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Letter
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# Efficacy and Safety of the Combination of Tirabrutinib and Entospletinib With or Without Obinutuzumab in Relapsed Chronic Lymphocytic Leukemia

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Targeting the B-cell receptor (BCR) pathway in chronic lymphocytic leukemia (CLL) with novel agents that inhibit Bruton's tyrosine kinase (BTK), such as ibrutinib and acalabrutinib, and those inhibiting the delta isoform of phosphatidylinositol 3-kinase, such as idelalisib, improved outcomes substantially.[1–3] Despite high overall response rates (ORRs) with these agents, complete remissions (CRs) are rare, and treatment is typically continued indefinitely until disease progression. Another potential target in the BCR pathway is spleen tyrosine kinase. Among patients with relapsed/refractory CLL, monotherapy with a selective spleen tyrosine kinase inhibitor, entospletinib, yielded an ORR of 61.0%; in a cohort that previously failed BTK and/or phosphatidylinositol 3-kinase inhibitors, ORR was 32.7%.[4,5] However, responses were mainly partial, and no CRs were reported. Combinations of targeted agents may deepen responses, shorten treatment duration, and possibly reduce dosages, improving tolerability.

Tirabrutinib, a second-generation BTK inhibitor, binds irreversibly and covalently to BTK. In a phase 1 trial, tirabrutinib was well tolerated in relapsed/refractory mature B-cell malignancies.[6] The ORR in the CLL cohort was 96% but most did not attain CR.[6] Among patients with relapsed/refractory CLL, tirabrutinib plus entospletinib proved safe and tolerable in a phase 1b trial, with an ORR of 100%. Most patients did not attain CR, and none achieved undetectable minimal residual disease (uMRD).[7] This phase 2 trial compared combinations of tirabrutinib and entospletinib with and without obinutuzumab (TEO/TE) in relapsed/refractory CLL. Methodology is provided in the Suppl. Information. After 6 patients were enrolled in the TE arm, a protocol amendment directed that all subsequent patients be enrolled in TEO due to low CR rates in the preceding phase 1b trial.[7] A similar phase 2 trial with combinations of tirabrutinib, idelalisib, and obinutuzumab will be reported separately.

Thirty-six patients with relapsed/refractory CLL were enrolled: 6 received TE; 30 received TEO (Suppl. Figure S1). Baseline demographics and characteristics are shown in Suppl. Table S1. Eight patients (22.2%) exhibited a *TP53* mutation, and 1 (2.8%) also exhibited a 17p deletion. Unmutated immunoglobulin heavy chain gene status as an unfavorable prognostic factor was present in 32/36 patients (88.9%).

In the TE arm, median duration of exposure to tirabrutinib was 104.5 (range, 102.1–105.6) weeks and 103.9 (101.9–105.1) to entospletinib. In the TEO arm, median exposure was 103.2 (4.0–105.9) weeks to tirabrutinib, 103.2 (4.0–105.9) to entospletinib, and 20.1 (2.1–35.0) to obinutuzumab.

The primary endpoint of CR at week 25 was not reached by any TE patient but was met by 2 TEO patients (6.7%; 90% confidence interval [CI], 1.2%–19.5%; **Table 1**). At week 25, ORR was 100% for TE (90% CI, 60.7%–100%) and 90.0% for TEO (90% CI, 76.1%–97.2%). The best percentage change

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*The study is registered under the clinicaltrials.gov identifier NCT02983617.*
*Supplemental digital content is available for this article.*

*HemaSphere (2022) 6:4(e692).*
*http://dx.doi.org/10.1097/HS9.0000000000000692.*
*Received: August 20, 2021 / Accepted: January 25, 2022*

