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ARTICLE

Outcomes and prognostic factors in 3306 patients with relapsed/refractory chronic lymphocytic leukemia treated with ibrutinib outside of clinical trials: A nationwide study

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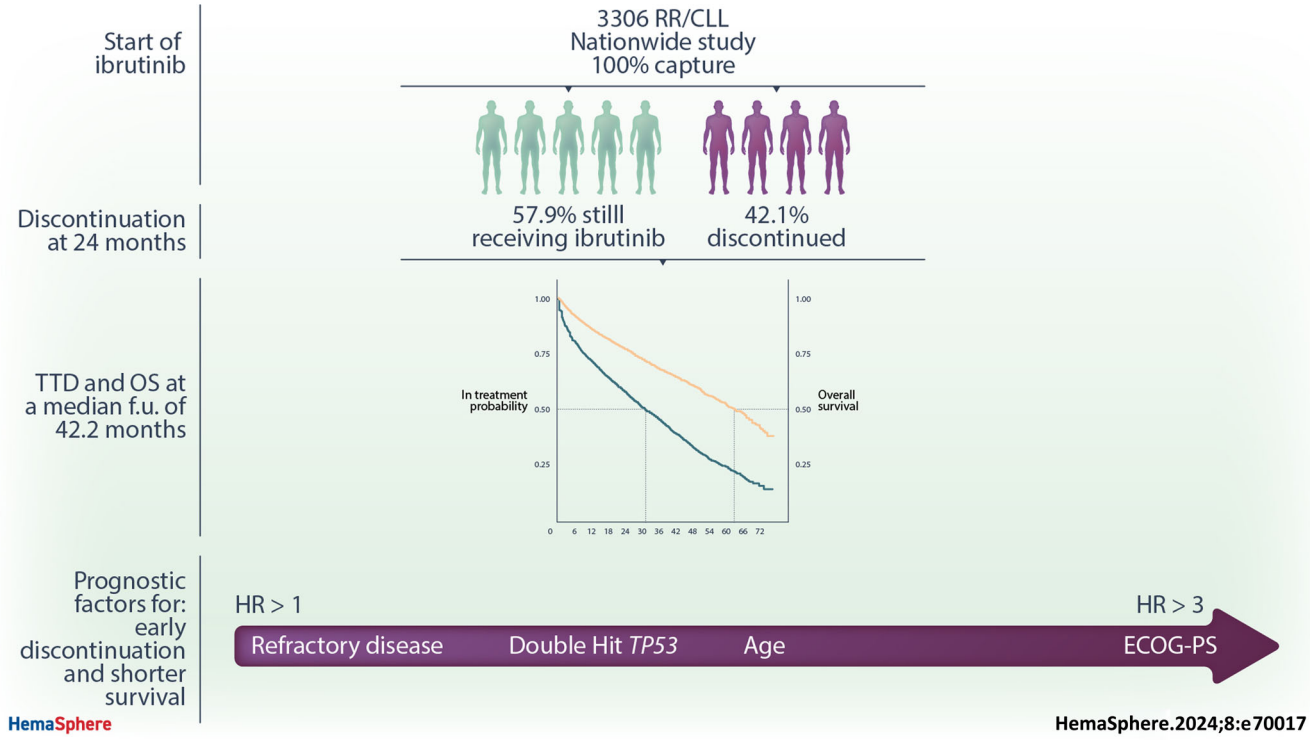
Graphical Abstract



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Outcomes and prognostic factors in 3306 patients with relapsed/refractory chronic lymphocytic leukemia treated with ibrutinib outside of clinical trials: A nationwide study

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Abstract

We performed a cohort study that included all patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) who received ibrutinib in the Italian National Health Service. With a median follow-up of 42.2 months (IQR 30.8–54.6 months), the study involved 3306 patients with a median age of 72.1 years, of whom 42.6% had received ≥2 previous lines of treatment. The estimated 24-month probabilities of being on treatment and alive were 57.9% (95% confidence interval [CI]: 59.6–56.2) and 76.6% (95% CI: 75.2–78.1), respectively. The median time to treatment discontinuation (TTD) was 31.3 months (95% CI: 29.5–33.5). Out of 3306 patients, 2015 (60.9%) discontinued treatment, with 993 cases attributed to death or disease progression (30.0% of all cases). Among the 1022 patients who discontinued treatment for reasons other than progression or death, 564 (17.1%) patients did so due to toxicity or medical decision, while 458 patients (13.8%) were lost to follow-up. Multivariable analysis revealed that age, Eastern Cooperative Oncology Group Performance Status, the number of previous lines of therapy, refractoriness to the last treatment, and reduced renal function were associated with shorter TTD and overall survival (OS). The coexistence of 17p− and *TP53* mutations had an independent unfavorable impact on TTD and OS. Nonstandard doses were associated with shorter TTD and advanced stage with shorter OS. The median OS postprogression and postdiscontinuation for other reasons were estimated at 12.9 (95% CI: 11.3–16.2) and 22.7 months (95% CI: 20.2–28.3), respectively. This large real-world study shows that ibrutinib is an effective treatment for R/R CLL. Baseline patient characteristics and double-hit *TP53* aberrations were associated with inferior prognosis, and discontinuation due to CLL progression portended a poor outcome.

INTRODUCTION

The first-in-class Bruton tyrosine kinase inhibitor (BTKi) ibrutinib is one of the options for the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).[1–3] Long-term follow-up showed prolonged disease control in heavily pretreated patient populations. Median progression-free survival (PFS) of 52 and 44.1 months and median duration of treatment of 39 and 41 months were reported in the Pivotal phase Ib/II PCYC-1102 study and the Resonate phase 3 trial, respectively.[4,5] Nevertheless, ibrutinib administration in a broader patient population with comorbidities, such as those treated in clinical practice, has shown a higher discontinuation rate, mainly due to tolerability issues associated with off-target effects.[6–9]

Real-world evidence (RWE) is an important research tool to obtain relevant clinical information in addition to interventional studies.[10] The Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Working Party (WP) on chronic lymphoproliferative disorders established a

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collaboration with the Italian Medicines Agency (AIFA) to analyze the effectiveness of novel agents outside of clinical trials in patients with CLL included in the AIFA drug registry. The drug registry is an electronic health record that includes all patients treated with a specific medical product within the drug reimbursement framework of the Italian National Health Service (INHSe).

