Comparative analysis of targeted novel therapies in relapsed, refractory chronic lymphocytic leukemia

Therapeutic options for chronic lymphocytic leukemia (CLL) patients have expanded over recent years as efficacious novel agents (NA) have received licensing approval, initially in relapsed, refractory (R/R) disease. Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor (BTKi) targeting B-cell receptor (BCR) pathway signaling. It has potent activity in relapsed disease as monotherapy[1] with significant benefit compared to ofatumumab and combined with bendamustine-rituximab (BR) *versus* BR.[2] Idelalisib also targets the BCR pathway by inhibiting the delta isoform of phosphoinositide 3-kinase (PI3Ki). It is licensed in combination with rituximab following improved progression-free survival (PFS) compared to rituximab in heavily pre-treated patients.[3] However, toxicity concerns now limit its use in R/R CLL, and the randomized ASCEND trial[4] has shown PFS superiority for the second generation BTKi acalabrutinib *versus* idelalisib-rituximab (hazard ratio [HR] 0.29; *P*<0.0001). Moreover, a large retrospective series has previously compared ibrutinib and idelalisib-rituximab as first NA (NA1)[5] and found a similar, indirect PFS advantage for ibrutinib. Venetoclax is a potent, oral small-molecule BCL2 inhibitor (BCL2i) licensed as monotherapy ± rituximab in R/R CLL.[6,7] Venetoclax is increasingly utilized at first relapse in combination with rituximab for a 2-year fixed duration.[6] However, to date, no prospective trials have directly compared ibrutinib with venetoclax as NA1 in R/R CLL. It remains a key unanswered question as to which of these two NA optimizes the balance of safety and efficacy when used as the NA1 in R/R CLL.

To address this, we report a large, international study to establish the efficacy of ibrutinib and venetoclax ± anti-CD20 as NA1 in R/R CLL. To our knowledge, this is the largest series comparing these two approaches as NA1.

To address this question, a single NA database was created from prior international, collaborative, multicenter retrospective analyses examining each NA to describe and compare the characteristics and outcomes of CLL patients treated with ibrutinib or venetoclax ± anti-CD20 as the NA1 between 2015-2019. To be eligible for comparison, patients could not have been treated with a targeted agent in the front-line setting and had to receive ibrutinib or venetoclax as NA1 no later than line 5. Twenty centers participated in this study from academic and community sites.

To define the study cohort for the primary analysis, medical chart reviews were performed to identify all con-secutive patients with CLL at each institution who received ibrutinib or venetoclax as NA1 in the R/R setting including only patients in routine clinical practice. To verify that cohorts were similar, baseline characteristics were collected prior to NA exposure. Using a standardized case report form, investigators collected data on pre-NA demographics, disease/prognostic characteristics (including del(17)p, complex karyotype [CK] defined: ≥3 aberrations, IGHV status, and *TP53* mutation), clinical and genetic characteristics, number and type of prior therapies. Toxicity data regarding dose interruptions, reductions, NA discontinuation, and reasons for discontinuation were collected.

Other primary endpoints were overall response rate (ORR) and PFS for the NA1. Investigators were requested to classify responses by International Workshop on CLL (iwCLL) criteria as complete remission (CR), partial remission (PR) (including PR with lymphocytosis), stable disease (SD), and progressive disease (PD).[8] PFS was defined as the time from NA1 to last follow-up, progression of CLL or death. Overall survival (OS) was defined as the time from NA1 to death from any cause. PFS and OS were estimated by the Kaplan-Meier method.[9] All other comparisons were descriptive. Comparisons were made using Cox regression or log-rank tests. Statistical analyses were performed using STATA 10.1. Follow-up was censored at most recent visit or death.

A total of 433 patients received a NA1: 385 ibrutinib; 48 venetoclax ± anti-CD20 (80% monotherapy). Data for PFS were available for 417 patients. Median follow-up was 14 months (ibrutinib) and 13.5 months (venetoclax), respectively. Each group had a median of two prior lines (range 1-4 for each). Median age of each cohort (ibrutinib: 69 years; venetoclax: 65 years) were similar, as were the proportion with adverse features such as del(17p) (Table 1).

Overall response rate and CR were: ibrutinib (71% and 12%, respectively) and venetoclax (96% and 56%, respectively). Venetoclax-treated patients had a statistically significantly higher CR rate *versus* ibrutinib (*P*<0.001). Figure 1A shows PFS of all patients stratified according to NA1. Using ibrutinib as the comparator (HR, 1.0), PFS HR for venetoclax was 0.29 (95%CI: 0.10-0.92; *P*=0.036) (Figure 1A). Using ibrutinib as the comparator for OS, HR was 1.2 (95%CI: 0.47-3.1; *P*=0.70) for the venetoclax-treated cohort (Figure 1B). When considering del(17p), del(11q), CK and IGHV status, we could not identify a subgroup that benefited in terms of PFS when comparing each NA1 (*data not shown*). Considering the whole cohort, only those with a CK (HR, 1.99 [1.1-3.80]; *P*=0.04) had a statistically significant inferior PFS.

Dose interruptions were recorded in 33% ibrutinib and 32% venetoclax-treated patients (Table 2). Dose reduc-

Table 1. Baseline characteristics of each novel therapy cohort.

