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Drugs for treating patients with chronic lymphocytic leukemia with FDA granted 'Breakthrough Therapy Status' — implications for patients

Leki stosowane u chorych na przewlekłą białaczkę limfocytową wyróżnione przez FDA statusem terapii przełomowej

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Abstract

The added value of a new drug can be defined in various ways, but the patient-focused approach obliges the clinical significance of additional health effects to be also considered. For any given new drug, the American Food and Drug Administration (FDA) determines the added value delivered to the current therapy standard by conducting an assessment based on: the extent of the delivered health effect regarding clinically significant endpoints, the duration of that effect and the importance of the clinical effect for treating a serious disease. In principle, preliminary scientific evidence for a new and original drug should clearly indicate an additional benefit compared to currently available therapeutic methods. In order to make such drugs available as quickly as possible to patients, the FDA has implemented programmes since the 1970s aimed at shortening development and approval processes of methods with therapeutic promise, particularly in treating patients suffering from serious diseases. The most recent programme of this type introduced by the FDA, grants an innovative drug the special status of a breakthrough therapy, from which the drug acquires numerous privileges. In the last ten to twenty months the FDA granted several molecules this status, thus significantly shortening the patient waiting time for drug marketing. In the FDA's opinion, such drugs offer breakthrough progress in treating patients with chronic lymphocytic leukemia.

Key words: breakthrough therapy, FDA, chronic lymphocytic leukemia, obinutuzumab, ibrutinib, idelalisib, drug approval

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Streszczenie

Wartość dodaną nowego leku można definiować w różny sposób, jednak podejście zorientowane na chorego obliguje do uwzględnienia również istotności klinicznej dodatkowego efektu zdrowotnego. W celu określenia wartości dodanej względem aktualnego standardu leczenia amerykańska Agencja ds. Żywności i Leków (FDA) przeprowadza ocenę nowego leku; wynik oceny zależy od wielkości oferowanego efektu zdrowotnego w zakresie istotnych klinicznie punktów końcowych, czasu utrzymywania się tego efektu oraz znaczenia efektu klinicznego dla leczenia ciężkiego schorzenia. Co do zasady wstępne dowody naukowe dotyczące nowego, oryginalnego leku powinny jasno wskazywać

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na dodatkową korzyść względem aktualnie dostępnych metod leczenia. W celu jak najszybszego udostępnienia chorym takiego leku w FDA od lat 70. ubiegłego wieku wdrażano programy służące skróceniu procesu rozwoju i rejestracji obiecującej metody leczenia, w szczególności gdy znajdowała zastosowanie w leczeniu chorych na ciężkie schorzenia. Najnowszy program tego typu wprowadzony przez FDA wiąże się z nadawaniem innowacyjnemu lekowi specjalnego statusu „breakthrough therapy", dzięki któremu lek uzyskuje liczne przywileje. W okresie ostatnich kilkunastu miesięcy FDA wyróżniła tym statusem kilka cząsteczek, co umożliwiło znaczne skrócenie czasu oczekiwania chorych na udostępnienie leków na rynku. W ocenie FDA leki te oferują przełomowy postęp w leczeniu chorych na przewlekłą białaczkę limfocytową.

Słowa kluczowe: terapia przełomowa, FDA, przewlekła białaczka limfocytowa, obinutuzumab, ibrutynib, idelalizyb, zatwierdzenie leku

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Introduction

In 2006, the number of patients estimated by the FDA who received innovative drugs as part of clinical trials (IND, Investigational New Drug) in life-threatening situations, was over 100 000 cases [1]. For those tested drugs, which proved to be significantly more effective than existing therapeutic options, specially developed programmes have hitherto, long been attempted for making early and effective drug treatment available to patients. Such drug development acceleration programmes thereby shorten the clinical test period, and provide early access for new therapeutic options to more patients. This is attested both by the Subpart E programme, which shortened mean clinical trials duration from 8.9 to 6.2 years, or the accelerated approval programme giving an average time reduction of 4.2 years [2].

A significantly reduced time for considering new drug approval applications by the FDA was also observed from over 30 months in 1980s to about 10 months in 2011 [3]. However, in order to guarantee patient treatment safety, a significant part of registration decisions are conditional on carrying out additional Phase 4 studies (confirmatory studies); indeed, after 2000 about 80% of drugs under the accelerated approval procedure were required to conduct such studies [4].