**Table 1.**

**Response at Week 25**

| All Patients | TE (n = 6) | TEO (n = 30) |
|---|---|---|
| Rate of CR at week 25 | 0 | 2 (6.7%) |
| 90% CI[a] | 0–39.3% | 1.2%–19.5% |
| Overall response rate at week 25[b] | 6 (100%) | 27 (90.0%) |
| 90% CI[a] | 60.7%–100% | 76.1%–97.2% |
| Response at week 25 | | |
| CR | 0 | 1 (3.3%) |
| CRi | 0 | 1 (3.3%) |
| PR | 5 (83.3%) | 25 (83.3%) |
| PRL | 1 (16.7%) | 0 |
| Nonresponse/missing[c] | 0 | 3 (10.0%) |
| uMRD < $10^{-4}$ CLL cells at week 25 | | |
| Bone marrow | 0 | 1 (3.3%) |
| Bone marrow (with CR/CRi) | 0 | 1 (3.3%) |
| Peripheral blood | 0 | 3 (10.0%) |
| Peripheral blood (with CR/CRi) | 0 | 1 (3.3%) |
| **del17p/mut *TP53*** | **TE (n = 1)** | **TEO (n = 7)** |
| Overall response rate at week 25[b] | 1 (100%) | 6 (85.7%) |
| 90% CI[a] | 5.0%–100% | 47.9%–99.3% |
| Response at week 25 | | |
| CRi | 0 | 1 (14.3%) |
| PR | 1 (100%) | 5 (71.4%) |
| Nonresponse/missing[c] | 0 | 1 (14.3%) |
| uMRD < $10^{-4}$ CLL cells at week 25 | | |
| Bone marrow | 0 | 0 |
| Peripheral blood | 0 | 2 (28.6%) |
| **IgHV unmutated** | **TE (n = 5)** | **TEO (n = 27)** |
| Overall response rate at week 25[b] | 5 (100%) | 24 (88.9%) |
| 90% CI[a] | 54.9%–100% | 73.7%–96.9% |
| Response at week 25 | | |
| CR | 0 | 1 (3.7%) |
| PR | 4 (80.0%) | 23 (85.2%) |
| PRL | 1 (20.0%) | 0 |
| Nonresponse/missing[c] | 0 | 3 (11.1%) |
| uMRD < $10^{-4}$ CLL cells at week 25 | | |
| Bone marrow | 0 | 1 (3.7%) |
| Peripheral blood | 0 | 2 (7.4%) |

Data shown as n (%) unless otherwise indicated.

[a]Two-sided CI based on Clopper-Pearson method.

[b]Overall response rate based on sum of pts who achieved CR, CRi, PR, PRL, and nPR throughout the entire study duration.

[c]Stable disease, progressive disease, nonevaluable, or missing data.

CI = confidence interval; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with incomplete recovery of bone marrow; IgHV = immunoglobulin heavy chain gene; MRD = minimal residual disease; nPR = nodular partial response; PR = partial response; PRL = partial response with lymphocytosis; pts = patients; TE = combination of tirabrutinib and entospletinib; TEO = triple combination therapy of tirabrutinib, entospletinib, and obinutuzumab; uMRD = undetectable MRD.

from baseline in the sum of the products of greatest perpendicular diameters is depicted in Suppl. Figure S2.

Previous studies showed that BCR pathway-inhibitor monotherapy induces low CR rates despite good ORRs.[3,8,9] The addition of obinutuzumab to frontline therapy with acalabrutinib showed increased CR rates compared with acalabrutininb monotherapy in prior treatment-naïve CLL.[2] Idelalisib and rituximab achieved an ORR of 81% without CR in relapsed/refractory CLL.[3] In contrast to frontline therapy, the combination of zanubrutinib, another next-generation BTK inhibitor, and obinutuzumab achieved an ORR of 92%, including 7 CRs (28%) in patients with relapsed/refractory CLL or small lymphocytic lymphoma after a median follow-up of 29 months.[10] Within the heterogeneous population of the CLL2-BIG trial, the combination of ibrutinib plus obinutuzumab with an optional bendamustine debulking yielded an ORR of 100% with 9.8% CR.[11] These reported CR rates are consistent with those presented here.

At week 25, no patient receiving TE had uMRD by flow cytometry, while 3 (10.0%) and 1 (3.3%) on TEO had uMRD in peripheral blood and bone marrow, respectively. The best rate of uMRD in peripheral blood was 0 for TE and 43.3% for TEO, while best rates of uMRD in bone marrow were 0 and 6.7% for TE and TEO, respectively (Suppl. Table S2). The course of minimal residual disease (MRD) results in bone marrow and peripheral blood for TEO and TE are shown in Suppl. Figures S3 and S4. Five of 13 patients who achieved uMRD in peripheral blood with TEO became MRD positive again afterwards. MRD was also assessed by next-generation sequencing (NGS) in peripheral blood as an exploratory analysis (Suppl. Figure S5). In the TEO arm (n = 29), 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 who had an additional assessment at the end of treatment or 6 months after, further decreases in MRD were observed, with 2 patients reaching uMRD at end of treatment. For 2 of 3 patients who reached uMRD at week 25 by flow cytometry, MRD remained detectable with the more sensitive NGS method (Suppl. Figure S6).