In this analysis, we present and discuss the effectiveness of ibrutinib in a nationwide and unbiased cohort of patients with R/R CLL, with the aim to assess how objective efficacy measures were influenced by patient demographics, performance status (PF), comorbidities, dose reduction, and the presence of 17p deletions and/or *TP53* mutations.

METHODS

Study design and data source

This is a nationwide prospective cohort study that included all patients with R/R CLL treated with ibrutinib in Italy between January 2016 and December 2020.

Data were obtained from the AIFA web platform of Monitoring Registries (wMRs).[11] AIFA wMRs is an administrative database with the main goal of monitoring the appropriateness of drug prescriptions in Italy. Data collected from the database have already been used to monitor the effectiveness and utilization of various drugs in Italy.[12,13]

The inclusion of clinicobiological and administrative data in the wMRS is mandatory for prescribing ibrutinib within the approved indications and under the drug reimbursement framework of the INHSe. This legal requirement has two important implications: (i) all patients were evaluated prior to the start of therapy and then followed during the entire treatment as previously described in detail[13] and (ii) our cohort represents a census of the patients treated with ibrutinib in the reference period and in the approved indication.

The data collected from the wMRS included the following information: (i) demographic and salient clinicobiological data; (ii) drug prescription (one prescription might cover from 30 up to 90 days of treatment); (iii) patient response at selected time points; (iv) end of treatment, with reason for discontinuation; and (v) patient status (alive/dead). The patients included in the registry received information about the purposes of the monitoring. Moreover, to enhance data completeness and improve the quality of our findings, the death dates of patients included in the registry were also obtained from the National Register Office for the Resident Population (ANPR), which is a central database maintained by the Ministry of the Interior of Italy (Decree 82/2005, art. 62).

Procedures

Ibrutinib was administered according to the recommendations reported in the summary of product characteristics (SmPCs). The recommended dose was 420 mg (three tablets) once daily, with dose adjustments to 280 or 140 mg in case of noncardiac/cardiac adverse events or concomitant administration with moderate CYP34A4 inhibitors. The decision to prescribe ibrutinib, as well as the starting dose and any later adjustment, was taken by the single specialist according to the SmPCs, international guidelines, and her/his best clinical judgment.

Ethical statement

According to Decree 196/2003 ("Italian Privacy Code") and Decree 101/2018 ("Harmonization Decree" harmonizing the Italian data protection laws with the provision of the General Data Protection Regulation 679/2016—GDPR), the processing of anonymized data does not require authorization by patients if carried out for public interest or public powers based on a provision of law.

Outcomes

The primary outcomes of the study were time to treatment discontinuation (TTD), time to progression, death and toxicity (TPDT), and overall survival (OS). TTD was defined as the time between the first administration of ibrutinib and the last dose before treatment discontinuation for any reason, including death or loss to follow-up, plus half the days of medication covered by the last prescription (see Supporting Information). Patients who were still undergoing treatment at the time of the data cutoff were censored.

TPDT is defined similarly to TTD, but censoring all patients who discontinued ibrutinib for reasons other than progression, death, or toxicity (PDT). OS was the time between the first administration of ibrutinib and the date of death for any reason. Postprogression OS and postdiscontinuation OS were defined as the time between treatment interruption due to disease progression or due to other reasons and date of death, respectively.

Potential follow-up was calculated for each patient as the time (months) between the first administration of ibrutinib and the data cutoff.

Statistical analysis

Time-to-event analyses (TTD, PDT, and OS) were performed using the Kaplan–Meier estimator. The reverse Kaplan–Meier method was used to estimate the median follow-up time. The impact of various covariates on TTD and OS was evaluated using Cox's proportional hazards models. In this case, proportional hazards assumptions were checked by testing for independence between Schoenfeld residuals and time and through graphical inspection (Supporting Information). Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was found to have a time-dependent coefficient and failed the assumption for both TTD and OS. To address this, we generated an interaction term between ECOG-PS and time, dividing the follow-up into four windows: (0–6), (6–12), (12–24), and (24+) months. Then, we compared ECOG-PS 0 versus 2+ or ECOG-PS 1 versus 2+ in each window. The dose prescribed at each prescription was also included in the TTD models as a time-dependent covariate.[14] Variable selection was performed using a stepwise method.

The association between baseline characteristics and dose reduction/reduced starting dose was evaluated using an AFT model with a log-normal parametrization, providing a direct effect on the log time to dose reduction.[15] This model was chosen because the Cox model's proportional hazards assumption was not met by all covariates and the methodology applied to the TTD and OS Cox models was unable to fix the deviations from the proportional hazards.

To analyze the prognostic impact of 17p deletion or *TP53* mutation alone (single-hit aberration) or the coexistence of these lesions in the same patient (double-hit aberration), we first performed a sensitivity analysis to highlight potential biases in mutational status reporting. All baseline characteristics were compared by means of a logistic regression, between patients with or without a complete set of information on 17p status and *TP53* sequence (Supporting Information). Later, we analyzed the effect of none, single, or double-hit aberration on TTD and OS using Cox proportional hazards models in the subgroup of patients with the complete set of information. Multiple pairwise comparisons between no mutation, 17p deletion,

TP53 mutation, or double-hit aberration were performed using the multcomp R package and Tukey's multiple comparison test.[16]

All statistical analyses were performed using R.[16] Figures were produced using the ggplot2 package.[17] Numerical variables were described using median with first and third quartile ($q1$–$q3$) values, and categorical variables were described using frequencies.

RESULTS

Between January 2016 and December 2020, 3306 patients with R/R CLL were treated with ibrutinib at 215 hematology centers in Italy. All patients have a potential follow-up of at least 16 months, with a median follow-up of 42.2 months (IQR 30.8–54.6 months).