The actual granting of the breakthrough therapy designation introduced by the FDA in 2012, is an involved programme for maximally accelerating an otherwise restrictive and time-consuming administrative procedure. This procedure requires analysing the scientific evidence and reviewing the approval application for a drug intended to treat severe clinical conditions, for which preliminary scientific evidence indicates the possibility of significant improvements to patient's health regarding clinically significant endpoints when compared with the current therapy standards [5].

Recently, several innovative molecules have been granted breakthrough therapy status by the FDA. Particularly worth mentioning are the hematological drugs approved for treating CLL; obinutuzumab, ibrutinib and idelalisib.

Significance of breakthrough therapy status granted by FDA

The granting of such status expedites the evaluation of drugs used in treating life-threatening clinical conditions. The criteria for drug evaluation include preliminary clinical evidence, confirming significant improvement of at least one clinically significant endpoint when compared with the current standard. According to the FDA, a clinically significant endpoint most frequently depends on the incidence, mortality or the consequences of severe disease. It can be also related to:

- an effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit;
- an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease;
- significant improvement to both the safety profile and efficacy compared with the current therapy standards [6].

The procedure for granting drug breakthrough therapy status is like other fast track programmes and emphasises effectively decreasing the time taken in completing all formalities for granting marketing authorisation, engaging the manufacturer's

representatives and for efficiently using other fast track programmes. Details are described by the Food and Drug Administration Safety and Innovation Act (FDASIA) passed in 2012 by the USA Congress [7]. This states, that the breakthrough therapy status can be only granted to a drug which is:

- intended for monotherapy or in combination with other drugs when treating severe or life-threatening diseases or clinical conditions;
- when preliminary clinical data suggest significant improvements may be afforded compared with existing therapies, regarding at least one clinically significant endpoint.

Severe disease and clinical conditions have been defined in the FDA Guidance for Industry — Expedited Programs for Serious Conditions — Drugs and Biologics. These state; "A disease or condition substantially limiting patient's everyday functioning. Short-lasting and spontaneously regressing diseases constitute no sufficient justification. Moreover, the disease or clinical condition need not to be irreversible, if they are long-lasting or recurrent. Whether a given disease or clinical condition are serious, is a question of clinical assessment, with consideration of the influence on such factors as: survival, everyday functioning, possibility of progression of the untreated disease".

A manufacturer applying for breakthrough therapy status for a new drug, must demonstrate its effect on an important aspect of the disease, e.g. a direct effect on the symptoms of serious disease The application can be also justified by clinical benefits to patients that include:

- improving the diagnosis of serious disease, translated into better treatment results;
- reducing adverse reactions from the currently applied treatment;
- reducing serious adverse events compared with the current therapy standards [8].

Granting a drug breakthrough therapy status delivers tangible benefits to the manufacturer. For such drugs the regulations of the FDASIA act (section 902), provide for the following:

1) substantial FDA support for the applicant on effective drug development programmes, starting from Phase I studies;
2) staff consultations with manufacture's senior management about all benefits reserved for drugs approved in the fast track designation procedure;
3) consultations about optimal planning of phase III clinical trials,
4) appointing an interdisciplinary team of reviewers for drug evaluation (specialists in medicine, pharmacology, toxicology, chemistry, drug manufacturing, supervision and control);
5) appointing a leader of an interdisciplinary reviewing team and scientifically liaising between the team and sponsor;
6) involving experienced experts for interdisciplinary review of documentation submitted by a sponsor.

Ideally, the drug manufacturer should submit an application to the FDA for breakthrough therapy status before finalising the Phase II study preparation. Because this status is granted for speeding up the process of gathering and analysing scientific evidence (i.e. to support authorisation for the rapid marketing of any given new drugs), the FDA will not review any further applications after the final registration applications have been submitted; these being termed 'Biologic License Applications' (BLA) or 'New Drug Applications' (NDA). The 60 days reviewing period allotted to the FDA (for assigning breakthrough therapy status) is thus crucial to both manufacturers and patients awaiting a new treatment to become available. This, therefore obliges the FDA to prioritise such applications [9].