Improved CR and uMRD results have been achieved with combinations including B cell lymphoma-2 (BCL-2) inhibitors. Ibrutinib plus venetoclax showed an ORR of 89% with a CR rate of 51% and a uMRD rate of 53% in blood and 36% in bone marrow after 12 months of therapy.[12] Acalabrutinib plus obinutuzumab resulted in 4 of 22 relapsed/refractory patients who achieved partial response attaining bone marrow MRD negativity at 12 months.[13] Within the CLL2-BIG trial, an increase of uMRD in the peripheral blood from 47.5% at the end of 6 months of induction therapy to 71.2% after up to 24 months of maintenance therapy was observed.[11,14] This observation suggests that primary endpoint evaluation in this trial may have been premature. While MRD rates improved overall beyond week 25, improvement of CR rates could not be detected, since later computerized tomography scan or bone marrow biopsies were not required per protocol. It is possible CR rates may have been higher than observed.

A progression-free survival (PFS) event (disease progression or death, whichever occurred first) was recorded for 1 (16.7%, disease progression) patient who received TE and for 6 (20%) who received TEO (4 disease progressions [1 patient subsequently died] and 2 deaths). These deaths occurred >30 days after treatment ended and were assessed by the investigator as unrelated to study treatment. Median PFS in both arms was not reached (Suppl. Figure S7). The 24-month PFS rate was 100% (90% CI, not estimable [NE]–NE) for TE and 81.4% (64.8%–90.7%) for TEO. Median overall survival was also not reached for either arm; overall survival at month 24 was 100% (NE–NE) for TE and 85.1% (90% CI, 0.69%–93.2%) for TEO (Suppl. Figure S7). The median follow-up time was 25.1 and 24.9 months for TE and TEO, respectively. The estimated PFS at 24 months is comparable to those in the ELEVATE-TN trial, as 24-month PFS was 93% (95% CI, 87%–96%) with acalabrutinib plus obinutuzumab and 87% (81%–92%) with acalabrutinib monotherapy compared to 47% (39%–55%) with chemoimmunotherapy.[2]

All patients reported at least 1 treatment-emergent adverse event (TEAE; **Table 2**). Grade 3–5 TEAEs occurred in 2 patients (33.3%) receiving TE and 22 (73.3%) receiving TEO. Most common grade 3–5 TEAEs reported were neutropenia, urinary tract infections, and anemia. Bleeding was observed in 15 patients (41.7%), of whom 1 (2.8%) had a grade 5 bleeding; all others were grade 3 or less. Infections were reported in 31 patients (86.1%)—all were grade 3 or less. Serious adverse events (SAEs) occurred in 1 patient (16.7%) receiving TE (judged unrelated to treatment) and 15 patients (50.0%) receiving TEO. Of SAEs in the TEO arm, 9 patients (30.0%) had an SAE assessed related to tirabrutinib, while 8 (26.7%) were related to entospletinib, and 4 (13.3%) were related to obinutuzumab. Both combinations demonstrated a safety profile consistent with the individual