The baseline characteristics are shown in Table 1. The median time from diagnosis was 75.6 months, and the median age was 72.1 years; 90.5% of the patients had an ECOG-PS 0–1 and 42.6% of patients had received two or more previous lines of treatment. Advanced (3–4) Rai stage was reported in 45.3% of the patients, previous atrial fibrillation in 2.8%, and concomitant use of anticoagulants in 3.6%. Among 1808 patients tested (54.7% of the cohort) 27.3% had del(17p) and/or *TP53* mutations.

The starting dose of ibrutinib was 420, 280, and 140 mg in 3134 (94.8%), 127 (3.8%), and 45 (1.4%) patients, respectively. Although 2703 out of 3134 patients (86.2%) maintained the 420 mg full dose prescription every 30–90 days throughout the observation period, 495 patients (15.0%) and 189 patients (5.7%) received at least one prescription for 280 mg and 140 mg, respectively, after a median of exposure to ibrutinib of 10.2 months (IQR 4.1–22.7 months).

With a median follow-up of 42.2 months (IQR 30.8–54.6 months), the median TTD was 31.3 months (95% confidence interval [CI]: 29.5–33.5), with a 57.9% (95% CI: 56.2–59.6) probability of being on treatment at 24 months (Figure 1A). At data cutoff, 1291 (39.1%) patients were still on ibrutinib and 2015 (60.9%) discontinued treatment. Disease progression and death were the reasons for discontinuation in 552 patients (16.7% of all patients) and 441 (13.3%) patients, respectively, whereas patients discontinued treatment because of toxicity in 118 cases (3.6%), or medical/patient decision/other reasons in 446 cases (13.5%), with 458 patients (13.8%) lost at follow-up, as shown in Table 2.

As of the data cutoff, 1205 patients had died, with a median OS of 61.9 months (95% CI: 58.9–66.1) and a 76.6% OS rate at 24 months (95% CI: 75.2–78.1) (Figure 1B). The date of death was misreported for two patients (0.06%), who were excluded from the OS analysis.

Disease progression (552 events), death (441 events), or unacceptable toxicity (118 events) occurring during ibrutinib treatment were recorded in 1111 patients, with a median TPDT of 53.4 months

TABLE 1 Demographic and baseline characteristics in 3306 patients with R/R CLL.

	N (%)
Median time from diagnosis (IQR)	75.6 (39.8–122.4)
Age (years)	
Median (range)	72.1 (29.6–95.4)
<65/65–69/≥70 years	832 (25.2)/518 (15.6)/1956 (59.2)
Male/female	2134 (64.6)/1172 (35.4)
Rai stage 0/1/2/3/4	249 (7.5)/648 (19.6)/912 (27.6)/722 (21.8)/775 (23.5)
Bulky disease[a] and/or elevated lymphocyte count and/or severe splenomegaly	
No/yes	1099 (33.2)/2207 (66.8)
ECOG-PS 0/1/2/3/4	1586 (48.0)/1406 (42.5)/292 (8.8)/21 (0.6)/1 (0.1)
Previous lines of therapy[b] 1/2/3/≥4	1899 (57.4)/948 (28.7)/333 (10.1)/125 (3.8)
Duration of response after last treatment	
<6 months/6–12 months/>12 months/refractory	475 (14.4)/495 (15.0)/1896 (57.3)/439 (13.3)
Concomitant use of systemic anticoagulants	
No/yes	3186 (96.4)/120 (3.6)
Pre-existing severe heart disease	
No/yes	3219 (97.4)/87 (2.6)
Renal impairment	
No/yes	3042 (92.0)/264 (8.0)
Liver function	
Impaired/normal	20 (0.6)/3286 (99.4)
Previous atrial fibrillation or flutter	
No/yes	3215 (97.2)/91 (2.8)
del 17p-only/*TP53* mut-only/del 17p an *TP53* mut/no aberration[c]	107 (5.9)/184 (10.2)/203 (11.2)/1314 (72.7)

Abbreviations: CLL, chronic lymphocytic leukemia; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; mut, mutation; R/R, relapsed/refractory.

[a]Bulky disease: Presence of adenopathies with a diameter ≥5 cm.

[b]One missing value.

[c]Data are available in 1808 patients (54.7% of the cohort).

