The range of therapeutic options for chronic lymphocytic leukemia (CLL) has increased considerably. While novel agents inhibiting the B-cell receptor (BCR) pathway such as ibrutinib and idelalisib offer favorable toxicity profiles relative to chemoimmunotherapy, there is significant room for improvement in the depth and duration of response. Furthermore, treatment typically continues until progression or unacceptable toxicity. Combining targeted agents may offer the possibility of finite duration while improving response. Bruton’s tyrosine kinase (BTK) inhibition with ibrutinib has improved outcomes in CLL.1-3 However, deep responses with undetectable minimal residual disease (uMRD) are rare with monotherapy,4,5 and common side effects include diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue.6 Second-generation irreversible BTK inhibitors such as tirabrutinib act more selectively, improving safety profile.5 In a phase 1 study of tirabrutinib, 24 of 25 CLL patients had an objective response.7 In the same study population of 90 patients with relapsed/refractory B-cell malignancies, 75% of adverse events (AEs) were grade 1/2. One CLL patient exhibited a grade 3 bleeding event, but no clinically significant diarrhea, cardiac arrhythmias, or arthralgias were observed.7

The phosphatidylinositol 3-kinase inhibitor idelalisib plus rituximab is approved by the US Food and Drug Administration and European Medicines Agency for relapsed/refractory CLL. This combination significantly improved survival versus rituximab alone.8 A phase 1b study in previously treated CLL patients showed fixed-duration tirabrutinib plus idelalisib was tolerable but did not improve efficacy versus tirabrutinib alone.9 Here, we present a phase 2 trial assessing tirabrutinib and idelalisib with/without obinutuzumab (TIO and TI).

Methodology is provided in the Supplemental Digital Content. Following enrollment of 5 patients in the TI arm, a protocol amendment directed all subsequent patients be enrolled in TIO due to low complete remission (CR) rates in a preceding phase 1 trial.9 Thirty-five patients with CLL were enrolled; 5 received TI and 30 received TIO (Suppl. Figure S1). Demographics and baseline disease characteristics are in Suppl. Table S1. Eleven patients (31.4%) had a TP53 mutation, 6 (17.1%) had a 17p deletion, and 23 (65.7%) were immunoglobulin heavy-chain unmutated. All patients received venetoclax prior to TIO.

Median follow-up was 120.7 and 72.4 weeks for TI and TIO, respectively. The median (range) duration of exposure was 67.1 weeks (4.3–104.0 wk) for tirabrutinib and 60.9 weeks (1.6–104.0 wk) for idelalisib in the TI arm. For TIO, median exposure was 68.4 weeks (0.1–105.4 wk) for tirabrutinib, 64.4 weeks (0.1–105.4 wk) for idelalisib, and 20.1 weeks (0.1–22.4 wk) for obinutuzumab.

At week 25, CR rate was 0 for TI and 6.7% (2/30 patients; 90% confidence interval [CI], 1.2%–19.5%) for TIO, while overall response rate (ORR) was 60.0% (90% CI, 18.9%–92.4%)
for TI and 93.3% (90% CI, 80.5%–98.8%) for TIO (Table 1). The best percentage change from baseline in sum of the products of greatest perpendicular diameters is depicted in Suppl. Figure S2. Our findings are similar to those for current treatment combinations with BCR inhibitors and/or anti-CD20 antibodies, which achieve consistently low CR rates despite robust ORRs in relapsed/refractory CLL.8

At week 25, in the bone marrow, no patient had uMRD by flow. In peripheral blood, 2 patients (6.7%) on TIO had uMRD at week 25. The best rate of uMRD is presented in Table 1. The course of minimal residual disease (MRD) is depicted in Suppl. Figures S3 and S4. MRD was also assessed in peripheral blood using Next Generation Sequencing (NGS) as an exploratory analysis (Suppl. Figure S5). In the TIO arm, a decrease in MRD was observed for most patients at week 25; however, none had uMRD by NGS with a 10⁻⁶ cutoff. For patients with an additional assessment at the end of treatment or 6 months after, a trend toward further decreases in MRD was observed, but none reached uMRD by NGS. MRD as assessed by flow and NGS correlated (Suppl. Figure S6). For the 2 patients who reached uMRD at week 25 by flow, MRD remained detectable with the more sensitive NGS method.

