RESEARCH LETTER

blood advances

TO THE EDITOR:

Limited efficacy for ibrutinib and venetoclax in T-prolymphocytic leukemia: results from a phase 2 international study

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T-prolymphocytic leukemia (T-PLL) is a rare, aggressive T-lymphoid malignancy with a poor prognosis and short durations of response to chemotherapies.[1] Relapses are inevitable with standard-of-care front-line alemtuzumab and in most patients undergoing allogeneic stem cell transplantation (SCT).[2] Transient clinical responses in relapsed or refractory (R/R) T-PLL have been reported for the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax as single-agent[3] or combined with bendamustine.[4] Combination of venetoclax with ibrutinib, an inhibitor of Bruton tyrosine kinase of B-cells, produced clinical responses in heavily pretreated patients with R/R T-PLL due to increased BCL-2-dependent priming of T-PLL cells for apoptosis.[5]

We report results from the first international study evaluating antitumor activity and safety of ibrutinib plus venetoclax in patients with R/R T-PLL. This open-label, single-arm phase 2 study (NCT03873493) used an adaptive 2-stage design: stage 1 enrolled 14 patients; stage 2 would proceed with up to 23 additional patients if a response was observed in ≥4 patients by week 24. Eligible patients were adults with R/R T-PLL suitable for additional therapy, with no limit on previous lines of treatment (see supplemental Table 1). Prior allogeneic SCT was permitted, but previous treatment with BCL-2 inhibitors was not allowed. All patients provided written informed consent.

Patients received 420 mg ibrutinib orally once daily and oral venetoclax once daily starting with an in-hospital, 5-day, dose-accelerated 20-400 mg ramp-up, then continued at 400 mg as outpatient treatment (see supplemental Table 1). Patients could continue ibrutinib plus venetoclax for up to 2 years or until eligibility for SCT after reaching complete remission (CR), until progressive disease (PD), or unacceptable toxicity. The primary end point was overall response rate (ORR), defined as the proportion of patients who achieved CR, CR with incomplete count recovery (CRi), or partial remission (PR) as best overall response per investigator assessment according to 2019 T-PLL consensus criteria.[2] Secondary outcomes included safety and tolerability end points, proportion of patients achieving CR

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and proceeding to SCT, and antitumor activity outcome measures including progression-free survival (PFS), duration of response (DOR), disease control rate (CR + CRi + PR + stable disease [SD]), and overall survival (OS).

The study was conducted between 14 January 2020 and 4 November 2021, and 14 patients were enrolled (supplemental Figure 1). Median age was 66 years old (range, 46-80) with a median of 2 (range, 1-6) prior lines of T-PLL therapy, including 12 patients who received prior alemtuzumab (supplemental Table 1). Two patients previously underwent SCT, 50% had an Eastern Cooperative Oncology Group performance status of 0, and 54% had absolute lymphocyte counts $\leq 30 \times 10^3/\mu L$. All 14 patients received study treatment (supplemental Table 2). Median duration of treatment exposure was 13.9 weeks (range, 1.0-44.4) for ibrutinib and 13.7 weeks (range, 0.4-44.3) for venetoclax. Dose interruptions and reductions due to unrelated and possibly treatment-related adverse events are summarized in supplemental Figure 2.

In 14 patients evaluated, there was 1 PR, yielding an ORR of 7.1% (95% confidence interval [CI], 0.2-33.9; Figure 1). Three (21.4%) patients had SD, hence, the disease control rate was 28.6%. Nine (64.3%) patients had PD as best response, and 1 patient discontinued the study before the first protocol–defined response assessment. DOR for the patient who achieved PR was 23.1 weeks (supplemental Figure 2). SDs as best responses lasted 35.2, 15.2, and 15.2 weeks. Median PFS was 11.7 weeks (95% CI, 5.2-23.1; supplemental Table 3), and median time to next T-PLL treatment was 17.4 weeks (95% CI, 2.6-34.4). Kaplan-Meier plots of PFS and OS are presented in supplemental Figures 3 and 4. The median OS for all patients was 31.8 weeks (95% CI, 28.7-not evaluable). No patients achieved CR or were eligible for consolidating or salvage SCT.

All patients experienced at least 1 treatment-emergent adverse event (TEAE), and most had at least 1 TEAE considered related to ibrutinib (13 [92.9%]) or venetoclax (10 [71.4%]) (Table 1). Most (10 [71.4%]) patients experienced grade 3/4 TEAEs, and 8 (57.1%) reported serious adverse events. Grade 3/4 TEAEs in >10% of patients were anemia, nausea, and neutropenia (supplemental Table 4). One patient experienced atrial fibrillation (grade 3), and 5 patients experienced hemorrhage (all grade 1). No episodes of new or uncontrolled hypertension were reported. One grade-3 tumor lysis syndrome was attributed to cyclophosphamide administered following study treatment discontinuation. Cytomegalovirus reactivations were not reported. Treatment-emergent hematology laboratory abnormalities are shown in supplemental Table 5 and supplemental Figures 5-15. One patient (7.1%) discontinued study drugs due to neutropenia that was deemed possibly related to both drugs by the investigator. Discontinuation events also related to PD were excluded from the calculation. Ten deaths (71.4%) occurred during the study period (supplemental Table 2), with 9 related to PD and 1 due to acute respiratory failure secondary to COVID-19–related pneumonia.