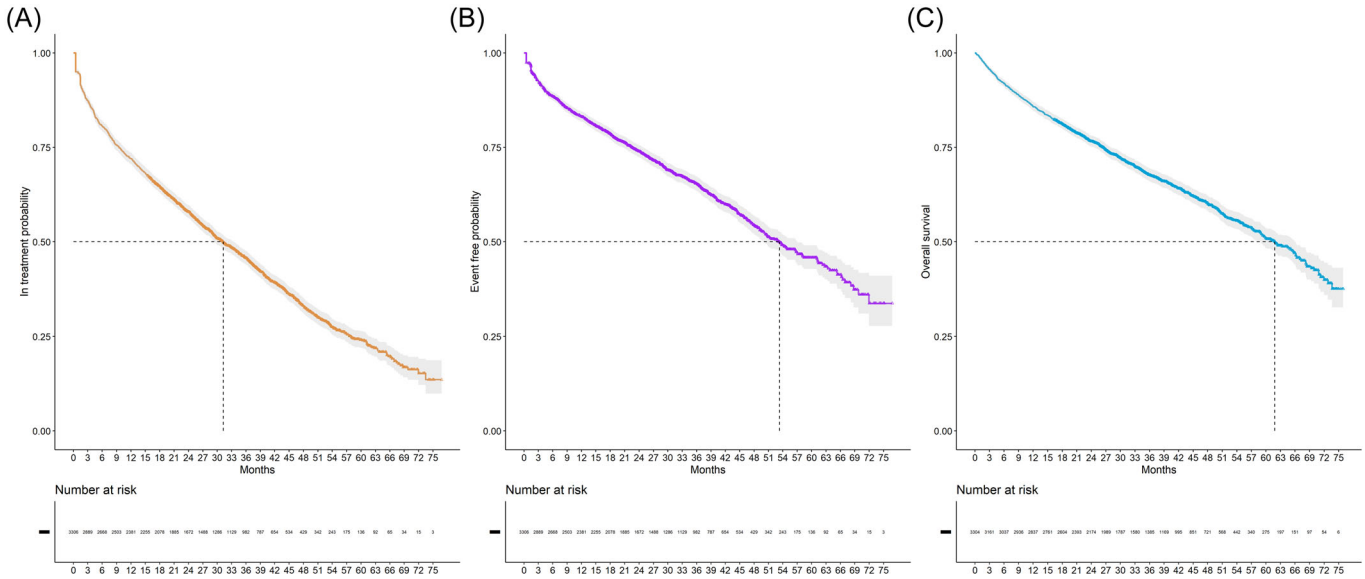

FIGURE 1 (A) Time to treatment discontinuation, (B) time to progression, death, or toxicity, and (C) overall survival.

TABLE 2 Reasons for discontinuation of ibrutinib treatment in 3306 patients.

	No. of patients	%
Discontinuation, yes/no	2015/1291	60.9/39.1
Reasons for discontinuation[a]		
Progression	552	16.7
Death	441	13.3
Toxicity	118	3.6
Medical or patient decision or other	446	13.5
Lost to follow-up	458	13.8

[a]Percentages calculated on the total number of patients (n = 3306).

(95% CI: 50.2–57.0) and a 73.9% probability to be PDT-free at 24 months (95% CI: 72.3–75.6) (Figure 1C).

Multivariable analyses of factors associated with TTD and OS are shown in Tables 3 and 4. Duration of response >12 months after the last line of therapy versus refractory disease had a significant impact on TTD (hazard ratio [HR] 0.75; 95% CI: 0.66–0.85) and OS (HR 0.66; 95% CI: 0.57–0.78), as was the case with the number of previous lines of therapy (Tables 3 and 4). Age ≥70 versus <65 was associated with shorter TTD and OS, while normal renal function had a protective impact on the probability of treatment discontinuation and OS. Though failing proportional hazards assumption (see Supporting Information S1: Tables 1 and 2 and Figures 1 and 2), when ECOG-PS was included in the models as an interaction term with time, it showed a strong impact on TTD and OS during the entire follow-up, with a more pronounced decrease of the risk of discontinuation or death for ECOG 0 or 1 versus 2+ in the first 6 months of follow-up (Tables 3 and 4).

The prescribed dose of ibrutinib was included in the model as a time-dependent variable. In particular, 280 or 140 mg were compared with 420 mg considering the entire length of the treatment. We observed a 43% (95% CI: 9%–89%) and 29% (95% CI: 9%–53%) increase in the risk of discontinuation for 140 and 240 mg, respectively, compared to the recommended dose. When analyzing the association between dose reduction or reduced starting dose with baseline characteristics using the accelerated failure time (AFT) model, a significant association (Supporting Information S1: Table 3) was observed between a decreased time to dose reduction and age ≥70 versus <65 years (86% time decrease; time ratio [TR] 0.14; 95% CI: 0.08–0.25), Rai stage 3–4 versus 0–2 (52% time decrease; TR 0.48 95% CI: 0.32–0.73), ECOG 1 versus 0 (54% time decrease; TR 0.46 95% CI: 0.29–0.71), ECOG 2 versus 0 (83% time decrease; TR 0.17 95% CI: 0.09–0.35), and duration of response 6–12 months versus >12 months (67% time decrease TR 0.33 95% CI: 0.19–0.57).

An advanced (3–4) Rai stage was associated with shorter OS (HR 1.17; 95% CI: 1.04–1.31). The median OS in patients who discontinued ibrutinib due to disease progression was 12.9 months (95% CI: 11.3–16.2), with a 24-month OS probability of 35.2% (95% CI: 30.7–40.4) (Figure 2A). The median OS in patients who discontinued the study drug for toxicity or other reasons was 22.7 months (95% CI: 20.2–28.3), with a 24-month OS probability of 48.2% (95% CI: 43.8–52.9) (Figure 2B).

The effect of the coexistence of del(17p) and *TP53* mutations (double-hit *TP53* aberrations) compared to having no mutation or either del(17p) or *TP53* mutations alone (single-hit) was evaluated on 1808 patients for whom information on both del(17p) and *TP53* were reported. To examine possible differences in the baseline characteristics between patients with and without the two genetic analyses, a logistic regression was performed as a sensitivity analysis. This analysis reported that these 1808 patients were younger and had a better ECOG-PS compared to patients not assessed for del(17p)/*TP53* status (Supporting Infomation S1: Table 4).

Among these 1808 patients, 203 had double-hit *TP53* aberrations with a median TTD of 25.0 months (95% CI: 20.7–29.8), 107 had single del(17p) with a median TTD of 35.4 months (95% CI: 29.0–45.8), and 184 had single *TP53* mutation with a median TTD of 38.1 months (95% CI: 29.8–47.2). The remaining 1314 had no *TP53* aberrations with a median TTD of 36.2 months (95% CI: 33.6–38.5). The median OS for patients with double-hit *TP53* aberrations, del(17p), *TP53* mutation, and those without *TP53* aberrations was 50.4 months (95% CI: 42.7–62.0), 62.5 months (95% CI: 51.6–NA), 61.1

TABLE 3 Multivariable analysis of factors predicting for TTD in 3306 patients.

