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Benefit/risk profile of idelalisib treatment in patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma

Ocena profilu korzyści i ryzyka leczenia idelalizybem u chorych na przewlekłą białaczkę limfocytową i chłoniaki nie-Hodgkina

Bartosz Puła[1], Agnieszka Giza[2], Monika Długosz-Danecka[2], Justyna Rybka[3], Edyta Subocz[4], Anna Waszczuk-Gajda[5], Magdalena Piotrowska[2], Magdalena Rej[6], Krzysztof Jamroziak[1], Wojciech Jurczak[2]

[1]Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[2]Department of Hematology, Jagiellonian University, Krakow, Poland
[3]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland
[4]Department of Hematology, Military Institute of Medicine, Warsaw, Poland
[5]Department of Hematology, Oncology and Internal Diseases, Medical University of Warsaw, Poland
[6]Department of Hematology University Children's Hospital, Krakow, Poland

Abstract

Idelalisib is a selective inhibitor of phosphoinositide 3-kinase δ, approved in relapsed/refractory (RR) chronic lymphocytic leukemia (CLL), first line CLL with del17p/TP53 mutation in patients unsuitable for immunochemotherapy and RR follicular lymphoma (FL) in whom at least two lines of therapy have failed. Despite good clinical efficacy, the development of this drug has been hampered due to its adverse events (i.e. autoimmune reactions and life-threatening opportunistic infections). In this retrospective study, we summarise the tolerability of idelalisib therapy in a Polish population, analysing 61 patients treated with idelalisib in monotherapy or idelalisib-based combination regimens. Idelalisib treatment was feasible for the majority of patients, with upper respiratory tract infections (N = 13.21%) being the most common adverse event (AE), and pneumonia (N = 11.18%) — the most prevalent grade 3 or higher non-hematological AE. We observed two cases of pneumonitis, one case of gastroenteritis, and no cases of liver transaminases elevation (all regarded as the AEs characteristic of idelalisib). Most of the patients were treated in haematology reference centres where physicians are more accustomed to dealing with opportunistic infections. Cotrimoxazole prophylaxis was given to 20 (32.8%) patients, whereas acyclovir prophylaxis was administered in 33 (54.1%) cases. This could explain the less frequent life-threatening infections and decreased mortality rate compared to the published registration studies. Our study confirms the high clinical efficacy of idelalisib in CLL and RR FL.

Key words: idelalisib, phosphoinositide 3-kinase inhibitor, chronic lymphocytic leukemia, non-Hodgkin lymphoma, treatment

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Address for correspondence: Agnieszka Giza MD, PhD, Department of Hematology, Jagiellonian University, ul. Kopernika 17, 31–501 Kraków, Poland, phone +48 424 76 00, fax +48 424 74 26, e-mail: agnieszka.giza4@wp.pl

Streszczenie

Idelalizyb jest selektywnym inhibitorem 3-kinazy fosfatydyloinozytolu δ zarejestrowanym do leczenia chorych na przewlekłą białaczką limfocytową (CLL), z opornością choroby lub nawrotem przynajmniej po jednej linii leczenia lub w leczeniu pierwszej linii u chorych z del17p lub mutacją TP53 niekwalifikujących się do immunochemoterapii, a także do leczenia chorych na chłoniaka grudkowego (FL) po dwóch liniach leczenia. Mimo dobrej skuteczności klinicznej rozwój leku był utrudniony ze względu na jego niekorzystne działania niepożądane (AE) (reakcje autoimmunologiczne i zagrażające życiu zakażenia oportunistyczne). W retrospektywnej analizie podsumowano tolerancję zastosowania idelalizybu w polskiej populacji, analizując 61 pacjentów leczonych idelalizybem w monoterapii lub według schematów skojarzonych z idelalizybem. Leczenie idelalizybem było możliwe u większości pacjentów, przy czym zakażenia górnych dróg oddechowych (n = 13,21%) były najczęstszym AE, a zapalenia płuc (n = 11,18%) — najczęściej występującym niehematologicznym zdarzeniem w stopniu 3. lub wyższym. Zaobserwowano 2 przypadki zapalenia pęcherzyków płucnych, jeden przypadek zapalenia żołądka i jelit, natomiast nie występowało podwyższenie aktywności aminotransferaz wątrobowych (wszystkie powyższe zdarzenia uznawano za charakterystyczne dla terapii idelalizybem). Większość chorych była leczona w hematologicznych ośrodkach referencyjnych, z personelem doświadczonym w zakresie postępowania i zapobiegania zakażeniom oportunistycznym. Profilaktykę kotrimoksazolem stosowano u 20 (32,8%) pacjentów, natomiast profilaktykę acyklowirem włączono u 33 (54,1%) chorych, co może tłumaczyć rzadsze występowanie infekcji zagrażających życiu i zmniejszoną śmiertelność niż w opublikowanych badaniach rejestracyjnych. Niniejszym autorzy wskazują również na wysoką skuteczność idelalizybu w leczeniu CLL oraz w nawrocie lub oporności FL.

