutinib and venetoclax have yet to be thoroughly investigated.[11]

In comparison to acalabrutinb, ibrutinib has broader off-target activity, including inhibition of interleukin-2-inducible T-cell kinase which fosters Th1 differentiation and enhances cytotoxic T-cell responses, critical in restoring immune surveillance in CLL.[12,13] Recent data suggest that T-cell-mediated cytotoxicity against CLL cells is augmented when epcoritamab is used in combination with BTKi or venetoclax.[14]

Moreover, ibrutinib disrupts CLL microenvironment interactions by inhibiting CXCR4/5 signaling and down-regulating adhesion molecules such as CD49d and VLA-4, potentially facilitating CLL cell egress from protective niches and increasing sensitivity to venetoclax.[13,15] In contrast, acalabrutinib's greater selectivity and limited off-target effects may

Table 1. Characteristics of patients of the acalabrutinib-venetoclax arm of the AMPLIFY trial and the ibrutinib-venetoclax fixed-duration cohort of the CAPTIVATE trial.

Characteristic, %	AMPLIFY AV arm N=291	CAPTIVATE FD IV arm N=159	*P*
Males	61.1	66.6	0.146
>65 years	27.1	28.3	0.437
Rai stage III/IV	47	27.6	<0.001
u*IGHV**	57.3	55.9	0.424
11q(del)	17.5	17.6	0.539
Complex karyotype	15.4	19.4	0.168
Del(17p)/*TP53* mut	0	16.9	<0.0001

*u*IGHV*: unmutated immunoglobulin heavy-chain variable. AV: acalabrutinib-venetoclax; FD: fixed-duration; IV: ibrutinib-venetoclax; mut: mutations; N: number.

Table 2. Three-year restricted mean survival time in patients from the CAPTIVATE ibrutinib-venetoclax fixed-duration cohort and the acalabrutinib-venetoclax arm of the AMPLIFY trial.

Patient population	3-year RMST in months (95% CI)	*P*
General population CAPTIVATE (IV-FD cohort)* AMPLIFY (AV arm)	 35.0 (34.1-35.8) 32.3 (31.2-33.6)	0.001
After censoring COVID-19-related deaths§ CAPTIVATE (IV-FD cohort)* AMPLIFY (AV arm)	 35.0 (34.1-35.8) 33.1 (32.1-34.1)	0.006
Patients with unmutated IGHV CAPTIVATE (IV-FD cohort) AMPLIFY (AV arm)	 35.2 (33.4-36.8) 31.9 (30.4-33.3)	0.02
Patients with mutated IGHV CAPTIVATE (IV-FD cohort) AMPLIFY (AV arm)	 35.0 (34.2-35.9) 33.0 (31.3-34.6)	0.16

AV: acalabrutinib-venetoclax; CI: Confidence Interval; FD: fixed-duration; IV: ibrutinib-venetoclax; RMST: restricted mean survival time. *TP53-mutated patients from the CAPTIVATE cohort were excluded to ensure homogeneity. §COVID19-related deaths: 10 of 291 or 3.4% in the AV arm of the AMLIFY trial, 1 of 159 or 0.6% In the IV FD cohort of the CAPTIVATE trial.