Characteristics	HRs	LCL	UCL	*p*
Gender	1.07	0.98	1.18	0.1363
Dose 140 vs. 420	1.43	1.09	1.89	0.0100
Dose 280 vs. 420	1.29	1.09	1.53	0.0025
Age 65–69 vs. 64–	1.05	0.90	1.22	0.5116
Age 70+ vs. 64–	1.52	1.36	1.71	<0.001
Previous lines 2 vs. 1	1.09	0.99	1.21	0.0853
Previous lines 3 vs. 1	1.15	1.00	1.33	0.0576
Previous lines 4+ vs. 1	1.26	1.02	1.56	0.0352
Duration of response <6 months vs. refractory disease	0.90	0.77	1.05	0.1842
Duration of response 6–12 months vs. refractory disease	0.86	0.74	1.00	0.0534
Duration of response >12 months vs. refractory disease	0.75	0.66	0.85	<0.001
Kidney function normal vs. impaired	0.81	0.69	0.95	0.0087
ECOG 1 vs. 0 0–6 months	1.52	1.27	1.81	<0.001
ECOG 2+ vs. 0 0–6 months	2.81	2.24	3.53	<0.001
ECOG 1 vs. 0 6–12 months	1.30	1.02	1.66	0.0372
ECOG 2+ vs. 0 6–12 months	1.47	0.98	2.20	0.0649
ECOG 1 vs. 0 12–24 months	1.18	0.96	1.44	0.1110
ECOG 2+ vs. 0 12–24 months	2.02	1.50	2.73	<0.001
ECOG 1 vs. 0 24+ months	1.08	0.92	1.27	0.3584
ECOG 2+ vs. 0 24+ months	1.72	1.28	2.30	<0.001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LCL, 95% low confidential limit; TTD, time to treatment discontinuation; UCL, 95% up confidential limit.

TABLE 4 Multivariable analysis of factors predicting for OS in 3306 patients.

Characteristics	HRs	LCL	UCL	*p*
Gender	1.12	0.99	1.26	0.0678
Age 65–69 vs. 64–	1.22	0.99	1.52	0.0681
Age 70+ vs. 64–	2.10	1.79	2.47	<0.001
Rai 3–4 vs. 0-2	1.17	1.04	1.31	0.0073
Previous lines 2 vs. 1	1.23	1.08	1.40	0.0014
Previous lines 3 vs. 1	1.39	1.16	1.66	<0.001
Previous lines 4+ vs. 1	1.47	1.13	1.90	0.0036
Duration of response <6 months vs. refractory disease	0.87	0.72	1.06	0.1581
Duration of response 6–12 months vs. refractory disease	0.92	0.76	1.11	0.3758
Duration of response >12 months vs. refractory disease	0.66	0.57	0.78	<0.001
Kidney function normal vs. impaired	0.77	0.63	0.93	0.0075
ECOG 1 vs. 0 0–6 months	1.86	1.39	2.49	<0.001
ECOG 2+ vs. 0 0–6 months	3.87	2.75	5.44	<0.001
ECOG 1 vs. 0 6–12 months	1.89	1.38	2.59	<0.001
ECOG 2+ vs. 0 6–12 months	2.17	1.38	3.41	<0.001
ECOG 1 vs. 0 12–24 months	1.45	1.13	1.86	0.0037
ECOG 2+ vs. 0 12–24 months	1.79	1.23	2.60	0.0024
ECOG 1 vs. 0 24+ months	1.19	0.98	1.46	0.0831
ECOG 2+ vs. 0 24+ months	1.85	1.37	2.50	<0.001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LCL, 95% low confidential limit; OS, overall survival; UCL, 95% up confidential limit.

months (52.6–NA), and 69.4 months (95% CI: 65.8–NA), respectively. The median OS for patients without a full set of data on *TP53* aberrations was 54.9 months (95% CI: 51.2–63.4).

As shown in Tables 5 and 6, single *TP53* aberrations had no impact on TTD and OS compared with patients without, whereas the coexistence of del(17p) and *TP53* mutations had an independent unfavorable impact on TTD and OS, as was the case with older age, ECOG-PS, and refractoriness to previous therapy. Male sex and the number of previous lines of therapy had an impact on OS. Supporting Information S1: Tables 5 and 6 report the pairwise comparison between no mutations, single-hit aberration, or double-hit aberrations. After adjusting using Tukey's multiple comparison tests, double-hit aberrations were also found to be significantly associated with an increased risk of treatment discontinuation compared to single-hit *TP53* aberrations. Similar results were also obtained for OS but with larger standard errors ($p = 0.077$).

Finally, we also evaluated whether the study findings, which included the COVID pandemic period, could be influenced by a change in patient characteristics. Supporting Information S1: Figure 3 shows the proportion of patients treated with ibrutinib in the R/R setting according to year of treatment start, as well as baseline characteristics mostly associated with discontinuation and death (age class, ECOG-PS class, RAI class, previous lines of therapy, duration of response after last treatment, and renal function). Changes were particularly observed in patients treated in 2019 and 2020. However, the generalizability of the results is not significantly affected by these trends, as the risk determinants appear largely unmodified. As part of sensitivity analysis, we performed the same Cox models used to generate Tables 3 and 4, excluding all patients treated in 2019 and 2020 (total patients included in the models: 1687). In Supporting Information S1: Tables 7 and 8, the HRs from both the sensitivity and main analyses point to similar directions and values, although confidence intervals are larger as a result of the decrease in the number of patients included in the models.

DISCUSSION

This nationwide study of 3306 patients with R/R CLL who received ibrutinib in the day-to-day clinical practice after its marketing authorization represents the largest series hitherto reported (Table 7). This cohort has the unique advantage of having a 100% capture rate of patients who were treated with the drug in our country. However, caution should be exercised when analyzing this data, as with any RWD series, due to the intrinsic treatment selection in routine clinical practice, which is based on individual baseline patient characteristics and individual physician's choice.[32] Notably, ibrutinib was the only targeted agent reimbursed by the INHSe for R/R CLL until the beginning of 2020, when approval was granted for the venetoclax and rituximab regimen. Indeed, venetoclax in monotherapy has been available since 2017, but only for patients not eligible to or with a disease that have failed BTKi treatment. When considering the study period, we observed changes in the types of treated patients that may be accounted for by several reasons including differences in the available therapeutic alternatives, increased confidence of prescribers