Słowa kluczowe: idelalizyb, inhibitor 3-kinazy fosfatydyloinozytolu, przewlekła białaczka limfocytowa, chłoniak nie-Hodgkina, leczenie

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Introduction

Over the last ten years, inhibitors of phosphoinositide 3-kinase (PI3K), essential for transmitting the signal from B-cell receptor, has become a novel therapeutic option in B cell non-Hodgkin lymphoma patients (NHL), especially in high-risk chronic lymphocytic leukaemia (CLL), and follicular lymphoma (FL) [1, 2].

Idelalisib (GS-1101, CAL101) is a first-in-class oral agent, selectively inhibiting phosphoinositide 3-kinase delta. Initial results in relapsed/refractory (RR) patients were very promising [1, 3–6]. It was approved in the United States (US) and Europe for the treatment of RR FL as a third and subsequent line of therapy. Furthermore, it was approved for the treatment of RR CLL by the Food and Drug Administration in the US, and additionally by the European Medicines Agency also as the first-line therapy of CLL patients harbouring del17p/*TP53* mutations which are not feasible for immunochemotherapy.

Despite such promising clinical efficacy, further development of the drug has been hampered due to life-threatening opportunistic infections. Six phase II and III clinical studies assessing idelalisib's efficacy in first- and second-line therapy were halted by the Safety Committee due to unacceptable infection-related mortality [7–11]. The even higher infection rate in RR cases is counterbalanced by the high anti-lymphoma efficacy of idelalisib, and so therefore it remains the standard of care in subsequent lines of therapy. The most common adverse events (AE) of idelalisib include transaminitis, diarrhoea, and upper and lower respiratory tract infections [7, 10, 12]. Furthermore, the immunosuppressive action of idelalisib predisposes to cytomegalovirus (CMV) reactivation and severe opportunistic lung infections (*e.g. Pneumocystis jiroveci*) [10]. In a few cases, the imbalance in T-cell function may result in severe diarrhoea and pneumonitis, the latter usually leading to discontinuation of idelalisib therapy, due to its severity [9, 10, 13].

In a recent observational case-matched study of the Polish Adult Leukemia Group (PALG), idelalisib in combination with rituximab showed a comparable efficacy to that of ibrutinib monotherapy,

Table 1. Summary of patients and clinical trials included in the analysis

Tabela 1. Podsumowanie danych pacjentów oraz badań klinicznych objętych analizą

NCT trial number	Primary disease	Number of patients	Regimen
NCT01980875	TN-CLL	12	Idelalisib + obinutuzumab
NCT02044822	TN-CLL	3	Idelalisib + rituximab
NCT01980888	TN-CLL	6	Idelalisib + bendamustine + rituximab
NCT01569295	RR-CLL	2	Idelalisib + bendamustine + rituximab
PALG study	RR-CLL	24	Idelalisib + rituximab
NCT01282424	RR-NHL	6	Idelalisib
NCT01732913	RR-NHL	3	Idelalisib + rituximab
NCT01732926	RR-NHL	5	Idelalisib + bendamustine + rituximab

TN-CLL (*nieleczona postać przewlekłej białaczki limfocytowej*) — treatment naïve chronic lymphocytic leukemia; RR-CLL (*nawrotowa i oporna postać przewlekłej białaczki limfocytowej*) — relapsed/refractory chronic lymphocytic leukemia; PALG (*Stowarzyszenie Polskiej Grupy ds. Leczenia Białaczek u Dorosłych*) — Polish Adult Leukemia Group; RR-NHL (*nawrotowa i oporna postać chłoniaka nie-Hodgkina*) — relapsed/refractory non-Hodgkin lymphoma

while maintaining an acceptable AE profile in high-risk relapsed and refractory CLL patients [14].