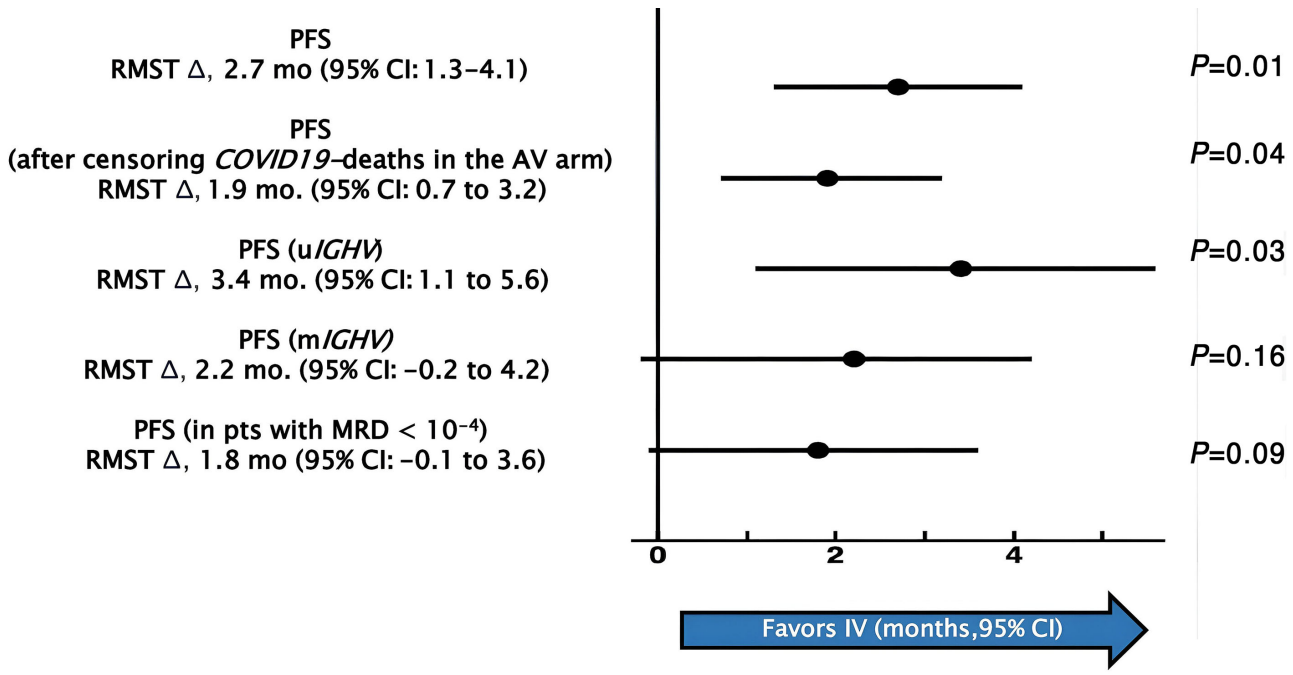

Figure 1. Forest plot comparing the 3-year progression-free survival benefit. Progression-free survival (PFS) was assessed as restricted mean survival time (RMST) difference (Δ), between patients (pts) treated with fixed-duration (FD) acalabrutinib-venetoclax (AV) in the AMPLIFY trial and *TP53* wild-type patients treated with FD ibrutinib-venetoclax (IV) in the CAPTIVATE trial. CI: Confidence Interval; m*IGHV*: mutated immunoglobulin heavy-chain variable; mo: months; u*IGHV*: unmutated immunoglobulin heavy-chain variable.

attenuate such immunomodulatory and microenvironmental interactions, contributing to comparatively lower uMRD rates and PFS.[1,5]

Our findings are consistent with data reported by Munir *et al.* at the 2025 EHA meeting.[16] Their analysis, using matching-adjusted indirect comparison (MAIC) methodology, compared patients receiving IV (pooled from the GLOW and the CAPTIVATE trials) to those on AV (the AMPLIFY trial), demonstrating superior PFS and higher rates of uMRD three months post treatment in the IV group.[16] Importantly, the study by Munir *et al.* offers additional support for our findings regarding the comparative efficacy of IV *versus* AV combinations.[16]

Our study, while informative, is subject to inherent limitations. Foremost among these is the reliance on indirect comparisons, which are constrained by variability in study designs and patient populations.[7] Notably, the AV arm included a higher proportion of patients with advanced Rai stages.[1] Additionally, the use of short-term time points for outcome assessment further limits the robustness of the comparisons. Specifically, a 3-year PFS time point was selected to align with the available data from the AMPLIFY study.[1] However, this timeframe may be insufficient for a disease such as CLL, thereby constraining our ability to perform a meaningful overall survival analysis.

Finally, although our data are statistically significant, their clinical relevance may be limited due to the modest PFS benefit observed with IV, specifically, an advantage of 1.9 months in RMST after censoring COVID-19-related deaths in the AMPLIFY trial. Nonetheless, these findings provide valuable insights that can generate new hypotheses for future research. However, definitive conclusions regarding comparative efficacy require validation through randomized controlled trials.

The safety profiles of BTKi require meticulous consideration.[1,3-5] To assess the clinical impact of our findings, it is essential to recognize that the potential improvements in safety and tolerability conferred by AV are of significant clinical relevance. Notably, the arrythmia and cardiovascular risks associated with ibrutinib need to be carefully assessed.[3-5] Second-generation BTK inhibitors, such as acalabrutinib, may offer fewer adverse events within the context of FD treatment paradigms.[1] Discontinuation rate comparisons between IV and AV are confounded by a higher incidence of COVID-19-related discontinuations in the AV arm of AMPLIFY (22%).[1] Nonetheless, atrial fibrillation (a hallmark BTKi-related adverse event) was observed in 4.5% of CAPTIVATE patients *versus* 0.7% in the AV arm of AMPLIFY.[1,3]

In conclusion, our data suggest that covalent BTK inhibitors may exhibit different efficacy when combined with BCL2 inhibitors such as venetoclax. Non-covalent BTK inhibitors, including pirtobrutinib, have also demonstrated promising efficacy in combination with venetoclax.[17] Further clinical trials are necessary to establish the optimal BTKi-BCL2 inhibitor combination.

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Contributions

SM designed this study, selected and evaluated studies in the literature, performed data extraction, evaluated and interpreted results, and wrote the manuscript. DA interpreted results and provided advice on the preparation of the manuscript. DG selected and evaluated studies in the literature, performed data extraction and statistical analyses, and evaluated the results. TDS evaluated and interpreted results, and wrote the manuscript. All authors reviewed and approved the manuscript.

Data-sharing statement

Data supporting the findings of this study are available from the corresponding author on request.

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