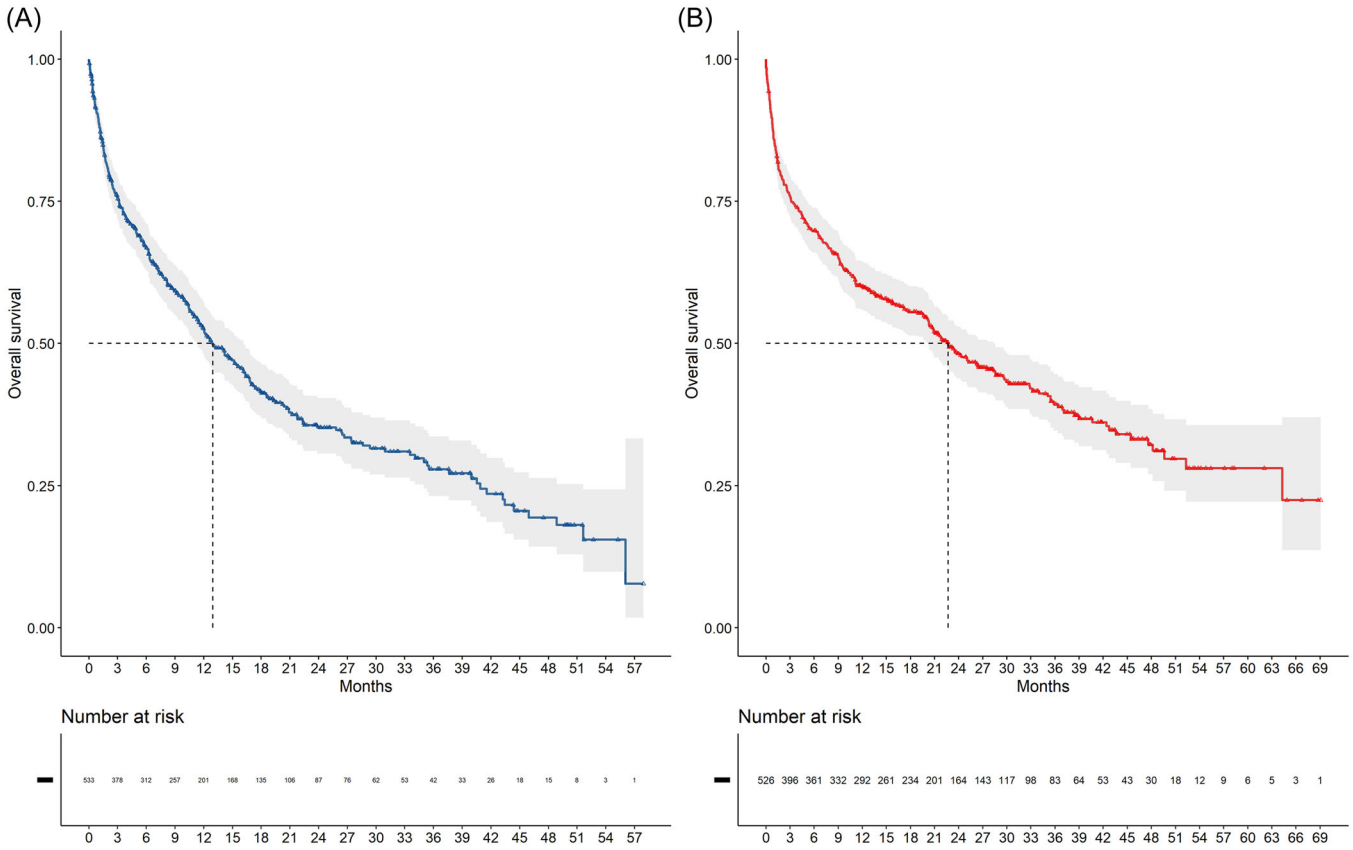

FIGURE 2 **(A) Overall survival postprogression and (B) postdiscontinuation for reasons different from progression.**

with the drug, COVID pandemic, and application of guidelines and recommendations. However, the generalizability of the study was not significantly affected by these trends.

Keeping in mind the limitations of data registry analysis, we adopted two robust outcomes: TTD and OS for our evaluation, and we were able to analyze this cohort with a minimum potential follow-up of 16 months and a 42.2-month median follow-up after treatment initiation, the longest so far reported in real-world studies.

The median TTD of 31.3 months recorded in our analysis and the estimated 24-month discontinuation rate of 42.1% show that ibrutinib was able to produce prolonged disease control in a cohort of patients with R/R CLL with a median age of 72 years and who received more than one previous lines of therapy in 42.6% of the cases. These data, along with a median OS of 61.9 months (63% OS rate at 24 months), confirm the effectiveness of ibrutinib also in the patients treated in our country.

Interestingly, these data are in line with those reported in clinical trials and show a superior treatment duration as compared with some real-world analyses previously reported (Table 7). Different reimbursement policies and availability of other targeted agents may account for the higher discontinuation rate reported in previous studies performed in other countries both in Europe and in the United States.[6,9,33,34] It is noteworthy that in our country, salvage treatment with other BTK inhibitors or with venetoclax was not available during a large part of the study period; this might explain the low incidence of discontinuations due to unacceptable toxicity in our study (3.6% of all cases and 11.6% of all discontinuation events except disease progression or death). The events of discontinuation due to medical/patient decision or other reasons occurred in 446 patients (13.5% of all cases and 43.6% of discontinuations except disease progression or death) may be accounted for by minor side effects of ibrutinib in a predominantly elderly population with polypharmacy. The registry did not capture the types of adverse events that lead to discontinuation.

This large data set allowed us to identify predictors of treatment duration and OS when using ibrutinib. At multivariable analysis, refractory disease, the number of prior lines of therapy, age, and reduced renal function were independently associated with shorter TTD and OS. Similarly, ECOG-PS, despite its time-dependent variability, showed a strong impact on the primary outcomes of this analysis, especially in the early phases of treatment.

