ANTICANCER RESEARCH *40*: 4059-4066 (2020)
doi:10.21873/anticanres.14403

Long-term Efficacy of Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia: Results of the Polish Adult Leukemia Study Group Observational Study

BARTOSZ PULA[1], ELZBIETA ISKIERKA-JAZDZEWSKA[2], MONIKA DLUGOSZ-DANECKA[3], AGNIESZKA SZYMCZYK[4], MAREK HUS[4], AGNIESZKA SZEREMET[5], JOANNA DROZD-SOKOLOWSKA[6], ANNA WASZCZUK-GAJDA[6], JAN M. ZAUCHA[7], JADWIGA HOLOJDA[8], WERONIKA PISZCZEK[9], PAWEL STECKIEWICZ[10], MALGORZATA WOJCIECHOWSKA[11], MICHAL OSOWIECKI[12], WANDA KNOPINSKA-POSLUSZNY[13], MAREK DUDZINSKI[14], DARIA ZAWIRSKA[15], EDYTA SUBOCZ[16], JANUSZ HALKA[16], ANDRZEJ PLUTA[17], RYSZARD WICHARY[18], BEATA KUMIEGA[19], BOZENA K. BUDZISZEWSKA[1], WOJCIECH JURCZAK[3], EWA LECH-MARANDA[20,21], KRZYSZTOF GIANNOPOULOS[22], TADEUSZ ROBAK[2] and KRZYSZTOF JAMROZIAK[1]

[1]Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland;
[2]Department of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland;
[3]Department of Clinical Oncology, Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland;
[4]Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland;
[5]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland;
[6]Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland;
[7]Department of Hematology and Transplantology, Medical University of Gdansk, Gdansk, Poland;
[8]Department of Hematology, Specialist District Hospital, Legnica, Poland;
[9]Department of Hematology, Copernicus Hospital, Torun, Poland;
[10]Department of Hematology, Holycross Cancer Center, Kielce, Poland;
[11]Department of Hematology, Specialist District Hospital, Olsztyn, Poland;
[12]Department of Lymphoid Malignancies, Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland;
[13]Department of Hematology, Independent Public Health Care of the Ministry of the Internal Affairs with the Oncology Centre, Olsztyn, Poland;
[14]Department of Hematology, Specialist District Hospital, Rzeszow, Poland;
[15]Department of Hematology, Jagiellonian University, Krakow, Poland;
[16]Department of Hematology, Military Institute of Medicine, Warsaw, Poland;
[17]Department of Hematological Oncology, Regional Specialist Hospital, Brzozow, Poland;
[18]Department of Hematology and Bone Marrow Transplantation, Katowice Medical Department, Silesian Medical University, Katowice, Poland;
[19]Department of Hematology, Specialist District Hospital, Nowy Sacz, Poland;
[20]Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland;
[21]Department of Hematology and Transfusion Medicine, Centre of Postgraduate Medical Education, Warsaw, Poland;
[22]Department of Experimental Hematooncology, Medical University of Lublin, Lublin, Poland

Correspondence to: Bartosz Puła, MD, Ph.D., Department of Hematology, Institute of Hematology and Transfusion Medicine, Indira Gandhi Str. 14, 02-776 Warsaw, Poland. Tel: +48 223496334, Fax: +48 223496335, e-mail: bartosz.pula@gmail.com

Key Words: Ibrutinib, chronic lymphocytic leukemia, therapy.

Abstract. *Background/Aim: To study the long-term clinical efficacy and tolerability of ibrutinib monotherapy in real-world relapsed and refractory chronic lymphocytic leukemia (RR-CLL) patients outside clinical trials. Patients and Methods: Clinical data of 171 RR-CLL patients treated with ibrutinib were collected within the observational study of the Polish*

Adult Leukemia Study Group. Results: Median patient age was 64 years. Patients were pretreated with 3 (1-10) median lines of therapy, while 42 (24.6%) had 17p deletion. The median observation time was 40 months (range=1-59 months), while median ibrutinib monotherapy reached 37.5 months (range=0.4-59.2 months). Response was noted in 132 (77.2%) patients. The estimated 5-year progression-free survival (PFS) and overall survival (OS) rates were 61.1% (95%CI=49.3-70.9%) and 56.8% (95%CI=45.6-66.6%), respectively. At the time of analysis 97 (56.7%) remained under ibrutinib monotherapy. Conclusion: Ibrutinib is clinically effective and tolerable as a monotherapy in real-world RR-CLL patients.

Chronic lymphocytic leukemia (CLL) is characterized by clonal proliferation and accumulation of mature B-cells co-expressing CD5 and CD23 within the blood, bone marrow and lymphatic organs (1). The disease affects predominantly older people and has a very heterogenous course depending on cytogenetic and molecular risk factors (2-4). The presence of 17p13 deletion (del17p) or point mutations in the *TP53* gene (*TP53*mut) result in loss of p53 protein oncosupressive function and are associated with poor outcome as well as refractoriness to immunochemotherapy based on anti-CD20 monoclonal antibodies (3, 5-10). In addition, such cases are more prone to transform to aggressive high-grade lymphoma (11).