**Table 2.**

**Number of Patients With Treatment-emergent Adverse Events**

| | TE (n = 6) | TEO (n = 30) | Total (N = 36) |
|---|---|---|---|
| Serious TEAEs | 1 (16.7%) | 15 (50.0%) | 16 (44.4%) |
| Any TEAEs | 6 (100%) | 30 (100%) | 36 (100%) |
| Grade 2[a] | 4 (66.7%) | 8 (26.7%) | 12 (33.3%) |
| Grade 3[a] | 2 (33.3%) | 9 (30.0%) | 11 (30.6%) |
| Grade 4[a] | 0 | 11 (36.7%) | 11 (30.6%) |
| Grade 5[a] | 0 | 2 (6.7%) | 2 (5.6%) |
| Relatedness of TEAEs | | | |
| Related to tirabrutinib | 3 (50.0%) | 27 (90.0%) | 30 (83.3%) |
| Related to entospletinib | 2 (33.3%) | 26 (86.7%) | 28 (77.8%) |
| Related to obinutuzumab | – | 22 (73.3%) | – |
| Most common TEAEs occurring in ≥20% of all patients | | | |
| Neutropenia | 0 | 14 (46.7%) | 14 (38.9%) |
| Nasopharyngitis | 4 (66.7%) | 10 (33.3%) | 14 (38.9%) |
| Fatigue | 2 (33.3%) | 10 (33.3%) | 12 (33.3%) |
| Pyrexia | 1 (16.7%) | 10 (33.3%) | 11 (30.6%) |
| Nausea | 2 (33.3%) | 9 (30.0%) | 11 (30.6%) |
| Cough | 1 (16.7%) | 9 (30.0%) | 10 (27.8%) |
| Hematoma | 2 (33.3%) | 7 (23.3%) | 9 (25.0%) |
| Constipation | 0 | 8 (26.7%) | 8 (22.2%) |
| Diarrhea | 1 (16.7%) | 7 (23.3%) | 8 (22.2%) |
| Grade 3–5 TEAEs | 2 (33.3%) | 22 (73.3%) | 24 (66.7%) |
| Neutropenia | 0 | 13 (43.3%) | 13 (36.1%) |
| Urinary tract infection | 0 | 3 (10.0%) | 3 (8.3%) |
| Anemia | 1 (16.7%) | 2 (6.7%) | 3 (8.3%) |
| Infusion-related reaction | 0 | 2 (6.7%) | 2 (5.6%) |
| Leukopenia | 0 | 2 (6.7%) | 2 (5.6%) |
| Syncope | 0 | 2 (6.7%) | 2 (5.6%) |
| Benign prostatic hyperplasia | 0 | 1 (3.3%) | 1 (2.8%) |
| Bronchitis | 0 | 1 (3.3%) | 1 (2.8%) |
| Bronchopulmonary aspergillosis | 0 | 1 (3.3%) | 1 (2.8%) |
| Cataract | 0 | 1 (3.3%) | 1 (2.8%) |
| Chills | 0 | 1 (3.3%) | 1 (2.8%) |
| COVID-19 pneumonia | 0 | 1 (3.3%) | 1 (2.8%) |
| Disease progression | 0 | 1 (3.3%) | 1 (2.8%) |
| Headache | 0 | 1 (3.3%) | 1 (2.8%) |
| Hydrocele | 0 | 1 (3.3%) | 1 (2.8%) |
| Hypokalemia | 0 | 1 (3.3%) | 1 (2.8%) |
| Hyponatremia | 0 | 1 (3.3%) | 1 (2.8%) |
| Lipase increased | 0 | 1 (3.3%) | 1 (2.8%) |
| Nasopharyngitis | 0 | 1 (3.3%) | 1 (2.8%) |
| Neutrophil count decreased | 0 | 1 (3.3%) | 1 (2.8%) |
| Peripheral arterial occlusive disease | 0 | 1 (3.3%) | 1 (2.8%) |
| Peritonsillitis | 0 | 1 (3.3%) | 1 (2.8%) |
| Platelet count decreased | 0 | 1 (3.3%) | 1 (2.8%) |
| Pneumonia | 0 | 1 (3.3%) | 1 (2.8%) |
| Subdural hematoma | 0 | 1 (3.3%) | 1 (2.8%) |
| Thrombocytopenia | 0 | 1 (3.3%) | 1 (2.8%) |
| Tracheobronchitis | 0 | 1 (3.3%) | 1 (2.8%) |
| Hypertriglyceridemia | 1 (16.7%) | 0 | 1 (2.8%) |
| Procedural hemorrhage | 1 (16.7%) | 0 | 1 (2.8%) |

Data shown as n (%).

[a]Most severe TEAE per patient.

TE = combination of tirabrutinib and entospletinib; TEAE = treatment-emergent adverse event; TEO = triple combination therapy of tirabrutinib, entospletinib, and obinutuzumab.

components, and no new safety signals emerged. Tirabrutinib continued to demonstrate a lack of cardiac toxicity. We cannot rule out an association of treatment, with 1 case of cardiac arrhythmias causing syncope and death. No other episode of cardiac arrhythmias, including atrial fibrillation, was reported in this trial despite arrhythmia being a known side effect associated with ibrutinib.[15]

No patient had a TEAE leading to dose reduction of tirabrutinib, entospletinib, or obinutuzumab. Eleven (30.6%) discontinued tirabrutinib, and 12 (33.3%) discontinued entospletinib. Seven patients (19.4%) discontinued tirabrutinib and discontinued entospletinib (22.2%) due to TEAEs; 2 patients (5.6%) discontinued both drugs at the investigator's discretion, and 2 discontinued both drugs for progressive disease. One patient (3.3%) discontinued obinutuzumab by patient's decision and 1 for progressive disease. Real-world discontinuation rates of 41% were reported for ibrutinib after 17 months of treatment in mainly relapsed/refractory CLL,[16] suggesting that fixed-duration therapies with a limited time of drug exposure might be more feasible than continuous therapies.