Interestingly, the prescription of a reduced dose of ibrutinib for a period of at least 1–3 months was significantly associated with shorter TTD, suggesting that suboptimal tolerance or compliance with the full dose may identify a subgroup of patients with higher probability of discontinuation who may benefit from close follow-up and switch to another agent.[23,35] It is true that the dose might be reduced as a consequence of toxicity, resulting in a tautological association when analyzing TTD. However, it is important to note that our time-dependent Cox models do not include dose modification as a variable but as a prescribed dose instead. In other words, we consider the dose prescribed to each patient each month, regardless of possible modification. What has been evaluated with respect to TTD is the cohort of patients belonging to a specific "dose group" each month, rather than dose modification. Moreover, we could also provide clinically useful information by quantifying the decreased time to dose reduction in relation to some baseline characteristics including age ≥70 versus <65 years (86% time decrease), RAI stage 3–4 versus 0–2 (52% time decrease), ECOG 1 versus 0 (54% time

TABLE 5 Multivariable analysis of factor predicting for TTD in 1808 patients with 17p− and/or *TP53* mutations or without.

Characteristics	HRs	LCL	UCL	*p*
del (17p) vs. none	1.03	0.80	1.32	0.8476
TP53 vs. none	1.01	0.82	1.24	0.9165
Both vs. none	1.41	1.18	1.68	<0.001
Gender	1.12	0.99	1.28	0.0787
Dose 140 vs. 420	1.46	0.94	2.27	0.0902
Dose 280 vs. 420	1.39	1.09	1.77	0.0081
Age 65–69 vs. 64–	1.17	0.96	1.43	0.1272
Age 70+ vs. 64–	1.52	1.30	1.77	<0.001
Rai 3–4 vs. 0–2	0.91	0.81	1.04	0.1557
ECOG 1 vs. 0	1.19	1.04	1.36	0.0100
ECOG 2+ vs. 0	1.92	1.56	2.37	<0.001
Previous lines 2 vs. 1	1.05	0.91	1.21	0.4672
Previous lines 3 vs. 1	1.18	0.96	1.43	0.1080
Previous lines 4+ vs. 1	1.07	0.77	1.51	0.6776
Duration of response <6 months vs. refractory disease	0.84	0.67	1.06	0.1468
Duration of response 6–12 months vs. refractory disease	0.89	0.71	1.11	0.2871
Duration of response >12 months vs. refractory disease	0.76	0.64	0.91	0.0031
Kidney function normal vs. impaired	0.77	0.61	0.97	0.0267

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LCL, 95% low confidential limit; TTD, time to treatment discontinuation; UCL, 95% up confidential limit.

TABLE 6 Multivariable analysis of factor predicting for OS in 1808 patients with 17p−/*TP53* mutations assessed.

Characteristics	HRs	LCL	UCL	*p*
del (17p) vs. none	1.16	0.82	1.63	0.3997
TP53 vs. none	1.16	0.89	1.52	0.2713
Both vs. none	1.71	1.36	2.14	<0.001
Gender	1.27	1.06	1.51	0.0083
Age 65–69 vs. 64–	1.51	1.12	2.03	0.0067
Age 70+ vs. 64–	2.50	1.98	3.14	<0.001
Rai 3–4 vs. 0–2	1.14	0.97	1.35	0.1183
Previous lines 2 vs. 1	1.34	1.11	1.61	0.0025
Previous lines 3 vs. 1	1.52	1.18	1.96	0.0011
Previous lines 4+ vs. 1	1.34	0.90	2.00	0.1504
Duration of response <6 months vs. refractory disease	0.82	0.61	1.09	0.1744
Duration of response 6–12 months vs. refractory disease	0.96	0.73	1.26	0.7554
Duration of response >12 months vs. refractory disease	0.67	0.53	0.86	0.0012
ECOG 1 vs. 0 0–6 months	1.86	1.23	2.80	0.0031
ECOG 2+ vs. 0 0–6 months	3.24	1.93	5.46	<0.001
ECOG 1 vs. 0 6–12 months	1.86	1.19	2.91	0.0063
ECOG 2+ vs. 0 6–12 months	1.54	0.73	3.25	0.2539
ECOG 1 vs. 0 12–24 months	1.34	0.93	1.95	0.1209
ECOG 2+ vs. 0 12–24 months	2.09	1.22	3.59	0.0074
ECOG 1 vs. 0 24+ months	1.02	0.77	1.35	0.8982
ECOG 2+ vs. 0 24+ months	1.97	1.31	2.95	0.0011

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LCL, 95% low confidential limit; OS, overall survival; UCL, 95% up confidential limit.

decrease), ECOG 2 versus 0 (83% time decrease), and duration of response 6–12 months versus >12 months (67% time decrease).

The prognostic significance of *TP53* aberrations in CLL in the era of targeted agents is under investigation and mixed results were previously reported with ibrutinib regimens. Some studies have observed an inferior outcome,[36–39] and others not.[40,41] In addition, a large study including 720 ibrutinib-treated patients within clinical trials and 84 patients from an independent validation cohort reported a negative prognostic impact of single-hit *TP53* aberrations in treatment-naïve and in previously treated patients.[18]

In our study, we were able to assess the prognostic impact of single-hit versus double-hit *TP53* aberrations in a large cohort of 1808 patients with R/R CLL. Sensitivity analysis found that this population included younger patients with fewer previous lines of treatment compared to patients without records on *TP53* status, a finding that might reflect the policy of offering a thorough genetic assessment in patients for whom a complete prognostication was deemed appropriate. The incidence of single and double-hit *TP53* lesions in our series is lower than was previously reported in other studies that included heavily pretreated patients.[4] It is worth noting that variability across centers in terms of methods and cutoff points for the detection of 17p-deletion and *TP53* mutations might have influenced the incidence of *TP53* abnormalities observed in this analysis. Even though the accuracy of data reported in the wMR has not been subject to external quality control, it is worth noting that the inclusion of available biologic data is a by-law requirement and that most centers that included patients in this study belong to the national GIMEMA research organization.[39] Nonetheless, we observed that the coexistence of del(17p) and *TP53* mutation in 203 patients (11.2%) was associated with significantly shorter TTD and OS as compared with 1314 patients (72.7%) without any aberration. On the contrary, single-hit *TP53* aberrations (107 patients [5.9%] with del (17p) and 184 [10.2%] with *TP53* mutations) had no impact on TTD and OS. In the final analysis of the Resonate trial, a trend toward an inferior PFS was noted in the subset of 38 patients with double-hit *TP53* aberrations as compared with 68 patients with neither del(17p) nor *TP53* mutations. No significant difference in PFS was noted in 63 patients with only del(17p) versus 131 patients without.[5] Taken together, these findings suggest that in R/R CLL, a gene dosage effect may explain the poorer prognosis for patients with double-hit *TP53* aberrations.[19] However, further studies are needed to elucidate the prognostic significance of the size of the 17p−clone, of the variant allele frequency of *TP53* mutations, and specific *TP53* mutations in patients receiving ibrutinib as salvage treatment.