Recent approvals of new anti-CD20 antibodies, ofatumumab and obinutuzumab, have brought modest improvement in treatment outcome, however did not manage to overcome the poor prognosis of patients with p53 abnormalities (4, 12, 13). Development of novel selective inhibitors of the B-cell receptor (BCR) and its downstream signaling kinases *e.g.* Bruton's tyrosine kinase (BTK) led to treatment outcome improvement (1, 4). Ibrutinib (PCI-32765) is an irreversible inhibitor of BTK inhibiting further signal transduction resulting in diminished proliferation and activation, as well as increased apoptosis rate of CLL cells (14, 15). The RESONATE trial (#NCT01578707) showed superiority of ibrutinib over ofatumumab in relation to overall relative response (ORR; 63% *vs.* 4.1%), progression-free survival (PFS) and overall survival (OS) when both compounds were used as monotherapy in relapsed and refractory CLL patients (16). Long-term outcomes were noted also in patients presenting with p53 pathway defects (17, 18). The published updates of the study showed that long-term administration of ibrutinib is safe with only 16% discontinuation rate due to adverse events (17, 18). This and other clinical trials on ibrutinib in relapsed or refractory and treatment-naïve CLL patients have been very promising and resulted in the approval of the compound in USA and EU (16, 17, 19, 20). As patients in clinical trials undergo strict selection criteria, results of randomized clinical trials may not be reliable in relation to real-world data (21). The published analyses of compassionate-use programs may be biased due to treatment of patients mostly within academic centers and to predefined inclusion criteria corresponding to those of clinical trials (22-26). A recent population-based study performed in Netherlands showed that unbiased by patient selection, treatment outcomes of ibrutinib monotherapy were lower than those achieved in clinical trials and compassionate-use programs (27).

Considering the accumulating data relating ibrutinib monotherapy effectiveness and tolerability, we report the updated long-term results of the Polish Adult Leukemia Group (PALG) observational study of ibrutinib compassionate-use program.

Patients and Methods

Study population. Data was acquired by the Polish Adult Leukemia Study Group (PALG) which included most of patients treated within the ibrutinib compassionate-use program in Poland initiated in 2014. The inclusion criteria to compassionate-use program for relapsed or refractory CLL patients in Poland were at least one of the following: a) 17p deletion; b) failure of two or more previous treatments (at least one with a purine analogue such as fludarabine); c) a progression-free interval of less than 24 months following completion of treatment with a nucleoside analogue, or a bendamustine containing regimen in combination with an anti-CD20 monoclonal antibody such as rituximab; d) failure to respond to prior chemotherapy-based treatment, stable disease, or disease progression on treatment and f) ineligibility for treatment or re-treatment with a purine analogue based therapy. The prospective observational study assessing ibrutinib efficacy and toxicity in CLL patients treated in the compassionate-use program was designed by PALG and approved by the Ethics Committee of the Institute of Hematology and Transfusion Medicine in Warsaw. The study was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The findings of the PALG observational study in the group of 165 RR-CLL cases treated with ibrutinib monotherapy for shorter duration of treatment have already been reported (25, 26, 28).

Patients received initially oral ibrutinib 420 mg continuously until progressive disease (PD), unacceptable toxicity or withdrawal of the consent. All analyzed patients, before initiation of therapy, had an absolute neutrophil count of at least 750 cells per microliter and adequate liver and kidney function. Cases with Richter transformation, central nervous system involvement and other serious uncontrolled diseases were excluded (26, 28). The presence of del17p was confirmed by interphase fluorescence in situ hybridization (FISH) using the Vysis CLL FISH Probe Kit (Abbott Molecular, Chicago, IL, USA). Because of limited access to TP53 mutation analysis, such molecular studies were not performed.

First disease assessment with radiological examination was planned after 4 months of ibrutinib treatment. Treatment indications and response assessments were based on the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria and performed by the enrolling physicians (29). The objective response rate was defined as the proportion of patients achieving a complete remission (CR), partial remission (PR) and partial remission with lymphocytosis (PR-L). PFS and OS time were calculated from the date of study entry until progression or death, or death from any

Table I. *Patient clinico-pathological characteristics*.

Parameter	All patients	Del17p patients
Number of patients	171	42
Observation time [median (range); mean±SD] (months)	40.1 [1.0-59.2]; 35.0±17.6	37.2 [1.7-57.5]; 32.3±19.4
Age [median (range); mean±SD] (years)	63 [39-85]; 63.3±9.7	64 [39-85]; 63.5±9.5
Gender (n, %)		
Male	95 (55.6)	23 (54.6)
Female	76 (44.4)	19 (45.4)
Rai classification (n, %)		
0-2	51 (29.8)	9 (21.4)
3-4	118 (69.0)	33 (78.6)
No data	2 (1.2)	0 (0.0)
ECOG performance status (n, %)		
0-1	120 (70.2)	30 (71.4)
2-4	49 (28.6)	12 (28.6)
No data	2 (1.2)	0 (0.0)
Lines of previous treatments [median (range)]	3 [1-10]	3 [1-8]
WBC [median (range); mean±SD] (G/l)	23 [1.6-490]; 59.3±78.7	19.2 [1.6-261]; 52.9±63.9
HGB [median (range); mean±SD] (g/dl)	12.0 [4.0-16.5]; 11.8±2.2	11.6 [7.3-16.2]; 11.6±1.9
PLT [median (range); mean±SD] (G/l)	111 [16-491]; 120±66	106 [16-307]; 116±67
History of autoimmune hemolytic anemia	37 (21.6)	5 (11.9)
History of autoimmune thrombocytopenia	26 (15.2)	5 (11.9)
Previous therapies (n, %)		
Rituximab	148 (86.5)	39 (92.3)
Purine analogs	144 (84.2)	38 (90.5)
Alkylating agents	168 (98.2)	40 (95.2)
Bendamustine	81 (47.4)	21 (50.0)
Anti-CD52	6 (3.5)	5 (11.9)
High-dose methylprednisolone	25 (14.6)	11 (26.2)
Anthracyclines	44 (25.7)	4 (9.5)
Cisplatin	3 (1.8)	1 (2.4)
Idelalisib	6 (3.5)	1 (2.4)
Allogeneic HSCT	1 (0.6)	0 (0.0)

ECOG: Eastern Cooperative Oncology Group; HGB: hemoglobin; HSCT: hematopoietic stem cell transplantation; PLT: platelets; SD: standard deviation; WBC: white blood count.

cause, respectively. Adverse events (AE) during treatment were graded based on the criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events Assessment, version 4.

