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CORRESPONDENCE

Continuous venetoclax in treatment-naive *TP53* disrupted patients with chronic lymphocytic leukemia: A chronic lymphocytic leukemia campus study

To the Editor:

Deletion of 17p13 (17p-) and/or *TP53* gene mutation (*TP53*m), collectively defined as *TP53* abnormalities (*TP53* abn), can be found in 8 to 10% of treatment-naive (TN) patients with chronic lymphocytic leukemia (CLL) and in up to 50% of relapsed/refractory cases.[1] In CLL *TP53* disruption is a negative prognostic and predictive biomarker, associated with shorter time to first treatment, karyotype complexity, Richter transformation as well as shorter survival.[2,3] In addition, this adverse genetic feature has been associated with an increased risk of treatment failure in patients treated with continuous BTK inhibitors (BTKi).[4,5]

Fixed duration venetoclax-based therapy, in combination with anti-CD20 monoclonal antibody, is a highly active treatment for TN and relapsed/refractory patients with CLL.[6,7] However, patients with *TP53* abnormalities display shorter measurable residual disease (MRD) doubling time and early relapse after the end of treatment.[6,7] Continuous treatment with BTKi is a valid option in *TP53* disrupted patients, counteracted by a relatively high rate of discontinuation due to adverse events,[8,9] beside second-generation BTK are better tolerated than ibrutinib. In the phase II study investigating venetoclax in TP53-disrupted patients with CLL, only five patients were TN, and 4/5 were remission-free after a median follow-up of 2 years.[10]

The aim of this study is to describe the efficacy and discontinuation rate of continuous venetoclax in TN CLL patients with *TP53* disruption.

Medical charts of patients with CLL from 16 centers belonging to the Italian CLL Campus network were retrospectively reviewed to identify CLL with del(17p) (assessed by FISH, cut-off 10%) and/or *TP53*m by Sanger sequencing of exons 2–11 treated front-line with tcontinuous venetoclax.[11] CLL diagnosis and response assessments were carried out according to the iwCLL guideline. Venetoclax was started with weekly ramp-up phase till 400 mg. Dose reductions were at the treating physician's discretion based on adverse events. MRD was assessed by flow cytometry according to ERIC recommendation as previously described.[12] Cases with $<1 \times 10^{-4}$ CLL events were considered undetectable MRD (uMRD4), as opposed to detectable (dMRD4). dMRD2 means detectable MRD with a threshold of 1×10^{-2}.

The primary endpoint of the study was the rate of treatment discontinuation. Secondary endpoints were overall response rate (ORR, complete remissions, CR, plus complete remissions with incomplete bone marrow recovery, CRi, and partial remissions, PR), progression-free survival (PFS), and overall survival (OS). A comparison with a cohort of 100 TN patients with *TP53* abn treated[8] with ibrutinib was also performed. Adverse events were classified according to the Common Terminology Criteria for adverse events (CTCAE) v5.0 grading. Categorical variables were compared with Fisher's exact or Chi-square test, while continuous variables were with the Mann–Whitney test. Survival curves were compared with the Log-rank test. Statistical analyses were performed with Prism 7. p values <.05 were considered as statistically significant.

Thirty-five TN CLL with TP53 abn were recruited between 2018 till June 2022 (Table S1). The median age was 69 years (range 46–84), median CIRS score was 3 (range 0–14), and 23% had a creatinine clearance <60 mL/min. LDH and β2-microglobulin were increased in almost 40% of patients. Seventy-four percentage of the patients harbored both deletion and mutation of *TP53* gene, 14.3% *TP53* mutation and 11.4% only 17p-; 71% were IGHV unmutated. Ten patients performed stimulated cytogenetic at baseline, nine had a complex (≥3 abnormalities) karyotype, and seven displayed ≥5 chromosomal rearrangements.

According to the tumor lysis syndrome (TLS) risk score,[6] 14% were classified at low-risk, 35% at intermediate-risk and 51% at high-risk. Nineteen patients (54%) were hospitalized during the ramp-up phase while the remaining were managed in the out-patient clinics. No patient developed clinical or biochemical TLS. Eighty-three % of patients were able to reach 400 mg of venetoclax, the remaining reached lower doses due to cytopenia or physician choice.

The best ORR was 86%, including 52% CRs and 34% partial responses PRs (Figure 1A). The median time to CR was 13.9 months (Figure 1F). MRD was assessed in the peripheral blood of 14 patients, achieving uMRD4 in six (43%), dMRD4 in seven (50%), and dMRD2 in one (6%) patient (Figure 1B). Nine patients performed MRD assessed in the bone marrow, showing uMRD4, dMRD4, and dMRD2 in two, five, and one patients, respectively. Two patients had uMRD4 in both compartments, three uMRD4 in the peripheral blood were dMRD4 in the bone marrow.

