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Continuous treatment with Ibrutinib in 100 untreated patients with *TP53* disrupted chronic lymphocytic leukemia: A real-life campus CLL study

To the Editor:

Disruption of the *TP53* gene, including 17p13 deletion (17p-) and/or *TP53* gene mutation (*TP53*m), can be found in 8%–10% of previously untreated chronic lymphocytic leukemia (CLL) patients and in up to 30%–40% of relapsed/refractory cases.[1] In CLL, TP53 disruption is a negative prognostic and predictive biomarker, associated with genome complexity, early relapse, and shorter survival after chemo-immunotherapy, as well as Richter syndrome (RS) transformation.[1–3] In addition, this adverse genetic feature has been associated with an increased risk of treatment failure in relapsed patients treated with BTK inhibitor[4–6] and with fixed duration venetoclax-based therapy in previously untreated and relapsed/refractory CLL patients.[7,8]

While ibrutinib has been shown to be highly active and able to induce long-lasting remission in CLL with unfavorable features, such as unmutated IGHV status or 11q22-23 deletion,[4] patients with *TP53* disruption were excluded from pivotal frontline trials.[9,10] Recently, the long-term results of two investigator-initiated phase 2 clinical trials with ibrutinib in untreated patients with *TP53* abnormalities support the upfront use of ibrutinib in this aggressive subset of CLL.[11,12]

The aim of this study was to describe the efficacy and the rate of treatment discontinuation rate in treatment-naive (TN) CLL patients harboring *TP53* disruption treated with ibrutinib as continuous therapy in the real-life setting.

Medical charts of CLL patients from 14 centers participating in the Italian CLL campus network were retrospectively reviewed to identify CLL with 17p- (FISH cut-off 10%) and/or *TP53*m (Sanger sequencing, exons 2–11) who received front-line therapy with ibrutinib.[13] Ibrutinib was administrated at 420 mg once a day, or at lower doses in the case of toxicities. The primary endpoint of the study was the discontinuation rate. Secondary endpoints were progression-free survival (PFS), time-to-next treatment (TTNT), and overall survival (OS). Survival after ibrutinib discontinuation was also assessed. CLL diagnosis and response assessment were evaluated

according to the iwCLL 2018 guidelines. The 4-factor and the survival risk scores (SRS) were also calculated.[5,14] Adverse events were classified according to the Common Terminology Criteria for adverse events (CTCAE) v5.0 grading. Statistical analyses were performed with Prism 7. p values < .05 were considered statistically significant.

One hundred TN CLL patients were recruited in this study. Fifty-one patients were male, the median age at the start of ibrutinib was 71 years (range 37–87), including 35 octogenarians, the median CIRS was 4 (range 0–13), 42 had a creatinine clearance <60 mL/min (Table 1). According to the Rai's classification, 27 patients were at stage III and 18 at stage IV. β2-microglobulin was increased in 28 patients. Seventy-seven patients were IGHV unmutated, 33 displayed only 17p-, 22 only *TP*53m, and 45 both 17p- and *TP*53m (Table 1).

The best overall response rate was 79%, including 9% of complete remissions (confirmed by bone marrow biopsy), 46% partial remissions, and 24% partial remissions with lymphocytosis (Table 1, Figure 1A). After a median follow-up of 24 months, 13 patients relapsed, 10 required further therapy, 2 developed an RS transformation, and 8 died (4 infections, 1 melanoma, 1 RS, and 1 sudden death). The median PFS, TTNT, and OS have not been reached. The 12, 24, and 36-month PFS was 91%, 82%, and 75%, respectively. The 12, 24, and 36-month TTNT was 94%, 89%, and 82%. The 12, 24, and 36-month OS was 96%, 92%, and 87% (Figure 1B). A significantly shorter PFS was observed in patients older than 75 years (2-years PFS 69% vs 89%, $p = .0433$), in those with both deletion 17p- and *TP*53m ($p = .0440$) and those who showed no response to ibrutinib (85% vs 66%, $p = .0034$) (Table S1). Predictors for a shorter TTNT and OS were the presence of a double hit *TP*53 disruption ($p = .0233$), and the lack of response to ibrutinib ($p = .0041$). Male gender and CIRS > 6 were also associated with a shorter survival. Interestingly, we observed that the higher 4-factor and SRS scores correlated with PFS, TTNT while the former score was the only one with an impact on OS (Table S1). While serum IgG levels decreased during ibrutinib treatment (8.28 ± 3.99 g/L vs 6.96 ± 3.61 g/L, $p = .0439$) IgA levels increased (1.06 ± 0.85 g/L vs 1.41 ± 0.87 g/L, $p = .0186$), while no differences in the IgM levels were observed (0.52 ± 0.67 g/L vs 0.56 ± 0.65 g/L, $p = .6477$).