Statistical analysis. Stata 15 (StataCorp LCC, College Station, TX, USA) was used for statistical analysis. PFS and OS analysis was performed using Kaplan–Meier and the log-rank test. Cox-proportional hazard model was used for multivariate survival analysis. In each case, the hazard ratio (HR) and 95% confidence interval (95%CI) were calculated. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient cohort description. Clinical data of one hundred and seventy-one RR-CLL patients treated with ibrutinib were collected (Table I). Median patient age upon initiation of therapy was 64 years (range=39-85 years). Ninety-five (55.6%) were men. Patients were heavily pretreated with 3 (range=1-10) median lines previous therapy, while 42 (24.6%) patients had confirmed del17p upon FISH analysis (42 out of 86 tested patients at the relapse status). The median observation time was 40 months (range=1-59 months), while ibrutinib monotherapy was administered for a median of 37.5 months (range=0.4-59.2 months). Patients' clinico-pathological data of the whole and the high-risk group with confirmed del17p are summarized in Table I.

Overall response and survival assessment. The best overall response rate (ORR) was 77.2% with 132 patients achieving a response to the treatment. In the analyzed cohort, 30 (17.5%) achieved CR, 62 (36.3%) PR, 40 (23.4%) PR-L, 34 (19.8%) SD and three (1.8%) initial progressions were noted. In two (1.2%) patients no response assessment could be performed. In the high-risk patients with del17p, the ORR was 83.3% and among these 7 (16.6%) achieved CR, 16 (28.1%) PR-L, 12 (28.6%) PR, five (11.9%) SD, one (2.4%) PD. However, in one (2.4%) case response could not be adequately assessed.

Table II. *Univariate and multivariate survival analysis and ibrutinib treatment time in the analyzed patient cohort.*

Parameter	Univariate analysis				Multivariate analysis			
	HR	95%CI		*p*-Value	HR	95%CI		*p*-Value
Progression-free survival (PFS)								
Best response (SD+PD *vs.* CR+PR+PR-L)	3.80	2.24	6.45	<0.001	4.37	2.26	8.45	<0.001
Rai classification (3-4 *vs.* 0-2)	2.15	1.30	3.55	0.003	2.48	1.36	4.50	0.003
Grade 3-4 adverse events (no *vs.* yes)	0.37	0.22	0.60	<0.001	0.56	0.32	1.00	0.050
Progression (yes *vs.* no)	5.40	3.26	8.95	<0.001	4.81	2.66	8.69	<0.001
B symptoms (yes *vs.* no)	1.88	0.99	3.54	0.052	2.10	1.05	4.23	0.037
Hemoglobin value	0.84	0.75	0.93	0.001	0.88	0.75	1.02	0.094
Treatment lines before ibrutinib (≤3 *vs.* >3)	1.14	1.02	1.27	0.021	1.18	1.02	1.35	0.025
Purine analogue treatment (yes *vs.* no)	0.75	0.40	1.41	0.365	0.35	0.16	0.74	0.006
Overall survival (OS)								
Best response (SD+PD *vs.* CR+PR+PR-L)	4.21	2.44	7.29	<0.001	5.63	2.83	11.21	<0.001
Rai classification (3-4 *vs.* 0-2)	2.35	1.39	3.97	0.001	2.31	1.25	4.26	0.007
Grade 3-4 adverse events (no *vs.* yes)	0.34	0.20	0.58	<0.001	0.40	0.22	0.73	0.003
Progression (yes *vs.* no)	3.73	2.19	6.36	<0.001	2.87	1.55	5.31	0.001
B symptoms (yes *vs.* no)	2.30	1.12	4.73	0.023	2.43	1.10	5.38	0.029
Hemoglobin value	0.83	0.75	0.93	0.001	0.85	0.73	0.99	0.032
Treatment lines before ibrutinib (>3 *vs.* ≤3)	1.12	1.00	1.26	0.052	1.18	1.02	1.38	0.029
Purine analogue treatment (yes *vs.* no)	0.72	0.37	1.40	0.337	0.29	0.13	0.65	0.003
Ibrutinib dose reduction (no *vs.* yes)	0.97	0.53	1.75	0.909	0.44	0.22	0.88	0.021
Ibrutinib treatment time								
Best response (SD+PD *vs.* CR+PR+PR-L)	4.16	2.57	6.74	<0.001	4.93	2.74	8.88	<0.001
Rai classification (3-4 *vs.* 0-2)	1.81	1.14	2.89	0.012	1.83	1.04	3.22	0.037
Grade 3-4 adverse events (no *vs.* yes)	0.37	0.23	0.58	<0.001	0.49	0.30	0.81	0.005
Progression (yes *vs.* no)	4.79	3.00	7.64	<0.001	4.42	2.60	7.51	<0.001
B symptoms (yes *vs.* no)	1.81	1.03	3.21	0.041	2.55	1.32	4.94	0.005
Immune thrombocytopenia history (yes *vs.* no)	1.17	0.64	2.13	0.608	0.44	0.19	1.05	0.064
Immune related CLL complications (yes *vs.* no)	1.75	1.09	2.81	0.020	1.95	1.02	3.70	0.042

CLL: Chronic lymphocytic leukemia; CR: complete remission; PR: partial remission; PR-L: partial remission with lymphocytosis; 95%CI: 95% confidence interval.