After a median follow-up of 22 months, nine patients decreased the venetoclax dose, and three discontinued therapy (grade four thrombocytopenia one and Richter transformation two). The cumulative incidence of venetoclax discontinuation at 12 and 24 months was 2.9% (95% CI 0%–57%) and 14% (95% CI 0%–55%) (Figure 1E). The

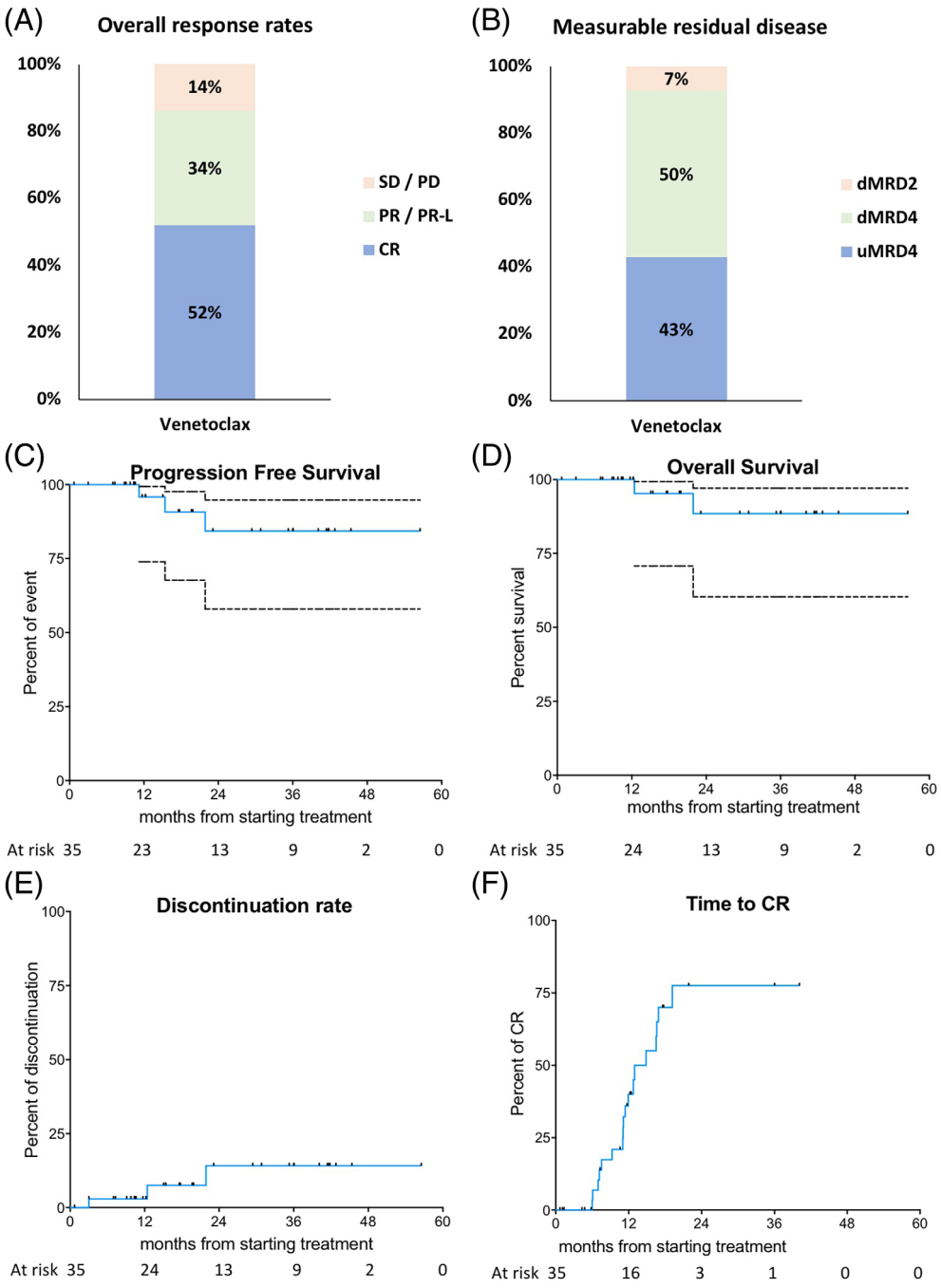

FIGURE 1 Efficacy and survival analysis. The upper panels show the histogram of response rates on the left (A) and measurable residual disease (MRD) rates on the right (B). Middle panels show the Kaplan–Meier curves of progression-free survival on the left (C) and overall survival on the right (D) with 95% confidential interval as dashed lines. In the lower panels, we reported the cumulative incidence of discontinuation rate on the left (E) and time to complete remission on the right (F). CR, complete response; dMRD2, detectable measurable residual diseases with a threshold 10^{-2}; dMRD4, detectable measurable residual diseases with a threshold 10^{-4}; PD, progressive diseases; PR, partial remission; PR-L, partial remission with lymphocytosis; SD, stable diseases; uMRD4, undetectable measurable residual diseases with a threshold 10^{-4}.

median PFS and OS were not reached. The 12-month PFS was 96% (95% CI 84%–99%) and 24 and 48-month PFS were both 84% (95% CI 58–95%), respectively (Figure 1C). All patients were alive after 12 months (95% CI 71–100) and the estimated 24-month OS was 88% (95% CI 60%–97%) (Figure 1D). Additional analyses have been reported in Tables S2 and S3.