In this study, we summarise the efficacy and adverse events profile in NHL and CLL patients treated with idelalisib in monotherapy or combination regimens within, as well as outside, clinical trials. We put a special emphasis on the occurrence of infections and the life-threatening AEs that are characteristic of idelalisib. If proper clinical routines are maintained, the occurrence of idelalisib AEs can be minimised, without jeopardising its efficacy [12, 15].

Material and methods

In this study, we retrospectively analysed 61 patients treated with idelalisib in monotherapy or idelalisib-based combination treatment within clinical trials performed in the Department of Haematology of the Jagiellonian University in Krakow and in a multicentre observational retrospective study of PALG, the results of which were recently reported (Table 1) [14].

Six of the eight studies included in our analysis were randomised, double blind, placebo-controlled and two-armed. One was open label and single-armed, where all of the subjects received an investigational product, and one trial was an observational study performed by PALG (patients were treated with idelalisib within the Named Patient Programme by Gilead Sciences). In our study, we wanted to discover the true incidence of idelalisib AE in patients managed by experienced physicians, so only centres with at least three patients were included in our analysis.

Clinical trial data gathering was based on patient files (including medical history) and the Electronic Case Report Forms (eCRF) database, whereas that of the PALG study was gathered via an electronic questionnaire. All of the patients had taken orally 150 mg of idelalisib, twice daily, as monotherapy or as part of combination regimens (Table 1). The idelalisib-rituximab treatment in the observational PALG study was given according to Study 116 protocol (NCT01539512) [1]. Adverse events during treatment were graded as per the criteria of the National Cancer Institute's Common Terminology Criteria for Adverse Events Assessment (CTCAE), version 4.0.

Statistical analysis was performed using Prism 6.0 (GraphPad, La Jolla, CA, USA) statistical software. Progression-free survival (PFS) and overall survival (OS) analysis was performed using Kaplan-Meier and log-rank tests.

Results

Patient characteristics

Patients' clinical data is set out in Table 2. The study comprised 21 treatment-naïve CLL (TN-CLL) cases, 26 relapsed and refractory CLL (RR-CLL), and 14 indolent relapsed and refractory NHL cases (RR-NHL). The latter group included three cases of small lymphocytic lymphoma (SLL), seven cases of follicular lymphoma (FL), two cases of lymphoplasmacytic lymphoma (LPL), and one case each of marginal zone lymphoma (MZL) and its splenic variant (SMZL). The median observation times of the TN-CLL, RR-CLL and RR-NHL cases were 5.2 (range 1.1–6.5) months,

Table 2. Patients' clinico-pathological characteristics*

Tabela 2. Charakterystyka kliniczno-patologiczna pacjentów

Parameter	TN-CLL	RR-CLL	RR-NHL
Number of patients	**21**	**26**	**14**
Observation time (median [range]; mean ± SD* [months])	5.1 [1–16.5] 7.23 ± 5.34	15.8 [0.2–29.5] 14.23 ± 7.25	11.2 [1.7–46.8] 16.3 ± 13.47
Age (median [range]; mean ± SD [years])	70 [60–87] 71.1 ± 6.85	65.5 [37–79] 64.85 ± 8.53	61.5 [39–79] 62 ± 11.44
Sex [N, %]: • male • female	 10 (47.6%) 11 (42.4%)	 16 (61.5%) 10 (39.5%)	 7 (50.0%) 7 (50.0%)
Rai classification [N, %]: • 0–2 • 3–4	 15 (71.4%) 6 (28.6%)	 9 (34.6%) 17 (63.4%)	
Ann-Arbor classification [N, %]: • 0–2 • 3–4			 1 (7.1%) 13 (92.3%)
ECOG performance status [N, %]: • 0–1 • 2–4 • no data	 19 (90.5%) 2 (9.5%) 0 (0.0%)	 23 (88.5%) 3 (11.5%) 0 (0.0%)	 6 (42.9%) 0 (0.0%) 8 (57.1%)
Lines of treatment (median [range])	0	4 [1–7]	3 [1–4]