In the reported observation period, 34 disease progressions were noted in the whole cohort, of which 3 cases were confirmed transformations to Hodgkin lymphoma and 31 CLL progressions (30). The median PFS was not achieved in the whole cohort, however, patients with del17p had a median PFS of 38.9 months. The estimated 4-year PFS rates were 60.9% (95%CI=52.6-68.2%) and 43.2% (95%CI=27.6-57.8%), respectively. At the time of analysis, 54 deaths were recorded; 17 (31.5%) due to disease progression and 35 (68.5%) due to adverse events related and unrelated to administered treatment. These were infection (n=8; 22.9%), ischemic stroke (n=1; 2.8%); sudden cardiac death (n=1; 2.8%), sepsis (n=3; 8.6%), suicide (n=1; 2.8%), disseminated urinary bladder cancer (n=1; 2.8%), unknown (n=7; 20%), pneumonia (n=5; 14.3%), lung cancer (n=2; 5.8%), cardiac insufficiency (n=1; 2.8%), breast cancer (n=1; 2.8%), chronic obstructive pulmonary disease (n=2; 5.8%), multiorgan failure (n=1; 2.8%), gastrointestinal tract bleeding (n=1; 2.8%). The median OS was not achieved in the whole cohort, however, in patients with del17p it reached 52.9 months. The respective 4-year OS rates were 65.4% (95%CI=57.3-72.4%) and 50.1% (95%CI=33.7-64.4%). Results of univariate and multivariate survival analysis regarding parameters influencing patients PFS, OS and ibrutinib treatment time are summarized in Table II. Of the significant factors associated with patient OS were no response (SD+PD; $p<0.001$), advanced Rai stage ($p=0.001$), presence of grade 3-4 AEs ($p<0.001$) and B symptoms ($p=0.023$) as well as lower initial hemoglobin values ($p=0.001$).

Ibrutinib tolerability and adverse events. At the time of analysis, 97 (56.7%) patients remained under ibrutinib monotherapy. The 4-year ibrutinib continuation rate was 55.2% (95%CI=47.0-62.6%) in the whole cohort and 38.6% (95%CI=23.8-53.2%) in the del17p patients.

The most frequent AEs observed during ibrutinib therapy included infections, hypertension, hematological toxicity, diarrhea, atrial fibrillation, hemorrhagic diathesis and rash

(Table III). Overall, 60 patients (35%) had at least one AE grade 3 or 4. Infections of any grade (mainly recurrent upper respiratory tract infections and pneumonia) were diagnosed in 85 patients (49.7%). Pneumonia was the most common high-grade AE with 18 cases (10.5%). New diagnosis of hypertension was observed in 23 patients (13.5%) and in five of them was grade 3. Deterioration in blood pressure control in patients with hypertension diagnosed before therapy with ibrutinib was noticed in 6 patients (3.5%). Atrial fibrillation was observed in 16 patients (9.4%) and in three of them was grade 3. Bleeding-related AEs of any grade occurred in 15 (8.7%) patients. Severe hemorrhagic events were reported in 4 patients (2.3%) including gastrointestinal bleeding (n=2, grade 3), hyphema (n=1, grade 3) and pulmonary hematoma (n=1, grade 3). A rash was observed in 23 patients (13.5%) and all were grade 1 or 2 AEs. Diarrhea was observed in 27 patients (15.8%) that was grade 3 in five patients. Diagnosis of secondary neoplasms during therapy with ibrutinib was noticed in 12 patients (7%).

Most AEs resolved without the need for suspending treatment. However, 56 (32.7%) patients required ibrutinib dose reductions and/or transient treatment interruptions. Dose reduction of ibrutinib was conducted in 46 patients (26.9%), mainly due to infections, hematological toxicity and diarrhea. In thirty-six and 10 of them, were reduced by one and two levels by reducing the dose to 280 mg and 140 mg, respectively. AEs were generally resolved or improved following dose reduction. Twenty-four patients (14%) required treatment interruptions (mainly due to diarrhea and infections).

Therapy with ibrutinib was discontinued in 74 patients (43.3%). The reasons for withdrawal of treatment were progressive disease (33 patients; 19.3%), AEs (30 patients; 17.5%) or other (11 patients; 6.4%). AEs that led to ibrutinib discontinuation included infections (n=15, with 6 cases of pneumonia), organ failure (n=6), secondary neoplasms (n=5), hemorrhagic diarrhea (n=3) and ischemic cerebellar stroke (n=1). Among patients with secondary neoplasms, three were diagnosed with lung cancer and the other two had disseminated urinary bladder cancer and primary peritoneal serous carcinoma. In all but one, discontinuation of therapy with ibrutinib was ordered at the moment of secondary neoplasm diagnosis. One patient with lung cancer was treated with ibrutinib till death due to this malignancy.