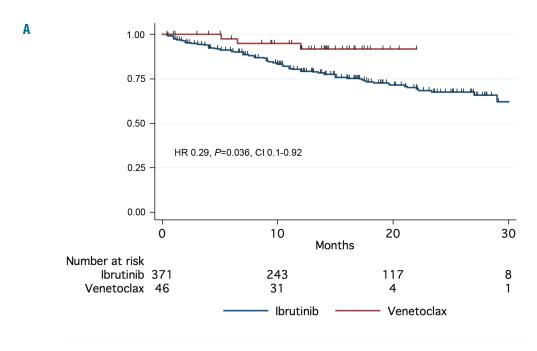| Baseline characteristics				
First novel therapy	N	Ibrutinib	N	Venetoclax +/- anti-CD20
Median age at treatment, years (range)	382	69 (27-95)	48	65 (39-87)
Median n. of prior therapies, (range)	385	2 (1-4)	48	2 (1-4)
Del(17p)	255	24%	47	34%
Complex karyotype	157	32%	17	24%
Elevated LDH	189	45%	20	45%

N/n: number; LDH: lactate dehydrogenase.

tions were recorded in 22% of ibrutinib and 26% venetoclax-treated patients. Overall discontinuation rates were 41% ibrutinib and 25% venetoclax (P=0.06). For ibrutinib, the most common discontinuation reasons were adverse events (AE) (22%), CLL progression (8%) and Richter's transformation (RT) (2%). For venetoclax, the most common discontinuation reasons were allogeneic stem cell transplantation (10%), CLL progression (4%), and unrelated death event (4%). RT was uncommon and comparable across cohorts (Table 2).

To our knowledge, this is the largest series comparing ibrutinib and venetoclax-based treatment in R/R CLL. In the first such analysis, we provide an indirect comparison of patients receiving ibrutinib and venetoclax as a NA1. We note that CR rates were higher with venetoclax treat-ment, which appeared to translate to a PFS advantage over ibrutinib but not an OS advantage. In light of this, and in the absence of randomized data comparing these approaches, our data provide reassurance that either option remains a reasonable approach as NA1 in R/R CLL. The PFS difference seen within this series may in part relate to the tolerability of each agent within routine clinical practice. Higher rates of discontinuation due to AE and frequent dose reductions/interruptions have been reported to be most pronounced in ibrutinib-treated patients[10,11] and AE are the most dominant cause for ibrutinib discontinuation within our data.

Our study has several limitations. It is retrospective, and its conclusions remain hypothesis generating. However, in the absence of ongoing randomized trials
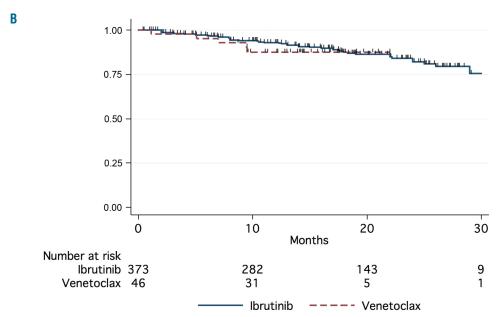

Figure 1. Survival outcome of patients with relapsed, refractory chronic lymphocytic leukemia CLL according to first novel agent received. (A) Progression-free survival according to novel targeted agent. (B) Overall survival according to novel targeted agent. HR: hazard ratio; CI: confidence interval.

Table 2. Dosing patterns and discontinuations according to novel agent.

Dosing patterns First novel therapy	Ibrutinib	Venetoclax +/- anti-CD20
Dose reductions	22%	26%
Dose interruptions	33%	32%
Discontinuation rate	41%	25%
Most common discontinuation reason	Adverse event 22%	Allogeneic stem cell transplantation 10%
Richter's transformation rate	2%	2%

comparing these two standard-of-care NA1 in CLL, our study may help to inform practice and aid future prospective trial design. We recognize the unavoidable biases associated with retrospective reporting, missing data, the lack of centralized response assessment and pathology review, and the potential for overestimating CR rates; however, any misclassification is likely to be non-differential. Information regarding dosing, interruptions, and toxicity were not prospectively collected leading to the risk of bias. To address this, we partnered with investigators with extensive experience in using NA and experienced in 'real-world' evidence collation. While the group has published similar datasets exploring NA sequencing,[5,10-13] this analysis is the first published indirect comparison of ibrutinib and venetoclax in R/R CLL as first NA from our 'real-world' database and provides important new data in terms of NA sequencing and selection.

Patients within our series had received a median of two prior lines pre-NA, with a relatively high rate of del(17p) (25% across all patients) and CK (31% across all patients) for whom data were available. This likely reflects the fact that, early on, these agents were prescribed to heavily pretreated, poor-risk patients. Use of NA is quickly being brought forward to first relapse[4] and front-line treatment.[14,15] It is possible that survival analyses would produce different results in less heavily pre-treated patients. However, given the lack of prospective comparative data, we believe our comparison provides valuable information for healthcare providers in the decision-making process regarding which NA to use first in R/R CLL. Given the nature of this population, making inferences regarding front-line therapy is challenging and was not our primary goal. We also did not aim to specifically answer questions regarding subsequent sequencing beyond NA1; this work is currently ongoing. Finally, the patient numbers in the venetoclax group are small compared to the ibrutinib group and we acknowledge analyses may be underpowered to detect any possible differences. Although the baseline characteristics are similar, smaller cohorts could provide greater heterogeneity. The difference in baseline characteristics reflects prescribing practice over recent years where the strongest evidence for NA1 within trials[1] and non-trial[10,11] was initially formed with ibrutinib. Finally, our data were collected prior to recent analyses suggesting CK with ≥5 aberrations selected the highest risk patients, and as such, our CK data should be interpreted in that light.

In conclusion, venetoclax and ibrutinib-based therapy as NA1 provide comparable OS outcomes in R/R CLL patients treated outside of trials. Our data suggest a significant PFS advantage for venetoclax-treated patients as

NA1, a finding that requires independent validation and reassessment for patients treated at first relapse outside of clinical trials. The selection of either as the NA1 should therefore be based on individual patient factors, drug access, deliverability, and patient preference.

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