In peripheral blood, uMRD results improved, particularly for TIO, after the primary endpoint (week 25) increasing from 6.7% to best uMRD of 36.7%. This may indicate that the time point chosen for the primary endpoint was premature. Lack of improvement in CR rates beyond week 25 may be attributable to failure to repeat the computed tomography scan and bone marrow biopsy necessary for CR validation/confirmation. BTK inhibitors in prior studies show CR rates increasing over time and with continuous treatment.10 Additional CD20 antibody administration may increase uMRD rates: MRD in the peripheral blood increased from 47.5% after 6 months with ibrutinib plus obinutuzumab to 71.2% after up to 24 months.11,12 Whether TIO uMRD rates will continue to improve over time and responses will be durable remains to be seen.

In Table 1, progression-free survival (PFS) events were recorded for 1 (20.0%) patient receiving TI due to death and 3 patients (60.0%) due to disease progression; in the TIO arm, there was 1 death (3.3%) and 1 (3.3%) patient with disease progression. Median PFS in the TI arm was 24.9 months (90% CI, 1.5–27.4 mo) and not reached (90% CI, 22.3–not reached) in the TIO arm (Suppl. Figure S7A). The 24-month PFS rates were 60.0% (90% CI, 19.1%–85.4%) for TI and 80.6% (90% CI, 41.1%–94.9%) for

### Table 1

**Response at Week 25 and Best Response Overall**

|                  | All Patients | Week 25 | Best Response |
|------------------|--------------|---------|---------------|
|                  | TI (n = 5)   | TIO (n = 30) | TI (n = 5) | TIO (n = 30) |
| Rate of CR       | 0            | 2 (6.7%) | 0             | 2 (6.7%)     |
| 90% CI          | 0.0–45.1     | 1.2–19.5 | 0.0–45.1      | 1.2–19.5     |
| ORR              | 3 (60.0%)    | 28 (93.3%) | 3 (60.0%) | 28 (93.3%)  |
| 90% CI          | 18.9–92.4    | 80.5–98.8 | 18.9–92.4    | 80.5–98.8    |
| Response        |              |         |               |               |
| CR              | 0            | 2 (6.7%) | 0             | 2 (6.7%)     |
| PR              | 3 (60.0%)    | 26 (86.7%) | 3 (60.0%) | 26 (86.7%)  |
| PRL             | 0            | 0        | 0             | 0             |
| Nonresponse/missing² | 2 (40.0%) | 2 (6.7%) | 2 (40.0%) | 2 (6.7%)     |
| uMRD <10⁻⁴ CLL cells |              |         |               |               |
| Bone marrow     | 0            | 0        | 0             | 1 (3.3%)     |
| Bone marrow (with CR/CRi) | 0       | 0        | 0             | 0             |
| Peripheral blood| 0            | 2 (6.7%) | 0             | 11 (36.7%)   |
| Peripheral blood (with CR/CRi) | 0     | 0        | 0             | 1 (3.3%)     |
| del17p/mutTP53  | n = 1        | n = 10   | n = 1         | n = 10       |
| ORR              | 1 (100%)     | 9 (90.0%) | 1 (100%)      | 9 (90.0%)    |
| 90% CI          | 5.0–100.0    | 60.6–99.5 | 5.0–100.0    | 60.6–99.5    |
| Response        |              |         |               |               |
| CR              | 0            | 0        | 0             | 0             |
| PR              | 1 (100%)     | 9 (90.0%) | 1 (100%)     | 9 (90.0%)    |
| PRL             | 0            | 1 (10.0%) | 0             | 1 (10.0%)    |
| Nonresponse/missing² | 0       | 0        | 0             | 0             |
| uMRD <10⁻⁴ CLL cells |              |         |               |               |
| Bone marrow     | 0            | 0        | 0             | 1 (10.0%)    |
| Peripheral blood| 0            | 1 (10.0%) | 0             | 4 (40.0%)    |
| IGHV Unmutated  | n = 4        | n = 19   | n = 4         | n = 19       |
| ORR              | 3 (75.0%)    | 18 (94.7%) | 3 (75.0%)   | 18 (94.7%)   |
| 90% CI          | 24.9–98.7    | 77.4–99.7 | 24.9–98.7    | 77.4–99.7    |
| Response        |              |         |               |               |
| CR              | 0            | 1 (5.3%) | 0             | 1 (5.3%)     |
| PR              | 3 (75.0%)    | 17 (89.5%) | 3 (75.0%) | 17 (89.5%)  |
| PRL             | 1 (25.0%)    | 1 (5.3%) | 1 (25.0%)    | 1 (5.3%)     |
| Nonresponse/missing² |              |         |               |               |
| uMRD <10⁻⁴ CLL cells |              |         |               |               |
| Peripheral blood| 0            | 1 (5.3%) | 0             | 6 (31.6%)    |

CI = confidence interval; CLL = chronic lymphocytic leukemia; CR = complete remission; CRi = complete remission with incomplete recovery of bone marrow; ORR = overall response rate; PR = partial remission; PRL = partial remission with lymphocytosis; TI = tirabrutinib + idelalisib; TIO = tirabrutinib + idelalisib + obinutuzumab; uMRD = undetectable minimal residual disease.