Causes of ibrutinib discontinuation other than disease progression or AEs included loss of contact with patient (n=6), patient decision (n=3), allogeneic stem cell transplantation (n=1) and suicide (n=1).

Table III. *Adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) observed during therapy with ibrutinib of patients with relapsed and refractory chronic lymphocytic leukemia.*

Adverse event	Any grade	Grade 3 or 4
Hypertension (new diagnosis or deterioration of blood pressure control)	29 (17.0%)	5 (2.9%)
Recurrent upper respiratory tract infections	28 (16.4%)	3 (1.8%)
Pneumonia	27 (15.8%)	18 (10.5%)
Diarrhea	27 (15.8%)	5 (2.9%)
Rash	23 (13.5%)	0
Atrial fibrillation	16 (9.4%)	3 (1.8%)
Neutropenia	16 (9.4%)	7 (4.1%)
Hemorrhagic diathesis	15 (8.8%)	4 (2.3%)
Urinary tract infection	8 (4.7%)	0
Thrombocytopenia	7 (4.1%)	3 (1.8%)
Zoster	5 (2,9%)	1 (0.6%)
Sinusitis	5 (2,9%)	0
Nausea and vomiting	4 (2.3%)	1 (0.6%)
Sepsis	4 (2.3%)	4 (2.3%)
Herpes	4 (2.3%)	0
Supraventricular arrythmia	3 (1.8%)	0
Arthralgia	3 (1.8%)	0
Heart failure	3 (1.8%)	1 (0.6%)
Mucositis	3 (1.8%)	0
Dizziness	3 (1.8%)	1
Transaminitis	3 (1.8%)	1 (0.6%)
Superficial thrombophlebitis	2 (1.2%)	0
Pyrexia	2 (1.2%)	0
Attention deficit disorder	2 (1.2%)	0
Acute renal failure	2 (1.2%)	1 (0.6%)
Edema	2 (1.2%)	0
Brittle nails	2 (1.2%)	0
Loss of appetite	1 (0.6%)	0
Gastroesophageal reflux disease (GERD)	1 (0.6%)	0
Pleural effusion	1 (0.6%)	0
Neuropathy	1 (0.6%)	0
Facial nerve paralysis	1 (0.6%)	0

Discussion

In the presented cohort of 171 RR-CLL patients, we describe the longest long-term follow-up of ibrutinib efficacy and tolerability among all, to our knowledge, published studies of compassionate-use programs of the compound (22-24, 27, 31). The initial report of compassionate-use of ibrutinib in the PALG cohort consisting of 165 RR-CLL patients showed comparable effectiveness and tolerability of the monotherapy to those presented in other ibrutinib compassionate-use studies (22-24, 26, 31, 32). With a median follow-up of 9.5 months, we reported a 75.9% ORR but the median PFS and OS were not reached. The estimated probability of 12-month PFS and OS rate was 79.7% and 81.1%, that was only marginally lower to that observed in the randomized RESONATE study (16). The initially presented results of the PALG cohort were better in relation to patient survival and the ibrutinib discontinuation rate was comparable to that of a nation-wide retrospective study of ibrutinib treatment in Netherlands (27). In that study, van der Straten *et al*. included all RR-CLL patients treated

with ibrutinib representing therefore a real-world population. This study included an older patient population compared to the data reported in clinical trials and compassionate–use programs of ibrutinib (27).

In this observational study, we report the updated follow-up of our RR-CLL cohort treated with ibrutinib within the compassionate-use program in Poland. With the extended follow-up of 40 months and ibrutinib treatment time reaching a median of 37.5 months the median PFS and OS were not reached in the whole cohort, however patients with del17p had a slightly worse outcome. These patients had a median PFS of 38.9 months that was comparable to that observed in an analogous cohort of the RESONATE trial (median follow-up of 44 months), in which patients with del17p presented with a median PFS of 41.2 months (17). The median OS in patients with this cytogenetic lesion reached 52.9 months confirming the high activity of ibrutinib also in high-risk CLL patients. As data regarding other cytogenetic lesions was not available in our study, further outcome comparisons were therefore not possible.

The PFS rate observed in our study and the RESONATE trial was also comparable, however, we did observe a slightly lower OS rate (4-year 65.4% *vs*. 3-year 74%). Although, a more detailed comparison between these studies was not possible due to patient selection bias and different post-ibrutinib treatment regimens. We, however, noticed some differences in reasons of treatment discontinuation. We observed a higher rate of ibrutinib discontinuation rate (43.3%) than that observed in the RESONATE trial (39%). Additionally, the differences in the reasons for therapy discontinuation varied (17). A significant discontinuation rate in the RESONATE trial was due to disease progression (27%), in which 14 cases of Richter transformations were diagnosed. On the contrary, in our observational study a comparable number of discontinuations were due to disease progression (19.3%; including 3 transformation to Hodgkin lymphoma) and adverse events (17.5%). Although the rate of ibrutinib discontinuation due to adverse events differed, we did not observe a significant difference in the adverse event profile of our patients. Infections were the dominant reason for treatment discontinuation. Furthermore, the adverse event profile was comparable to that reported in other compassionate–use programs and clinical trials (22-24, 26, 31, 32). We hypothesize, however, that minor bleeding incidents were lower than in other studies, as they were reported less frequently by patients and/or treating physicians. Interestingly, multivariate analysis of ibrutinib treatment time identified that positive history of autoimmune hemolytic anemia and autoimmune related complications were associated with increased risk of ibrutinib discontinuation. We did not, however, note occurrence of such complications under ibrutinib therapy in our cohort.