Regarding safety, we recorded grade ≥3 (G ≥ 3) adverse events in 23 (67%) patients, including hematological toxicity in 14 (11 neutropenia, 2 anemia, 1 thrombocytopenia), second malignancies in three, diarrhea in three, infections in two and major bleeding in two. Atrial fibrillation occurred in two patients. Immunoglobulin levels remained stable during the treatment (Figure S1A).

Furthermore, we compared the efficacy and discontinuation rate of these venetoclax-treatment patients with a previously published cohort of TN patients with *TP53* abn and treated with ibrutinib at the same institutions ($n = 100$, comparable for the main clinic-biological variables excepting for a lower rate of deleted and mutated cases, median follow-up 24 months, Table S4). We observed a higher CR rate (51% vs. 9%, $p < .0001$), lower incidence of discontinuation (two-year 14% vs. 35%, $p = .0151$), and a trend for a better PFS (two-year 83% vs. 78%, HR 0.36, 95%CI 0.15–0.86, $p = .0812$) in patients receiving venetoclax (Figure S1B–D). Comparing adverse events, we also observed a higher rate of cytopenia with venetoclax (57% vs. 11%, $p < .0001$), in particular, grade ≥three neutropenia was

more common (32% vs. 4%, $p < .0001$), but a lower rate of severe infections occurred (6% vs. 22%, $p = .0386$) (Table S5).

The optimal treatment of CLL patients harboring *TP53* abn has not been identified. The excellent results of continuous BTKis therapy within clinical trials are hampered by a high rate of treatment discontinuation outside of clinical trials, in particular for Ibrutinib. Despite second-generation BTKis, acalabrutinib and zanubrutinib, are better tolerated than ibrutinib in the relapsed patients. In addition, whether a continuous single agent might be better than a double or triple fixed-duration treatment still remains unclear,[7] (Supplementary references S1–S7). The main results from combinational studies have been summarized in Table S4. In addition, the CLL17 trial (NCT04608318) that compares continuous ibrutinib versus fixed duration venetoclax plus obinutuzumab or BTKi, does not include a continuous venetoclax arm. Considering all the limits of an indirect comparison between our retrospective study, which also included young and fit patients, and prospective clinical trials, it seems that with venetoclax single-agent uMRD rate is lower than the one achieved with combination therapies. Conversely, estimated PFS seems better with continuous venetoclax than venetoclax-obinutuzumab, but superimposable lower than venetoclax-BTKis (Table S6). On the other hand, continuous venetoclax might favor the development of *BCL2* mutations or other mechanisms of resistance,[13] that limit its use in further lines of therapy. The main llimitation of this study is its retrospective nature. In order to decrease selection bias, we asked the investigators to include all the patients with *TP53* abn treated frontline with continuous venetoclax as well as all the experienced adverse events. Furthermore, since these patients were managed outside clinical trials most of them were not assessed with bone marrow MRD.

To our knowledge, we report the largest study of continuous venetoclax in TN CLL patients with *TP53* deletion and/or mutation, indicating a high efficacy of venetoclax in this subset of patients, not previously studied systematically in clinical trials. The use of continuous venetoclax in TN CLL patients with *TP53* disruption, though not approved in all countries, deserves further investigation, as it can be an effective alternative option besides BTKI when continuous treatment is deemed beneficial.

AUTHOR CONTRIBUTIONS

Andrea Visentin designed the study, performed the statistical analysis, visited patients, and wrote the article; Francesca Cibien, Candida Vitale, Gianluigi Reda, Alessandro Sanna, Daniela Pietrasanta, Monia Marchetti, Roberta Murru, Massimo Gentile, Gian Matteo Rigolin, Isacco Ferrarini, Lydia Scarfò, Paolo Sportoletti, Lucia Farina, Giulia Proietti, Enrico Derenzini, Alessandro Cellini, Francesco Angotzi, Chiara Adele Cavarretta, Valeria Ruocco, Ivan Zatta provided intellectual inputs and visited patients; Valentina Trimarco performed MRD analysis at Padua hospital; Francesca Romana Mauro, Antonio Cuneo, Robin Foà, Stefano Molica, Marta Coscia, Luca Laurenti, Paolo Ghia, Livio Trentin visited patients, provided intellectual inputs and reviewed the article.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available due to the data protection and lack of consent from the patients. Access to data is strictly limited to the researchers who have obtained permission for data processing.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.