Twenty-eight patients discontinued treatment, 20 due to adverse events (8 infections, 5 atrial fibrillations, 4 others, and 3 deaths), 6 due to CLL progression, and 2 because of RS. The cumulative 12- and 24-month rate of ibrutinib discontinuations for the whole cohort was 18% and 32%, respectively (Figure 1C). In particular, it was 17% and 26% due to adverse events, 1% and 5% due to CLL relapse, and 1% and 3% because of RS (Figure 1C). Patients who discontinued ibrutinib due to adverse events had the worse outcome. The median PFS was only 18.6 months for patients who discontinued permanently ibrutinib, while it was not reached for patients who restarted ibrutinib after the resolution of the adverse event ($p < .0001$, Figure 1D). Patients who discontinued ibrutinib permanently due to an adverse event had also a 6-fold higher risk of death compared to patients who continued or restarted ibrutinib after transient interruption. The 2 years OS for patients who discontinued ibrutinib and those who continued/restarted ibrutinib was 76% and 97% (hazard ratio 6.4, 95% CI 4.2–11, $p < .0001$, Figure 1E). After a median observation of 14 months after ibrutinib discontinuation, the estimated median PFS and TTNT were 11 and 20 months, respectively (Figure 1F). The 2 years OS after ibrutinib discontinuation was 66%. Adverse events are summarized in Table S2, 22 infective events (9 grade ≥ 3), 8 atrial fibrillations, and 8 minor bleedings occurred.

Recently, the NIH[12] and the MDACC[11] published updated results of ibrutinib in TN CLL with 17p deletion and/or *TP*53 mutation. Table 1 compares the outcome and the characteristics of patients included in these trials and in the present study. Although our real-world study enrolled much older (71 vs 62 vs 63 years), as well as comorbid patients, the 2 years and the estimated 5 years PFS and OS were similar to those achieved in the clinical trials (Table 1). These findings support the efficacy of ibrutinib in elderly patients with TP53 disruption.[15] In our study, we found a lower best response rate (79% vs 96% vs 97%, Chi-square test $p < .0001$). This is likely related to a shorter follow-up in our study compared to the trials (2 vs 6 vs 6.5 years), since the degree of response with ibrutinib is known to improve over time.[10] Interestingly, we observed that the depth of response did not impact on PFS (Table S1) and, conversely that discontinuation due to adverse events significantly impinge on PFS and OS, suggesting that continuous treatment with ibrutinib might be more relevant rather than disease eradication in *TP*53 disrupted CLL patients. Although cross-trial comparisons are methodologically arguable, it is noteworthy that the venetoclax-based fixed duration therapy, which is known to induce undetectable minimal residual disease, is not associated with more durable remissions. The 3 years PFS with venetoclax-obinutuzumab in TN CLL patients with 17p- ($n = 17$) and TP53m ($n = 25$) is 48.5% and 60.4%, respectively.[8]

Herein, we report the largest real-world study of ibrutinib in TN CLL patients with *TP*53 abnormalities, confirming the efficacy of continuous ibrutinib in unselected patients with this poor prognostic and predictive aberration who are treated in the clinical practice. Our results also highlight the adverse impact of permanent ibrutinib discontinuation in this subset of patients. Furthermore, ibrutinib discontinuation was not uncommon in this elderly population but only a few patients needed further treatments. Inactivation of both *TP*53 genes, that is, 17p- and *TP*53m, as well as high prognostic scores, was associated with early relapses. Whether TN CLL patients with *TP*53 disruption should be treated with continuous BTK inhibitors or with fixed-duration venetoclax-based therapy is unclear and deserves further investigation in randomized clinical trials.