At the time of analysis and ibrutinib compassionate use in Poland, post-ibrutinib treatment options were limited only to chemoimmunotherapy or clinical trials. Venetoclax, which is regarded as treatment of choice in the setting of ibrutinib intolerance or resistance, was not funded at that time and was only available for clinical trials (33, 34). This may partially explain the lower OS rate and patient survival observed in our study in relation to that observed in RESONATE trial (18).

It should be underlined that the observational character of the analysis as well as the relatively modest number of included patients with del17p are important limitations of our study. Furthermore, due to the observational nature of the study, we did not manage to fully characterize our cohort regarding the mutational status of the *IGHV* gene, cytogenetic and molecular risk factors (including the *TP53* mutation status) and assessment of concomitant diseases utilizing the cumulative illness rating scale (CIRS). These assessments could be important in interpreting the spectrum of disease progression types and treatment related adverse events.

Conclusion

This study confirmed the good clinical efficacy and tolerability of ibrutinib monotherapy in real-world RR-CLL patients. Although the outcome of patients with del17p was worse than that observed in other cytogenetic risk groups, ibrutinib monotherapy may result in long-lasting responses. The lower OS rate observed in this study in relation to that reported in RESONATE trial indicates the importance of the availability of effective post-ibrutinib treatment.

Conflicts of Interest

The Authors state that they have no conflicts of interest in regard to this study.

Authors' Contributions

BP, KJ collected and analyzed study data, supervised the study, wrote and revised the manuscript. EIJ gathered and analyzed study data, wrote and revised the manuscript. MDD, AS, MH, ASZ, JDS, AWG, JMZ, JH, WP, PS, MW, MO, WKP, MD, DZ, ES, JH, AP, RW, BK, KB, WJ, ELM, KG and TR collected and analyzed study data. All Authors approved the final manuscript.

Acknowledgements

The Authors express their gratitude to the treating physicians and members of PALG participating in the compassionate-use program of ibrutinib in Poland and in the PALG observational studies.

References

1 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, Hillmen P, Keating M, Montserrat E, Chiorazzi N, Stilgenbauer S, Rai KR, Byrd JC, Eichhorst B,

O'Brien S, Robak T, Seymour JF and Kipps TJ: Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. Blood *131(25)*: 2745-2760, 2018. PMID: 29540348. DOI: 10.1182/blood-2017-09-806398

2 Landau DA, Carter SL, Stojanov P, McKenna A, Stevenson K, Lawrence MS, Sougnez C, Stewart C, Sivachenko A, Wang L, Wan Y, Zhang W, Shukla SA, Vartanov A, Fernandes SM, Saksena G, Cibulskis K, Tesar B, Gabriel S, Hacohen N, Meyerson M, Lander ES, Neuberg D, Brown JR, Getz G and Wu CJ: Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell *152(4)*: 714-726, 2013. PMID: 23415222. DOI: 10.1016/j.cell.2013.01.019

3 Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, Kluth S, Bozic I, Lawrence M, Bottcher S, Carter SL, Cibulskis K, Mertens D, Sougnez CL, Rosenberg M, Hess JM, Edelmann J, Kless S, Kneba M, Ritgen M, Fink A, Fischer K, Gabriel S, Lander ES, Nowak MA, Dohner H, Hallek M, Neuberg D, Getz G, Stilgenbauer S and Wu CJ: Mutations driving CLL and their evolution in progression and relapse. Nature *526(7574)*: 525-530, 2015. PMID: 26466571. DOI: 10.1038/nature15395

4 Jamroziak K, Pula B and Walewski J: Current Treatment of Chronic Lymphocytic Leukemia. Curr Treat Options Oncol *18(1)*: 5, 2017. PMID: 28185174. DOI: 10.1007/s11864-017-0448-2

5 Zenz T, Eichhorst B, Busch R, Denzel T, Habe S, Winkler D, Buhler A, Edelmann J, Bergmann M, Hopfinger G, Hensel M, Hallek M, Dohner H and Stilgenbauer S: TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol *28(29)*: 4473-4479, 2010. PMID: 20697090. DOI: 10.1200/JCO.2009.27.8762

6 Zenz T, Habe S, Denzel T, Mohr J, Winkler D, Buhler A, Sarno A, Groner S, Mertens D, Busch R, Hallek M, Dohner H and Stilgenbauer S: Detailed analysis of p53 pathway defects in fludarabine-refractory chronic lymphocytic leukemia (CLL): dissecting the contribution of 17p deletion, TP53 mutation, p53-p21 dysfunction, and miR34a in a prospective clinical trial. Blood *114(13)*: 2589-2597, 2009. PMID: 19643983. DOI: 10.1182/blood-2009-05-224071

7 Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, Dohner K, Bentz M and Lichter P: Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med *343(26)*: 1910-1916, 2000. PMID: 11136261. DOI: 10.1056/NEJM200012283432602

8 Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grunhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris-Cappio F, Seymour JF, Berrebi A, Jager U, Cazin B, Trneny M, Westermann A, Wendtner CM, Eichhorst BF, Staib P, Buhler A, Winkler D, Zenz T, Bottcher S, Ritgen M, Mendila M, Kneba M, Dohner H and Stilgenbauer S: Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet *376(9747)*: 1164-1174, 2010. PMID: 20888994. DOI: 10.1016/S0140-6736(10)61381-5