The wMRs allowed us to trace back the outcome of the patients who discontinued ibrutinib due to progression or toxicity, medical/patient decisions, and other reasons. The median OS of 12.9 and 22.7 months observed in our analysis in patients who discontinued ibrutinib due to CLL progression or toxicity/other reasons underlines the importance of further analysis on the subsequent therapy strategies in the different patient subgroups.

In conclusion, this large nationwide survey, the longest RW study, showed that ibrutinib is an effective salvage treatment in R/R CLL. Baseline clinical characteristics, such as age, renal function, ECOG-PS,

TABLE 7 Discontinuations and survival data with ibrutinib in R/R CLL in real-world studies and in clinical trials.

No. of patients	Median age	Median no. of previous lines	% with 17p− or *TP53* mutation	Median follow-up (months)	Discontinuation (months or rate)[a]	Survival (months or rate)	Study and reference
Real-world data							
3306	72.1	1	NA	42	Median 31.3; 42.1% at 24 months	76.6% at 24 months	Present study
315	69	2	34	16	26.3% at 12 months	83.8% at 12 months	UK CLL forum[6]
95	69	3	63	30	49% at 30 months	63% at data cutoff	Sweden[7]
616	60	NR	26	17	41% at data cutoff	≈75% at 24 months[b]	United States[9]
155	70	3	31.4[c]	14.2	52% at data cutoff	77% at 12 months	Dutch[18]
166	72.8	NR	39.6	23.7	42% at data cutoff	76.4% at 24 months	Denmark[19]
171	64	3	24.6	40	43% at data cutoff	65.4% at 48 months	Poland[20]
1126	72	2	NR	NR	Median time on ibrutinib 47 months	NR	Australia and New Zealand[21]
71	79	3	26.2	5	32.4% at study cutoff	91% at 12 months	France[22]
364[d]	72.3	3	NR	7.6	Median 23.4 months	NR	United States[23]
Clinical trials							
85	66	4	33	20.9	36% at study cutoff	83% at 26 months	PCI-32765[24]
101	64	≥4	34	36	47% at 36 months	79% at 30 months	PCYC-1102[25]
195	67	3	51	9.4	13.8% at data cutoff	90% at 12 months	Resonate[26]
				44	54% at data cutoff	74% at 36 months	Resonate[27]
145	64	2	100	27.6	50% at data cutoff	75% at 24 months	Resonate-17[28]
308		3	37	20	25% at data cutoff	NR	OSU[29]
265	65	2	50.9	40.9	41.1% at data cutoff	72.5% at data cutoff	ELEVATE-RR[30]
325	68	1	23	29.6	26.2% at data cutoff	85.3% at data cutoff	ALPINE[31]

Abbreviations: CLL, chronic lymphocytic leukemia; CT, clinical trial; NA, not applicable; NR, not reported; OSU, Ohio State University; R/R, relapsed/refractory; RWD, real-world data.

[a]Unless otherwise reported.

[b]Derived from the overall survival curve.

[c]Available in 55.5% of cases.

[d]Includes 18.1% of patients who received ibrutinib as first-line treatment.

number of previous lines of therapy, dose reductions, and double-hit *TP53* aberrations, independently impact the treatment outcome.

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AUTHOR CONTRIBUTIONS

Gian Matteo Rigolin, Pier Paolo Olimpieri, Paolo Ghia, Antonio Cuneo, and Pierluigi Russo were responsible for designing the study, analyzing data, interpreting results, and writing the manuscript. Pier Paolo Olimpieri, Valentina Summa, and Simone Celant performed statistical analyses. Lydia Scarfò, Maria Pia Ballardini, Antonio Urso, Silvia Gambara, and Francesco Cavazzini contributed to data collection and analysis. All authors provided feedback on the report, reviewed the manuscript for important intellectual content, and approved the final version.

CONFLICT OF INTEREST STATEMENT

Gian Matteo Rigolin received honoraria for participation in the speaker's bureau from Abbvie, AstraZeneca, and Janssen, as well as travel grants from Janssen. Lydia Scarfò received honoraria for advisory board participation from AbbVie, AstraZeneca, BeiGene, and Janssen, as well as travel grants from Beigene and Janssen; she is on the speaker bureau for Octapharma. Antonio Cuneo received honoraria for participation in the speaker's bureau and advisory board from Abbvie, AstraZeneca, Beigene, Janssen, and Lilly. Paolo Ghia received research support from AbbVie, AstraZeneca, BMS, and Janssen and honoraria from AbbVie, AstraZeneca, BeiGene, BMS, Janssen, Lilly/Loxo Oncology, MSD, and Roche, and is an editor of *HemaSphere*. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data were obtained from an administrative database and sharing is not applicable due to legal issues. No new data were created in this study.

ETHICS STATEMENT

According to Decree 196/2003 ("Italian Privacy Code") and Decree 101/2018 ("Harmonization Decree" harmonizing the Italian data protection laws with the provision of the General Data Protection Regulation 679/2016—GDPR), the processing of anonymized data does not require authorization by patients if it is carried out for public interest or public powers based on a provision of law.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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