The key differences between granting drug breakthrough therapy status and drug approval in the fast track programme are the requirements that a new drug has to meet for qualification. In applying for breakthrough therapy status the criteria are very rigorous. A significant improvement in clinical benefit to patients must be shown to a clinically significant endpoint, compared with current treatment standards. However to qualify for the fast track programme the FDA may grant those drugs with clinical or non-clinical data which suggest possible health benefits for patients with a serious disease, for whom no therapeutic options are available (unmet medical needs).

It is the manufacturer, who should usually submit an application for granting drug breakthrough therapy status, however if after reviewing the preliminary scientific evidence, the FDA considers the product meeting the adequate criteria and that the privileges associated with granting that status could expedite the availability of the drug to patients, then the office itself may suggest the manufacturer to submit such an application [9].

Chronic lymphocytic leukemia

This is a clonal lymphoproliferative disease, where B cell lymphocytes uncontrollably proliferate and accumulate in the peripheral blood, bone marrow,

lymph nodes, spleen and liver. These cells resemble small mature lymphocytes possessing B-line immunophenotype and CD5 surface marker expression. CLL is the most commonly diagnosed leukemia in European and North American countries occurring at rates of 4.2/100,000 of the population.

CLL patients constitute a heterogeneous clinical group, where in most cases the therapeutic goal includes obtaining a complete remission (CR), prolongation of the progression-free survival (PFS), improvement of the overall survival (OS) and the quality of life (QoL). Intensifying the therapy is not possible for all patients, particularly the elderly with numerous comorbidities (less fit or slow–go patients) [10]. In particular, the latter cases have rarely been considered for clinical trials, in which the median age of patients is usually 50–60 years, while in the general population the median age at the onset of CLL is 72 years [11].

Alkylating drugs, such as chlorambucil and cyclophosphamide formed the basis of CLL therapy for many years. In the last two decades however, the number of therapeutic options used against this disease, has significantly increased. Currently, the armamentarium of medicinal products now approved includes amongst others; purine analogues (fludarabine, cladribine, pentostatin) and monoclonal antibodies (rituximab, ofatumumab, alemtuzumab) [12]. The most difficult therapeutic decisions concern the so-called slow–go patients because the homogeneous, widely accepted standards for chemotherapy choice in that group of patients are absent. In particular, no homogeneous standard of management has been established for patients failing to qualify for treatment with straining regimens: purine analogue in full doses + cyclophosphamide + rituximab. The current diagnostic and therapeutic recommendations made by the Polish Society of Hematology and Transfusion Medicine Workgroup on CLL suggest chlorambucil monotheraphy, rituximab in combination with chlorambucil, a purine analogue with cyclophosphamide in reduced dose with or without rituximab, rituximab in combination with bendamustine, monotherapy with fludarabine, cladribine, bendamustine or rituximab [13]. Chlorambucil monotherapy, being until recently the "gold standard" of CLL treatment (in view of its relatively good tolerance and the possibility of long term oral administration and low cost), is still used as symptomatic treatment in elderly patients with comorbidities, or in subsequent lines of CLL therapy. COP (cyclophosphamide, vincristine, prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) regimens are of similar significance. The choice of therapy depends on the experience of the physician and medical centre as well as current reimbursement policies.

Recently, the growing hopes of both clinical societies and government agencies responsible for drug registration have been raised by new groups of molecules: glycoengineered anti-CD20 antibodies and B-cell receptor (BCR) signalling pathway kinase inhibitors, for which the preliminary results from clinical trials have proved very promising.

Obinutuzumab

Obinutuzumab is a humanised type II IgG1 subclass monoclonal antibody against the CD20 antigen. Owing to glycoengineering of the Fc fragment, obinutuzumab has a higher affinity to FcγRIII receptors on effector cells, such as natural killer cells (NK), macrophages, monocytes, as compared with antibodies not modified with glycoengineering methods. In preclinical studies it was found that obinutuzumab induced direct cell death and mediated the process of antibody-dependent cellular phagocytosis (ADCP), while inducing complement-dependent cytotoxity (CDC) to a significantly lesser degree than type I antibodies.