*Comparison between the high-dose methylprednisolone, ibrutinib and idelalisib treated patients; ECOG — Eastern Cooperative Study Group; SD (*odchylenie standardowe*) — standard deviation; TN-CLL (*nieleczona postać przewlekłej białaczki limfocytowej*) — treatment naïve chronic lymphocytic leukemia; RR-CLL (*nawrotowa i oporna postać przewlekłej białaczki limfocytowej*) — relapsed/refractory chronic lymphocytic leukemia; RR-NHL (*nawrotowa i oporna postać chłoniaka nie-Hodgkina*) — relapsed/refractory non-Hodgkin lymphoma

15.8 (range 0.26–29.5) months, and 11.2 (range 1.7–46.8) months, respectively.

Outcome assessment

All TN-CLL patients treated with idelalisib participated in clinical trials that were closed prematurely by the Safety Committee due to excess ive infection-related mortality. None of the 21 patients from our cohort died, but a response was formally assessed as per protocol in only 10 of the 21. Therefore, for the purposes of a better comparison, the responses in all cohorts were calculated per assessed patient only (Table 3). In TN-CLL, we observed a 100% overall response rate (ORR), with four (40%) of the patients achieving complete remission (CR) and six (60%) partial remission (PR) and partial remission with lymphocytosis (PR-L).

In the RR-CLL cohort, the ORR reached 92.0%, with seven (28%) CR and 16 (64%) PR + PR-L. Moreover, one case each (4%) of stable disease (SD) and progressive disease (PD) was noted. Only one patient did not undergo disease assessment (receiving a single dose of rituximab and idelalisib and developing thereafter an influenza type A pneumonia and tumour lysis syndrome). A comparable level of response was observed in the analysed indolent RR-NHL cases, in which 85.7% ORR was reached. In this group, three (21.4%) CR and nine (64.4%) PR were observed. In the remaining two patients, SD and PD in one case each (7.1%) was noted.

In the specified observation time, progression of the disease was noted in 11 cases. Most of the disease progressions were observed in the NHL cohort (six, 42.9%), followed by the RR-CLL cohort (five, 19.2%). No progressions or deaths were observed in the TN-CLL patients within the described observation time. In total, nine deaths (five in the NHL and four in the RR-CLL cohort) were observed. Of the RR-NHL patients, four of the reported deaths were related to severe pneumonia and the fifth due to cardiac insufficiency. Nevertheless, at that time these RR-NHL patients were under subsequent other than idelalisib-based therapies due to earlier refractoriness to idelalisib. In the RR-CLL cohort, four casualties were noted, solely in the PALG study cohort (one death was attributable to disease progression, the second to TLS resulting in cardiac arrest, the third to pneumonia, and the fourth died at home probably due to an unknown infection).

Survival analysis (Figure 1) shows that in TN--CLL cases median PFS and OS was not reached and the respective 6-month PFS and OS rates were 100%. In RR-CLL cases, the median PFS and OS was not reached either. The estimated 12-month

Table 3. Best responses to particular treatment regimens with idelalisib in the analysed patient group

Tabela 3. Najlepsze odpowiedzi na poszczególne terapie idelalizybem w analizowanej grupie pacjentów

Parameter	TN-CLL	RR-CLL	RR-NHL
Number of pts.	21	26	14
Response: • CR • PR + PR-L • SD • PD • not assessed	 4 (40% of assessed pts.) 6 (60% of assessed pts.) 0 (0.0) 0 (0.0) 11 (52.3%)	 7 (28.0% of assessed pts.) 16 [3 PR-L] (64% of assessed pts.) 1 (4.0% of assessed pts.) 1 (4.0% of assessed pts.) 1 (3.8% of assessed pts.)	 3 (21.4%) 9 (64.4%) 1 (7.1%) (7.1%) 0 (0.0%)
Overall response rate (ORR): • CR + PR + PR-L • no response • not assessed	 10 (100% of assessed pts.) 0 (0.0%) 11 (52.3%)	 23 (92.0% of assessed pts.) 2 (8.0% of assessed pts.) 1 (3.8%)	 12 (85.7%) 2 (14.3%) 0 (0.0%)