9 Strati P, Keating MJ, O'Brien SM, Ferrajoli A, Burger J, Faderl S, Tambaro FP, Jain N and Wierda WG: Outcomes of first-line treatment for chronic lymphocytic leukemia with 17p deletion. Haematologica *99(8)*: 1350-1355, 2014. PMID: 24859876. DOI: 10.3324/haematol.2014.104661

10 Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, Lange E, Koppler H, Kiehl M, Sokler M, Schlag R, Vehling-Kaiser U, Kochling G, Ploger C, Gregor M, Plesner T, Trneny M, Fischer K, Dohner H, Kneba M, Wendtner CM, Klapper W, Kreuzer KA, Stilgenbauer S, Bottcher S and Hallek M: First-line chemoimmunotherapy with bendamustine and rituximab *versus* fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol *17(7)*: 928-942, 2016. PMID: 27216274. DOI: 10.1016/S1470-2045(16)30051-1

11 Pula B, Salomon-Perzynski A, Prochorec-Sobieszek M and Jamroziak K: Immunochemotherapy for Richter syndrome: current insights. Immunotargets Ther *8*: 1-14, 2019. PMID: 30788335. DOI: 10.2147/ITT.S167456

12 Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, Dyer MJ, Padmanabhan S, Piotrowska M, Kozak T, Chan G, Davis R, Losic N, Wilms J, Russell CA and Osterborg A: Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol *28(10)*: 1749-1755, 2010. PMID: 20194866. DOI: 10.1200/JCO.2009.25.3187

13 Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Dohner H, Langerak AW, Ritgen M, Kneba M, Asikanius E, Humphrey K, Wenger M and Hallek M: Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med *370(12)*: 1101-1110, 2014. PMID: 24401022. DOI: 10.1056/NEJMoa1313984

14 Herman SE, Gordon AL, Hertlein E, Ramanunni A, Zhang X, Jaglowski S, Flynn J, Jones J, Blum KA, Buggy JJ, Hamdy A, Johnson AJ and Byrd JC: Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood *117(23)*: 6287-6296, 2011. PMID: 21422473. DOI: 10.1182/blood-2011-01-328484

15 Herman SE, Mustafa RZ, Gyamfi JA, Pittaluga S, Chang S, Chang B, Farooqui M and Wiestner A: Ibrutinib inhibits BCR and NF-kappaB signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. Blood *123(21)*: 3286-3295, 2014. PMID: 24659631. DOI: 10.1182/blood-2014-02-548610

16 Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S, Barr PM, Furman RR, Kipps TJ, Cymbalista F, Pocock C, Thornton P, Caligaris-Cappio F, Robak T, Delgado J, Schuster SJ, Montillo M, Schuh A, de Vos S, Gill D, Bloor A, Dearden C, Moreno C, Jones JJ, Chu AD, Fardis M, McGreivy J, Clow F, James DF and Hillmen P: Ibrutinib *versus* ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med *371(3)*: 213-223, 2014. PMID: 24881631. DOI: 10.1056/NEJMoa1400376

17 Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Barr PM, Furman RR, Kipps TJ, Thornton P, Moreno C, Montillo M, Pagel JM, Burger JA, Woyach JA, Dai S, Vezan R, James DF and Brown JR: Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood *133(19)*: 2031-2042, 2019. PMID: 30842083. DOI: 10.1182/blood-2018-08-8702

18 Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Kipps TJ, Moreno C, Montillo M, Burger JA, Byrd JC, Hillmen P, Dai S,

Szoke A, Dean JP and Woyach JA: Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol *94(12)*: 1353-1363, 2019. PMID: 31512258. DOI: 10.1002/ajh.25638

19 O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, Osterborg A, Siddiqi T, Thirman MJ, Furman RR, Ilhan O, Keating MJ, Call TG, Brown JR, Stevens-Brogan M, Li Y, Clow F, James DF, Chu AD, Hallek M and Stilgenbauer S: Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol *17(10)*: 1409-1418, 2016. PMID: 27637985. DOI: 10.1016/S1470-2045(16)30212-1

20 Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, Bairey O, Hillmen P, Bartlett NL, Li J, Simpson D, Grosicki S, Devereux S, McCarthy H, Coutre S, Quach H, Gaidano G, Maslyak Z, Stevens DA, Janssens A, Offner F, Mayer J, O'Dwyer M, Hellmann A, Schuh A, Siddiqi T, Polliack A, Tam CS, Suri D, Cheng M, Clow F, Styles L, James DF and Kipps TJ: Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med *373(25)*: 2425-2437, 2015. PMID: 26639149. DOI: 10.1056/NEJMoa1509388

21 Meyer RM: Generalizing the results of cancer clinical trials. J Clin Oncol *28(2)*: 187-189, 2010. PMID: 19933900. DOI: 10.1200/JCO.2009.25.8608

22 Winqvist M, Andersson PO, Asklid A, Karlsson K, Karlsson C, Lauri B, Lundin J, Mattsson M, Norin S, Sandstedt A, Rosenquist R, Spath F, Hansson L and Osterborg A: Long-term real-world results of ibrutinib therapy in patients with relapsed or refractory chronic lymphocytic leukemia: 30-month follow up of the Swedish compassionate use cohort. Haematologica *104(5)*: e208-e210, 2019. PMID: 30514799. DOI: 10.3324/haematol.2018.198820