Obinutuzumab in combination with chlorambucil was approved in the EU in 2014 (towards the end of 2013 by FDA) for treating adult patients with treatment-naïve chronic lymphocytic leukemia, in whom, in view of comorbidities, contraindications to full-dose fludarabine are present. The condition made for granting marketing authorisation to the manufacturer was to submit periodical drug safety reports, according to the requirements set out in the European Union Reference Date (EURD) list. The first periodical drug safety report is scheduled for submission eight months after registration of the drug in the EU [14].

The decision for approval was based mainly on the results of a phase 3 multi-centre, open-label, randomised, three-arm clinical trial, which assessed the effectiveness and safety of obinutuzumab administration in combination with chlorambucil vs therapy with rituximab combined with chlorambucil, or chlorambucil monotherapy in patients with treatment-naïve CLL and significant comorbidities and/or decreased creatinine clearance [15, 16].

All study subjects (n = 781) were randomised in a 2:2:1 ratio into one of the following arms:

- obinutuzumab and chlorambucil;
- rituximab and chlorambucil;
- chlorambucil monotherapy.

Table 1. Data on the effectiveness of treatment with obinutuzumab combined with chlorambucil, based on the registration study (NCT01010061) (source [16])

Tabela 1. Dane dotyczące skuteczności leczenia obinutuzumabem w połączeniu z chlorambucylem na podstawie badania rejestracyjnego (NCT01010061) (źródło [16])

Analyzed parameter	Phase Ia		Phase 2	
	Chlorambucil N = 118	Obinutuzumab + chlorambucil N = 238	Rituximab + chlorambucil N = 330	Obinutuzumab + chlorambucil N = 333
Median PFS assessed by the investigator — months (percentage of patients with an event)	11.1 months (81.4%)	26.7 months (39.1%)	15.2 months (60.3%)	26.7 months (31.2%)
Relative risk and p-value (log rank stratified test)	0.18 (0.13; 0.24) p < 0.0001		0.39 (0.31; 0.49) p < 0.0001	
Median PFS assessed by an independent review committee (percentage of patients with an event)	11.2 months (76.3%)	27.2 months (37.4%)	14.9 months (55.5%)	26.7 months (30.9%)
Relative risk (RR) and p-value (log rank stratified test)	0.19 (0.14; 0.27) p < 0.0001		0.42 (0.33; 0.54) p < 0.0001	
Index of responses to treatment after therapy completion (percentage of treatment-responders)	31.4%	77.3%	65.0%	78.4%
p-value (chi-square conformity test)	p < 0.0001		p = 0.0001	
Index of responses to treatment after therapy completion (percentage of complete remissions)	0.0%	22.3%	7.0%	20.7%

PFS — progression-free survival

Patients with CLL, in whom comorbidities were assessed, were enrolled; i.e. coexistent disease score exceeded 6 according to the Cumulative Illness Rating Scale or renal function impairment was present (creatinine clearance < 70 ml/min). Patients were excluded with impaired liver function (grade 3 in NCI-CTC scale), ASPAT and ALAT activities exceeding more than five times the upper limit of normal for longer than two weeks, bilirubin concentration exceeding more than three times the upper limit of normal and renal failure (creatinine clearance < 30 ml/min). Patients with at least one organ/system failure rated 4 points according to CIRS, with the exception of diseases of the eyes, ears, nose, throat and larynx, were also excluded from the trial. The median result of comorbidity assessment was 8. In 42% of the patients qualified for the trial, the creatinine clearance was below 70 ml/min and the result of comorbidity assessment according to CIRS was above 6 points. 34% of the patients were qualified only on the basis of assessing the comorbidities, and 23% solely on the basis of impaired renal function.

The majority of the subjects were given obinutuzumab intravenously at an initial dose of 1000 mg on the 1st, 8th and 15th days of the first treatment cycle. In each subsequent treatment cycle (cycles 2 to 6), subjects received 1000 mg obinutuzumab only on the 1st day of the cycle. Chlorambucil was administered orally in 0.5 mg/kg body weight dose on the 1st and 15th days of each treatment cycle (cycles 1 to 6). The baseline characteristics of the patients in individual groups were well balanced. The median age of the study subjects was 73 years, and 44% of the patients were aged 75 years, or more. At baseline, 225 of the patients were qualified as stage A, according to the Binet classification, 42% as stage B and 36% as stage C.