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TABLE 1 Clinico-biological variables of patients in the current and other studies

	Current study ($n = 100$)	Sivina et al. ($n = 27$)	Ahn et al. ($n = 34$)
Age (years)			
Median (range)	71 (37–87)	62 (48–79)	63 (33–82)
Gender			
Male	51%	67%	65%
Female	49%	33%	35%
Stage			
I–II	55%	67%	38%
III	27%	n.a.	n.a.
IV	18%	33%[a]	62%[a]
CIRS			
Median (range)	4 (0–13)	n.a.	n.a.
Creatinine Cl (mL/min)			
Median (range)	63 (15–115)	n.a.	n.a.
β2-microglobulin			
<5 mg/L	72%	41%[b]	62%[b]
≥5 mg/L	28%	59%[b]	38%[b]
IGHV			
U-IGHV	77%	78%	62%
M-IGHV	23%	11%	38%
*TP*53 abn			
17p- only	33%		94%
*TP*53m only	22%	n.a.	5.9%
17p- and *TP*53m	45%		n.a.
Dose maximal			
140 mg	15%	100%	100%
280 mg	12%	0%	0%
420 mg	73%	0%	0%
Best response iwCLL			
CR, PR, PR-L	9%, 46%, 24%	37%, 52%, 7%	30%, 64%, 3%
SD or PD	17%, 4%	4%	0%, 3%
4 Factor score			
1	45%		
2	37%	n.a.	n.a.
3	18%		
Survival risk score			
0	38%		
1–3	49%	n.a.	n.a.
4–5	13%		
2 years			
PFS	82%	>80%	85%
OS	92%	>80%	88%
Estimated 5 years			
PFS	69%	∼65%	70%
OS	87%	∼79%	85%

[a]Includes Rai stage III and IV.
[b]Cut-off value > 3.5 and > 4 mg/mL in the Sivina et al. and Ahn IE et al. studies.