23 Ysebaert L, Aurran-Schleinitz T, Dartigeas C, Dilhuydy MS, Feugier P, Michallet AS, Tournilhac O, Dupuis J, Sinet P, Albrecht C and Cymbalista F: Real-world results of ibrutinib in relapsed/refractory CLL in France: Early results on a large series of 428 patients. Am J Hematol *92(8)*: E166-e168, 2017. PMID: 28439916. DOI: 10.1002/ajh.24773

24 Hillmen P, Diels J, Healy N, Iraqi W, Aschan J and Wildgust M: Ibrutinib for chronic lymphocytic leukemia: international experience from a named patient program. Haematologica *103(5)*: e204-e206, 2018. PMID: 29419428. DOI: 10.3324/haematol.2017.178798

25 Iskierka-Jazdzewska E, Pula B, Szeremet A, Hus M, Golos A, Holojda J, Piszczek W, Steckiewicz P, Wojciechowska M, Zaucha JM, Warzocha K and Jamroziak K: Ibrutinib discontinuation in patients with relapsed or refractory chronic lymphocytic leukemia treated in a compassionate use program: A report from the Polish Adult Leukemia Study Group (PALG). Adv Clin Exp Med *28(8)*: 1051-1057, 2019. PMID: 31199879. DOI: 10.17219/acem/99911

26 Iskierka-Jazdzewska E, Hus M, Giannopoulos K, Madro E, Holojda J, Piotrowska M, Zaucha JM, Piszczek W, Szeremet A, Wojciechowska M, Steckiewicz P, Knopinska-Posluszny W, Osowiecki M, Drozd-Sokolowska J, Kumiega B, Kyrcz-Krzemien S, Halka J, Dudzinski M, Wieszczy P, Robak T, Warzocha K and Jamroziak K: Efficacy and toxicity of compassionate ibrutinib use in relapsed/refractory chronic lymphocytic leukemia in Poland: analysis of the Polish Adult Leukemia Group (PALG). Leuk Lymphoma *58(10)*: 2485-2488, 2017. PMID: 28278701. DOI: 10.1080/10428194.2017.1292353

27 van der Straten L, Levin MD, Visser O, Blijlevens NMA, Cornelissen JJ, Doorduijn JK, Kater AP and Dinmohamed AG: The effectiveness of ibrutinib in chronic lymphocytic leukaemia: a nationwide, population-based study in the Netherlands. Br J Haematol *188(6)*: e109-e112, 2020. PMID: 31991479. DOI: 10.1111/bjh.16391

28 Pula B, Budziszewska BK, Rybka J, Gil L, Subocz E, Dlugosz-Danecka M, Zawirska D, Waszczuk-Gajda A, Iskierka-Jazdzewska E, Kopacz A, Szymczyk A, Czyz J, Lech-Maranda E, Warzocha K and Jamroziak K: Comparable efficacy of idelalisib plus rituximab and ibrutinib in relapsed/refractory chronic lymphocytic leukemia: A retrospective case matched study of the Polish Adult Leukemia Group (PALG). Anticancer Res *38(5)*: 3025-3030, 2018. PMID: 29715135. DOI: 10.21873/anticanres.12557

29 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, Hillmen P, Keating MJ, Montserrat E, Rai KR and Kipps TJ: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood *111(12)*: 5446-5456, 2008. PMID: 18216293. DOI: 10.1182/blood-2007-06-093906

30 Jamroziak K, Szymczyk A, Hus M, Wojciechowska M, Knopinska-Posluszny W, Holojda J, Halaburda K, Warzocha K and Iskierka-Jazdzewska E: Hodgkin's variant of Richter's transformation during ibrutinib therapy in a series of CLL patients; the Polish Adult Leukemia Group report (PALG). Eur J Haematol *100(4)*: 389-391, 2018. PMID: 29243346. DOI: 10.1111/ejh.13016

31 UK CLL Forum: Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica *101(12)*: 1563-1572, 2016. PMID: 27756834. DOI: 10.3324/haematol.2016.147900

32 Winqvist M, Asklid A, Andersson PO, Karlsson K, Karlsson C, Lauri B, Lundin J, Mattsson M, Norin S, Sandstedt A, Hansson L and Osterborg A: Real-world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: data from 95 consecutive patients treated in a compassionate use program. A study from the Swedish Chronic Lymphocytic Leukemia Group. Haematologica *101(12)*: 1573-1580, 2016. PMID: 27198718. DOI: 10.3324/haematol.2016.144576

33 Innocenti I, Morelli F, Autore F, Piciocchi A, Frustaci A, Mauro FR, Schiattone L, Trentin L, Del Poeta G, Reda G, Rigolin GM, Ibatici A, Ciolli S, Coscia M, Sportoletti P, Murru R, Levato L, Gentile M, D'Arena G, Efremov DG, Tedeschi A, Scarfo L, Cuneo A, Foa R and Laurenti L: Venetoclax in CLL patients who progress after B-cell receptor inhibitor treatment: a retrospective multi-centre Italian experience. Br J Haematol *187(1)*: e8-e11, 2019. PMID: 31364153. DOI: 10.1111/bjh.16123

34 Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD, Furman RR, Lamanna N, Barr PM, Zhou L, Chyla B, Salem AH, Verdugo M, Humerickhouse RA, Potluri J, Coutre S, Woyach J and Byrd JC: Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol *19(1)*: 65-75, 2018. PMID: 29246803. DOI: 10.1016/S1470-2045(17)30909-9

Received May 17, 2020
Revised June 2, 2020
Accepted June 3, 2020