In summary, both TE and TEO were tolerable and demonstrated therapeutic activity, despite low CR rates in patients with relapsed/refractory CLL. Sequencing of therapies is becoming increasingly important; therefore, combining different BCR pathway inhibitors may be of relevance to reserve BCL-2 inhibitors for later in CLL treatment. A longer follow-up is needed for comparing the effectiveness of continuous treatment with time-limited combination therapies.

## AUTHOR CONTRIBUTIONS

Conception or design of the work: Hallek, Eichhorst, Kutsch. Data collection: Kutsch, Pallasch, Tausch, Bohme, Ritgen, Liersch, Wacker, Jacobs, Trappe, Dreger, Fischer, Fink, Stilgenbauer, Hallek, Eichhorst. Data analysis and interpretation: Kutsch, Eichhorst, Zhai, Li, Jürgensmeier, Rajakumaraswamy, Bhargava. Drafting the article: Kutsch, Eichhorst, Zhai, Li, Jürgensmeier, Rajakumaraswamy, Bhargava. Critical revision of the article: Kutsch, Eichhorst, Fischer, Trappe, Stilgenbauer, Rajakumaraswamy, Hallek. Final approval of the version to be published: all authors.

## DISCLOSURES

NK has received research funding and travel support from Gilead Sciences, Inc.; honoraria from AstraZeneca; and travel support from Janssen and Celgene. CP has received honoraria from Astellas; Gilead Sciences, Inc.; and Roche; and has received research funding from Gilead Sciences, Inc.; and Sanofi. ET is part of the speakers bureaus for and has membership in the Board of Directors or advisory committees for AbbVie, Janssen-Cilag, and Roche. VB is a member of the speakers bureau for, has provided consultancy for, and has received honoraria from Roche; Janssen-Cilag; Celgene; AbbVie; Gilead Sciences, Inc.; Novartis; Takeda; BMS; and Pfizer. MR is a member of either the Board of Directors or advisory committees for AbbVie, AstraZeneca, Janssen-Cilag, MSD, and Roche; and has received research funding from AbbVie and Roche. AW is a member of either the Board of Directors or advisory committees for Amgen, BMS, Celgene, Incyte, Janssen, and Roche; and has received research funding from BMS, Celgene, and Janssen. RUT declares institutional grants from Atara and Roche, honoraria for consultancy from Atara, and travel support from AbbVie, AstraZeneca, Atara, Celgene, GSK, Janssen, AstraZeneca, and Roche. PD is a member of the speakers bureau for, provides consulting for, and has received honoraria and research funding from Gilead Sciences, Inc. KF has received honoraria from AbbVie and Roche and travel grants from Roche. A-MF has received research funding from Celgene and honoraria from Janssen. SS is a member of the advisory board for and has received honoraria, research grants, and travel support from AbbVie; Amgen; AstraZeneca; Celgene; Gilead Sciences, Inc.; GSK; Hoffmann-La Roche; Janssen; and Novartis. BL is employed by Gilead Sciences, Inc. SZ, JMJ, and NR are employed by and have equity ownership in Gilead Sciences, Inc. PB is employed by Gilead Sciences, Inc.; and has equity ownership in AVEO Pharmaceuticals; Gilead Sciences, Inc.; and Sanofi. MH has provided consultancy for, is a member of the speakers bureau for, and has received honoraria and research funding from AbbVie; AstraZeneca; Celgene; Gilead Sciences, Inc.; Janssen; and Roche. BFE has received research funding from AbbVie; BeiGene; Gilead Sciences, Inc.; Janssen-Cilag; and Roche Pharma; is part of the speakers bureau for AbbVie; Celgene; Gilead Sciences, Inc.; Janssen-Cilag; Novartis; and Roche Pharma; has received travel support from AbbVie; Celgene; Gilead Sciences, Inc.; Janssen-Cilag; Novartis; and Roche Pharma; and has membership in the Board of Directors or advisory committees for AbbVie; ArQule; AstraZeneca; Celgene; Gilead Sciences,

Inc.; Janssen-Cilag; Novartis; Oxford Biomedica (UK); and Roche Pharma. The remaining authors have no conflicts of interest to disclose.

## SOURCES OF FUNDING

This study was supported by research funding from Gilead Sciences, Inc. Editorial support was provided by Helen Rodgers, PhD, of AlphaScientia, LLC, and was funded by Gilead Sciences, Inc.

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