²Two-sided CI based on Pearson method.

The proportion of patients who achieved CR, CRi, PR, or PRL.

²Stable disease, progressive disease, nonevaluable, or missing data.
TIO. Median overall survival (OS) was not reached for either arm (Suppl. Figure S7B). The 24-month OS rates were 80.0% (90% CI, 31.4%–95.8%) for TI and 96.7% (90% CI, 83.9%–99.3%) for TIO.

Venetoclax plus rituximab (VR) achieved a CR rate of 27% and an ORR of 93%. Compared to our results, uMRD rate was higher, but the 2-year PFS of both studies was comparable (84.9% [VR] versus 80.6% [TIO]). Venetoclax, ibrutinib, and obinutuzumab showed an ORR of 92% with 12% CRs in relapsed/refractory CLL patients after 8 cycles; at 2 months after cycle 14, ORR was 88% with 40% CRs and a uMRD rate of 50%. In comparison, TIO appears to induce lower CR and uMRD rates. Sequencing of BCR pathway inhibitors and venetoclax is an important consideration, and combination therapies of 2 BCR inhibitors rather than a BTK inhibitor plus venetoclax may spare venetoclax for later treatment lines.

One patient (2.9%) had a treatment-emergent AE (TEAE) leading to dose reduction of tirabrutinib. No patient had a TEAE leading to dose reduction of idelalisib or obinutuzumab. TEAEs leading to drug interruption occurred in 22 of 35 patients (62.9%) for tirabrutinib, in 23 of 35 (65.7%) for idelalisib, and 12 of 30 (40.0%) for obinutuzumab. At data cutoff, 17 of 35 patients (48.6%) were still ongoing, while 11 (31.4%) completed the study. Sixteen patients (45.7%) were still receiving tirabrutinib, including 2 receiving tirabrutinib without idelalisib. Seven patients (20.0%) completed tirabrutinib per protocol. Eight patients (22.9%) prematurely discontinued tirabrutinib for AE; 2 patients died (5.7%), and 2 (5.7%) elected to discontinue. Fourteen of 35 patients (40.0%) were still receiving idelalisib, and 6 (17.1%) completed per protocol. Eleven (31.4%) patients prematurely discontinued idelalisib for AEs; 2 patients died (5.7%), and 2 (5.7%) elected to discontinue. Twenty-eight of 30 patients (93.3%) completed obinutuzumab per protocol; 1 patient (3.3%) did not complete obinutuzumab due to an AE, and the other patient (3.3%) died.

Compared to our findings, ibrutinib’s discontinuation rate at 17 months is 41% and mainly attributed to toxicity. This is consistent with rates reported after longer follow-up. At a median follow-up of 65.3 months, only 41% of patients received more than 4 years of therapy, and only 22% of patients remained on ibrutinib until study closure.

At least 1 TEAE was reported for all patients. A summary of safety information is presented in Table 2. Bleeding was observed in 14 of 35 patients (40%); the majority were grade 1 (12 patients). Infections were reported in 28 of 35 patients (80%)—all were grade 3 or less. No atrial fibrillation, pneumonitis, or Pneumocystis jirovecii pneumonia ( prophylaxis given) were reported. Diarrhea (grade 1/2) occurred in 11 of 35 patients (31.4%). Elevated transaminases occurred in 3 of 35 patients (8.6%). Serious AEs (SAEs) were reported in 3 TI patients (60%) and 11 TIO patients (36.7%). Of these, 9 patients (25.7%) had an SAE that was assessed as related to tirabrutinib, 8 (22.9%) as related to idelalisib, and 5 (16.7%) as related to obinutuzumab. Two patients had a TEAE leading to death: a 63-year-old male receiving TI had a grade 5 acute cardiac failure (related to TI) and a 68-year-old female on TIO had a grade 5 cerebral infarction (assessed unrelated to any study drug).

Both combinations were consistent with the safety profiles of the individual drugs, and no new safety signals emerged. Atrial fibrillation, observed with ibrutinib treatment, and pneumonitis, observed with idelalisib treatment, were not reported in this trial, possibly due to reduced doses and small sample size.