TN-CLL (*nieleczona postać przewlekłej białaczki limfocytowej*) — treatment naïve chronic lymphocytic leukaemia; RR-CLL (*nawrotowa i oporna postać przewlekłej białaczki limfocytowej*) — relapsed/refractory chronic lymphocytic leukemia; RR-NHL (*nawrotowa i oporna postać chłoniaka nie-Hodgkina*) — relapsed/refractory non-Hodgkin lymphoma; pts. (*pacjenci*) — patients; CR (*całkowita remisja*) — complete remission; PR (*częściowa remisja*) — partial remission; PR-L (*częściowa remisja z limfocytozą*) — partial remission with lymphocytosis; SD (*stabilizacja choroby*) — stable disease; PD (*progresja choroby*) — progressive disease

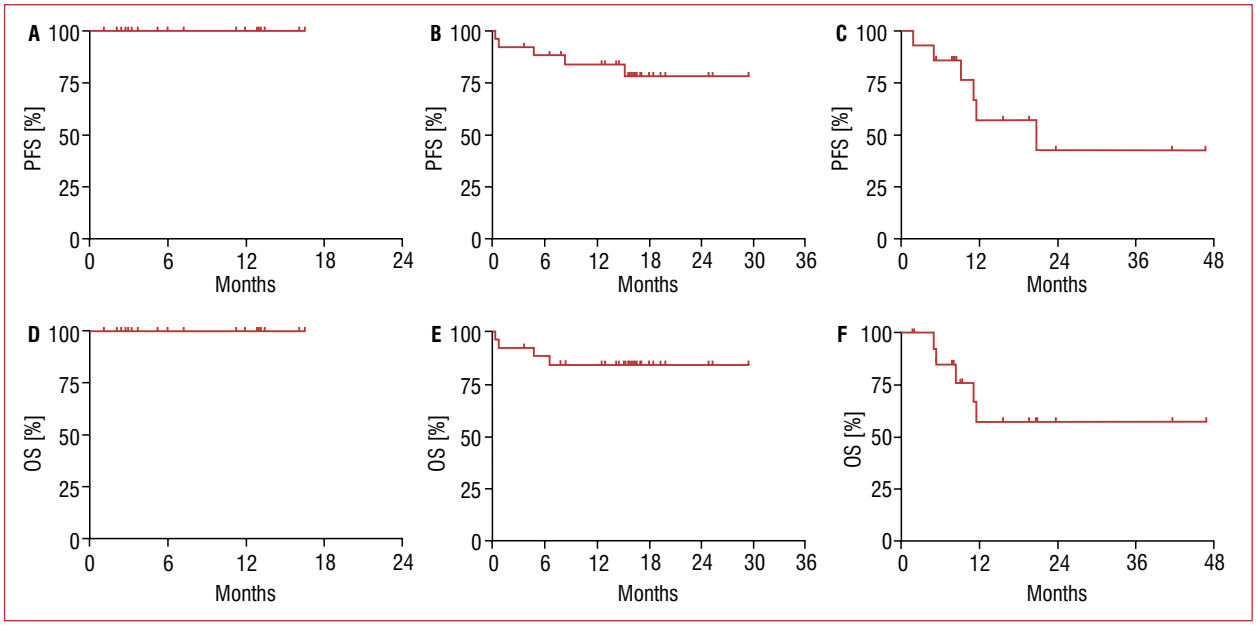

Figure 1A–F. Kaplan-Meier survival curves of progression-free survival (PFS) (**A–C**) and overall survival (OS) (**D–F**) of idelalisib-based treated patients with treatment naïve chronic lymphocytic leukemia (CLL) (**A, D**), relapsed/refractory CLL (**B, E**) and relapsed/refractory non-Hodgkin lymphoma (**C, F**)

Rycina 1A–F. Krzywe Kaplana-Meiera czasu wolnego od progresji (PFS) (**A–C**) oraz przeżycia całkowitego (OS) (**D–F**) w przypadku terapii opartej na zastosowaniu idelalizybu w przypadkach dotychczas nieleczonej postaci przewlekłej białaczki limfocytowej (CLL) (**A, D**), nawrotowej i opornej postaci CLL (**B, E**) oraz nawrotowych i opornych postaci chłoniaka nie-Hodgkina (**C, F**)

PFS rate was 83.3%, whereas the OS rate was 84.3%. In the analysed NHL cases, the median PFS was 20.7 months with an estimated 12-month PFS rate of 57.1%. However, the median OS in this cohort was not reached and the estimated 12-month OS rate was 57.1%.