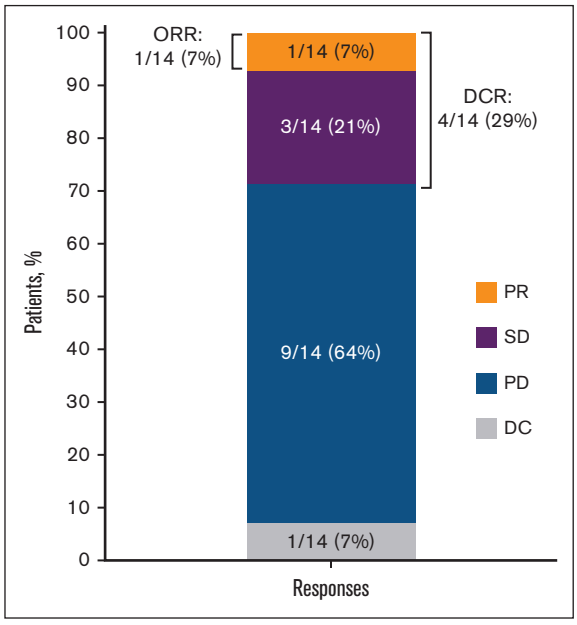

Figure 1. Best overall response to ibrutinib-venetoclax treatment (N=14). DC, discontinued; DCR, disease control rate; PD, progressive disease; PR, partial response; ORR, overall response rate; SD, stable disease.

This milestone study was the first international prospective clinical trial in patients with T-PLL. Fourteen patients with R/R T-PLL were recruited within 10 months, with 13 enrolled within 4 months following a hold due to the COVID-19 pandemic. This highly efficient recruitment by investigators of the International T-PLL Study Group (ITPLLSG; a vivid exchange platform), as compared with larger monocentric or national studies,[6-8] demonstrates the importance of a collaborative network of committed researchers jointly addressing challenges associated with rare diseases, establishing an important framework for rapid translation of preclinical data to clinical trials.

In this study, steady-state pre-dose plasma concentrations of both ibrutinib and venetoclax, available in 6 patients who received full dosing of both drugs, were similar to those seen in monotherapy trials,[9] and the combination did not increase exposures to either agent as previously seen for venetoclax.[10] The safety profile was

Table 1. Safety overview

Event, N (%)	All patients (N=14)
Any grade TEAE*	14 (100)
Grade 3/4 TEAE	10 (71.4)
SAE	8 (57.1)
Venetoclax-related TEAE	10 (71.4)
Ibrutinib-related TEAE	13 (92.9)
AE leading to venetoclax interruption	9 (64.3)
AE leading to venetoclax reduction	2 (14.3)
AE leading to venetoclax discontinuation excluding progression†	1 (7.1)
AE leading to ibrutinib interruption	10 (71.4)
AE leading to ibrutinib reduction	1 (7.1)
AE leading to ibrutinib discontinuation excluding progression†	1 (7.1)
AE leading to death	5 (35.7)
Death	10 (71.4)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*TEAE was defined as any event with onset after the first does of study drug to no more than 30 days after the first dose of study drug.
†Events that had PD as a reason for study drug discontinuation were excluded.

consistent with that of previous venetoclax studies in R/R T-PLL,[4] and also for this combination in other disease settings.[10,11]

The antitumor activity of ibrutinib and venetoclax in stage 1 (ORR, 7.1%) did not meet prespecified criteria for proceeding to stage 2. Response rates of 45% to 76% in R/R T-PLL have been reported for chemotherapy/alemtuzumab–based strategies, although these responses were of short duration and OS was only 6 to 10 months.[1] Response duration for ibrutinib plus venetoclax in this study was 23.1 weeks (a single PR), and the median OS was 31.8 weeks. Observed lymphocytosis was related to disease progression and not to compartment shifts described for Bruton tyrosine kinase inhibition in CLL.[1]

We conclude that there is no clinical benefit of ibrutinib plus venetoclax in most R/R T-PLL, conceivably due to primary or acquired resistance, including increased myeloid cell luekemia-1 activity that is unaddressed by and/or a result of BCL-2 inhibition.[12] This lack of efficacy contrasts promising preclinical data from this combination in T-PLL cells[5,13] and challenges assumptions that preclinical drug profiling data reliably predict clinical responses. More advanced sensitivity screens are being developed: single-cell drug profiling recently demonstrated more sensitive guidance of treatment decisions[14]; BH3 profiling in co-culture systems suggested activity for venetoclax with the Janus kinase inhibitor ruxolitinib, but clinical confirmation is needed.

Overall, the combination of ibrutinib and venetoclax did not demonstrate meaningful activity in patients with R/R T-PLL, and therefore does not warrant further study in this population. These results emphasize the importance of well-designed clinical trials rather than case studies or retrospective analyses to inform clinical practice change, even in rare diseases. Continued research into novel drug combinations is critical to address the unmet need for effective treatment options in patients with T-PLL.

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