Fixed-duration TIO was efficacious, albeit exhibiting some relevant toxicity, in relapsed/refractory CLL. It will be interesting to see if uMRD rate continues to improve with longer follow-up. Whether the combination of 2 BCR inhibitors advantages over combinations of BCR inhibitors plus B-cell lymphoma 2 inhibitors needs to be studied prospectively.

| TEAEs | TI (n = 5) | TIO (n = 30) | Total (n = 35) |
|-------|-----------|-------------|---------------|
| Neutropenia | 0 | 11 (36.7%) | 11 (31.4%) |
| Fatigue | 1 (20.0%) | 10 (33.3%) | 11 (31.4%) |
| Diarrhea | 2 (40.0%) | 9 (30.0%) | 11 (31.4%) |
| Nasopharyngitis | 0 | 9 (30.0%) | 9 (25.7%) |
| Rash | 0 | 8 (26.7%) | 8 (22.9%) |
| Back pain | 1 (20.0%) | 7 (23.3%) | 8 (22.9%) |
| Nausea | 2 (40.0%) | 6 (20.0%) | 8 (22.9%) |
| Upper respiratory tract infection | 2 (40.0%) | 6 (20.0%) | 8 (22.9%) |
| Thrombocytopenia | 0 | 7 (23.3%) | 7 (20.0%) |
| Chills | 1 (20.0%) | 6 (20.0%) | 7 (20.0%) |
| Hematoma | 1 (20.0%) | 6 (20.0%) | 7 (20.0%) |
| Grade 3–5 TEAE | 4 (80.0%) | 26 (86.7%) | 30 (85.7%) |

Most common TEAEs:

| Occurring in ≥20% of all patients | TI | TIO | Total |
|-----------------------------------|----|----|-------|
| Neutropenia | 0 | 11 (36.7%) | 11 (31.4%) |
| Fatigue | 1 (20.0%) | 10 (33.3%) | 11 (31.4%) |
| Diarrhea | 2 (40.0%) | 9 (30.0%) | 11 (31.4%) |
| Nasopharyngitis | 0 | 9 (30.0%) | 9 (25.7%) |
| Rash | 0 | 8 (26.7%) | 8 (22.9%) |
| Back pain | 1 (20.0%) | 7 (23.3%) | 8 (22.9%) |
| Nausea | 2 (40.0%) | 6 (20.0%) | 8 (22.9%) |
| Upper respiratory tract infection | 2 (40.0%) | 6 (20.0%) | 8 (22.9%) |
| Thrombocytopenia | 0 | 7 (23.3%) | 7 (20.0%) |
| Chills | 1 (20.0%) | 6 (20.0%) | 7 (20.0%) |
| Hematoma | 1 (20.0%) | 6 (20.0%) | 7 (20.0%) |

| Occurring in ≥5% of any treatment group | TI | TIO | Total |
|----------------------------------------|----|----|-------|
| Neutropenia | 0 | 11 (36.7%) | 11 (31.4%) |
| Neutrophil count decreased | 0 | 4 (13.3%) | 4 (11.4%) |
| Hypertension | 0 | 3 (10.0%) | 3 (8.6%) |
| Leukopenia | 0 | 3 (10.0%) | 3 (8.6%) |
| Hepatic enzyme increased | 0 | 2 (6.7%) | 2 (5.7%) |
| Platelet count decreased | 0 | 2 (6.7%) | 2 (5.7%) |
| Rash | 0 | 2 (6.7%) | 2 (5.7%) |
| Thrombocytopenia | 0 | 2 (6.7%) | 2 (5.7%) |
| Aspartate aminotransferase increased | 1 (20.0%) | 1 (3.3%) | 2 (5.7%) |
| Cardiac failure, acute | 1 (20.0%) | 0 | 1 (2.9%) |
| Dermatitis, allergic | 1 (20.0%) | 0 | 1 (2.9%) |
| Nephrolithiasis | 1 (20.0%) | 0 | 1 (2.9%) |
| Oral pustule | 1 (20.0%) | 0 | 1 (2.9%) |
| Ureterolithiasis | 1 (20.0%) | 0 | 1 (2.9%) |

NA = not applicable; TEAE = treatment-emergent adverse event; TI = tirabrutinib + idelalisib; TIO = tirabrutinib + idelalisib + obinutuzumab.

*Most severe TEAE per patient.

**AUTHOR CONTRIBUTIONS**

NK, MH, and BE involved in the conception or design of the work. NK, CP, TD, HH, KUC, UG, JK, AK, ET, KE, AMF, CMW, MR, SS, MH, and BE involved in data collection. NK, DZ, BL, JMJ, NR, PB, and BE involved in data analysis and interpretation. NK, DZ, JMJ, NR, PB, and BE involved in drafting the article. NK, ET, KE, NR, MH, and BE involved in critical revision of the article. All authors involved in final approval of the version to be published.

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