Tolerability and adverse events profile assessment

Our study found idelalisib treatment to be characterised by reasonable tolerability. This however varied between the analysed cohorts. Infections were the most common AEs noted in

all of the studied patients. Upper respiratory tract infections, regardless of severity, were the most prevalent AE in the TN-CLL group (42.9%) and the RR-NHL group (28.6%). However, in all of the studied cases only infections of grades 1 and 2 were observed. Other types of infectious AEs, such as herpes zoster reactivation, bronchitis, and urinary tract infections, were infrequent and not severe. The most prevalent grade 3 or above non-hematological AE was pneumonia, which was noted in 27.0% of RR-CLL cases, 14.3% of RR-NHL cases, and 9.5% of TN-CLL cases. Neutropenia of grades 3 and 4 was observed in 33.3% of TN-CLL cases and in 15.4% of RR-CLL cases ; however in RR-NHL patients it was not noted. Of the characteristic idelalisib-related AEs, two cases of pneumonitis (one each in the RR-CLL and the NHL cohort) and one case of gastroenteritis in a RR-NHL patient were noted, although elevation of liver transaminases was not observed.

Discussion

Idelalisib is known for its clinical efficacy in high-risk relapsed and refractory CLL and NHL. However, it is also known for its characteristic AE profile with elevation of liver transaminases, diarrhoea/colitis, and pneumonitis as well as an increase in the rate of opportunistic infections, mainly *P. jiroveci* and CMV [1, 6, 9, 11, 12, 16]. The incidence of the idelalisib treatment-related AEs varies. In relapsed and refractory CLL and NHL, diarrhoea or colitis of grade 3 or above has been noted in approximately 14% of cases, hepatotoxicity measured as an elevation of liver transaminases more than 5× the upper limit of normal (ULN) has been noted in 14% of patients, and pneumonitis in 3% of patients across clinical trials [9, 10, 12]. The loss of T-cell regulatory suppression function and augmentation autoimmune reaction has been regarded as the main reason for idelalisib-associated colitis and pneumonitis, due to the fact that the AE profile in treatment-naïve CLL patients is more severe compared to that observed in heavily pretreated CLL and NHL patient cohorts [1, 6, 7, 17].

Due to the above-mentioned AE profile and some fatal outcomes observed within clinical trials, idelalisib prescribing information contains a black box warning of fatal and/or severe diarrhoea or colitis, hepatotoxicity, pneumonitis and intestinal perforation [9, 10].

Neutropenia was noted in approximately 30––40% of patients across phase 1–3 clinical trials. The most common severe infections reported in clinical trials with idelalisib were pneumonia (7–20%), febrile neutropenia (5–11%), bacteremia and sepsis (6–7%), and cellulitis (1–5%) [1, 4]. Data from two clinical trials (phases 1 and 3) show that 3% of patients treated with idelalisib had *P. jirovecii* pneumonia, one patient experienced CMV reactivation, and two patients suffered invasive fungal pneumonia [1, 4, 17].

Idelalisib in combination with rituximab and bendamustine led to a further increase of occurrence of grade 3 or above neutropenia (60%) and febrile neutropenia (23%) [11]. Infections were noted more frequently in an idelalisib group compared to a placebo group (69% vs. 59%) and were mainly of bacterial etiology. Furthermore, in an experimental idelalisib-rituximab-bendamustine arm, six patients died (vs. three in a placebo group) due to pneumonia and septic shock. The rate of opportunistic infections (*P. jirovecci*) and CMV were also higher (2% and 6% of patients in the idelalisib group compared to none and 1% in the placebo group) [11]. Therefore, cotrimoxazole and acyclovir prophylaxis is mandatory during idelalisib treatment [18, 19].