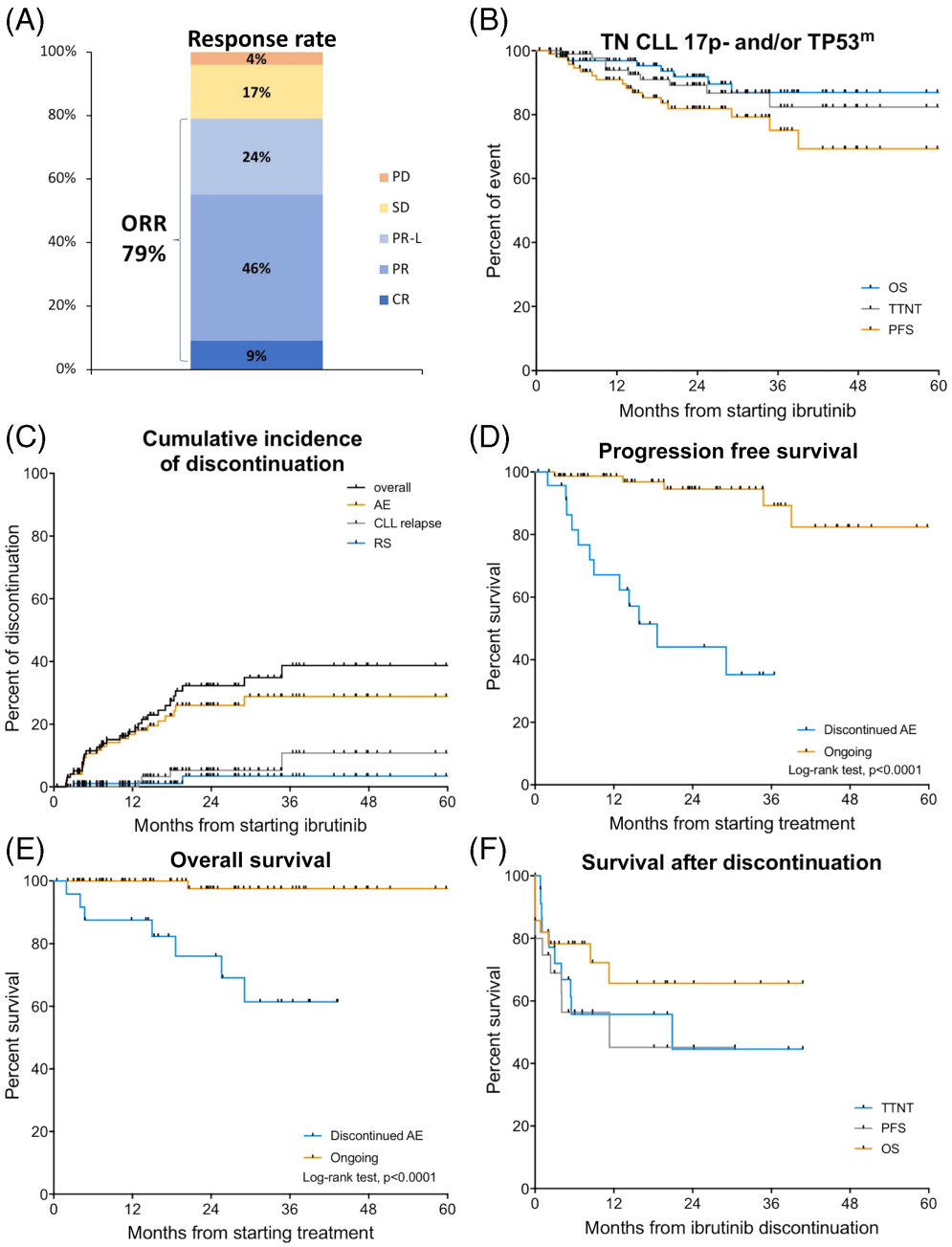

FIGURE 1 Response rate and survival curves of front-line ibrutinib in CLL patients with TP53 abnormalities. (A) histogram response rate. The overall response rate (ORR) was 79%, including 9% complete remissions (CR), 46% partial remissions (PR), and 24% partial remissions with lymphocytosis (PR-L); 17% patients had a stable disease and 4% a progressive disease (PD). (B) progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) for all the 100 CLL patients treated with ibrutinib. (C) cumulative incidence of discontinuation for the whole cohort of 100 patients, for patients who discontinued for adverse events (AE), and for CLL progression or Richter syndrome (RS) transformation. Panels (D) and (E) show PFS and OS of patients who discontinued ibrutinib due to AEs and of those who continued or restarted ibrutinib at resolution of the AEs, respectively. The lower right (F) panel shows PFS, TTNT, and OS after ibrutinib discontinuation

CONFLICT OF INTEREST

AV received honoraria from Janssen, Abbvie, CSL Behring, Italfarmaco. LT received research funding from Gilead, Roche, Janssen and Takeda, advisory board for Roche, Takeda, Abbvie, AstraZeneca. GMR received research funding from Gilead. FRM advisory board for Janssen, Takeda, and Abbvie. AC advisory board and speaker bureau for Roche, Abbvie, Gilead, and Janssen. RF advisory board or speaker bureau for Roche, Abbvie, Celgene, Incyte, Amgen, Janssen, Gilead, and Novartis. LL Honoraria from Abbvie, Janssen, Astra Zeneca, Beigene. FMQ Advisor role for AstraZeneca and Janssen; speaker for Janssen; consultant for Sandoz. LS received honoraria from AbbVie, AstraZeneca, and Janssen.

AUTHORS CONTRIBUTIONS

AC designed the study, performed the statistical analysis, visited patients, and wrote the article; FC, CV, GR, AF, SC, DP, MM, RM, MG, GMR, FMQ, LS, PS, SP, FP provided intellectual inputs and visited patients; FRM, AC, RF, SM, MC, LL, LT visited patients, provided intellectual inputs, and reviewed the article.

DATA AVAILABILITY STATEMENT

The data sets 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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