Interestingly, other than a response profile in CLL and FL cases that was comparable to other clinical trials, we did observe a tolerable adverse events profile of idelalisib-based regimens in the analysed CLL and NHL patient population (Table 4). Firstly, the main difference between our and other studies is the absence of liver transaminases elevation, also in the TN-CLL cohort, which is regarded as a characteristic feature of idelalisib treatment, especially in young CLL patients with no history of immunochemotherapy [1, 6, 7]. Secondly, diarrhoea and colitis of grade 3 and above were observed only in one patient, whereas mild diarrhoea was noted only in a single patient from the TN-CLL and NHL cohorts [1, 6, 7]. Unexpectedly, tumour lysis syndrome (TLS) of grade 3 was observed in two RR-CLL patients treated within the observational PALG study. In one of these cases, the TLS resulted in cardiac arrest leading ultimately to death.

Similarly, other studies found that neutropenia, especially in the CLL patients, and infections were common. Upper respiratory tract infections and pneumonia were the most prevalent. The routine use of antibiotics combined with granulocyte colony-stimulating factor allowed for their effective management in the majority of cases. In addition, single cases of pneumonitis were observed in the RR-CLL and NHL groups, although one of them was rather caused by a severe influenza type A pneumonia in a heavily pretreated RR-CLL pa-

Table 4. Adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) observed during idelalisib-based regimens in chronic lymphocytic leukemia and non-Hodgkin lymphoma

Tabela 4. Obserwowane działania niepożądane zgodne z wytycznymi *Common Terminology Criteria for Adverse Events* (CTCAE) w trakcie terapii schematami z zastosowanie idelalizybu przewlekłej białaczki limfocytowej oraz chłoniaków nie-Hodgkina

Adverse events	TN-CLL (N = 21)		RR-CLL (N = 26)		NHL (N = 14)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Upper respiratory tract infection	9 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (28.6%)	0 (0.0%)
Pneumonia	4 (19.0%)	2 (9.5%)	7 (27.0%)	7 (27.0%)	2 (14.3%)	2 (14.3%)
Acute sinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)
Bronchitis	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)
Pneumonitis	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (7.1%)	1 (7.1%)
Heart failure, acute	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (7.1%)	1 (7.1%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sepsis	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (7.1%)	1 (7.1%)
Tumour lysis syndrome	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (7.7%)	0 (0.0%)	0 (0.0%)
Zoster	3 (14.3%)	0 (0.0%)	2 (7.7%)	0 (0.0%)	1 (7.1%)	0 (0.0%)
Gastroenteritis	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)
Neutropenia	7 (33.3%)	7 (33.3%)	0 (0.0%)	4 (15.4%)	0 (0.0%)	0 (0.0%)

TN-CLL (*nieleczona postać przewlekłej białaczki limfocytowej*) — treatment naïve chronic lymphocytic leukaemia; RR-CLL (*nawrotowa i oporna postać przewlekłej białaczki limfocytowej*) — relapsed/refractory chronic lymphocytic leukemia; RR-NHL (*nawrotowa i oporna postać chłoniaka nie-Hodgkina*) — relapsed/refractory non-Hodgkin lymphoma

tient [14]. We observed no CMV reactivation, nor *P. jirovecii* opportunistic infection, at the time of data analysis. It is worth noting that cotrimoxazole prophylaxis was given to 20 (32.8%) patients, whereas acyclovir prophylaxis was administered in 33 (54.1%) cases. However, during the analysed treatment period, *P. jirovecii* prophylaxis was not yet regarded as mandatory at the time [18].

We must underline that the idelalisib tolerability results we have here presented should be treated with caution due to the limitations of this descriptive study.

Firstly, we performed a pooled analysis of clinical trial patients as well as 'real-world' RR-CLL patients who were qualified for the idelalisib named patient programme of PALG [14]. Patients qualified for the PALG study were heavily pretreated with three or more therapies and had been refractory to the previous line of therapy. This might help explain the unsatisfactory treatment tolerability and response in some of the participants.

Furthermore, altogether the number of analysed patients was low, most of them were treated within a single clinical centre.

Lastly, follow-up times were rather short, rendering the data concerning the occurrence of opportunistic infections somewhat incomplete and inconclusive.

Nevertheless, considering the tolerable AE profile of idelalisib in the described patient cohort, the use of this drug, always accompanied by cotrimoxazole and acyclovir prophylaxis, should be taken into consideration in the therapy of cases of relapsed/refractory CLL and FL.

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