The primary endpoint in that trial was the progression-free survival (PFS). The secondary endpoints included:

- overall survival (OS);
- progression-free survival assessed by an independent review committee (IRC);
- treatment response rates at the time of therapy completion, including the proportion of patients testing negative for minimal residual disease (MRD);
- event-free survival (EFS);
- time to administration of a subsequent line of antileukemic treatment;
- adverse effects (AEs) rate.

During Phase 2 of the study, obinutuzumab treatment combined with chlorambucil was compared with rituximab in combination with chlorambucil in 663 patients. The efficacy for both phases of the study are shown in the Table 1.

The median PFS assessed by the investigators was 26.7 months in the group treated with obinutuzumab combined with chlorambucil and 11.1 months in the group treated with chlorambucil monotherapy (hazard ratio [HR] = 0.18, $p < 0.001$). A significant advantage in PFS was demonstrated for obinutuzumab combined with chlorambucil and also when compared with rituximab combined with chlorambucil (26.7 months vs. 15.2 months, respectively; HR = 0.39, $p < 0.001$).

The results of analysis of subgroups for PFS (according to gender, age, Binet clinical staging, CIRS score, $beta_2$-microglobulin, IGHV mutational status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with those observed in the general population of patients qualified for the treatment (intention-to-treat [ITT] analysis).

At the time of analysis median OS was not achieved in any of the study arms, however the results obtained suggest that administrating obinutuzumab combined with chlorambucil showed a statistically significant survival improvement when compared with chlorambucil monotherapy. The mortality rate in individual groups was 9% vs. 20%, respectively (HR = 0.41; 95% confidence interval [CI], 0.23–0.74, $p = 0.002$). No statistically significant advantage was demonstrated in survival rates in the group treated with obinutuzumab combined with chlorambucil over the group treated with rituximab in combination with chlorambucil (HR = 0.66; 95% CI: 0.41–1.06, $p = 0.08$). The mortality rates in these groups were 8% vs. 12%, respectively.

In summary, the risk of disease progression or patient death was lower in those groups receiving obinutuzumab combined with chlorambucil when compared with the group on rituximab with chlorambucil and the group treated with chlorambucil monotherapy in all subgroups; with the exception of the subgroup of patients with the 17p deletion. In the small group of patients with this 17p deletion, only a benefit was observed when compared with the group receiving chlorambucil (HR = 0.42, $p = 0.0892$); no benefit was seen when compared with the group on rituximab with chlorambucil. In individual subgroups, a reduction was found in the risk of disease progression or death, which was from 92% to 58% for the group treated with obinutuzumab and chlorambucil compared to the group receiving chlorambucil alone and from 72% to 29% for the group on obinutuzumab with chlorambucil compared to the group treated with rituximab and chlorambucil.

It is worth stressing that in the assessment undertaken during the treatment, using QLQC30 and QLQ-CLL-16 questionnaires, no significant differences were found for any subscale. The data from the follow-up period are limited, particularly for the group treated with chlorambucil monotherapy. Nevertheless, until now no data has been published, which indicate any significant differences in the quality of life for the follow-up period. The assessment of health-associated quality of life demonstrated no statistically significant differences during the treatment period.

The registration study has shown that adverse events occurred most frequently in the group treated with obinutuzumab. Grade 3, or higher, adverse reactions developed in 73% and 50%, when comparing the obinutuzumab-chlorambucil group with chlorambucil monotherapy; in 56% and 50%, comparing the rituximab-chlorambucil group with chlorambucil monotherapy; and, finally, in 70% and 55% of patients when comparing the obinutuzumab––chlorambucil and rituximab–chlorambucil groups.

The most frequent adverse events (irrespectively of the degree of intensity) in patients from the group treated with obinutuzumab + chlorambucil compared with chlorambucil monotherapy included infusion-related reactions, which developed in a majority of patients during the first treatment cycle (69% vs. 0%). However, the incidence of infusion-related reactions gradually decreased: from 65% with infusion of the first 1000 mg obinutuzumab dose to below 3% with subsequent infusions. The symptoms of infusion-related reactions usually included: dyspnoea, hypotension, nausea, vomiting, chills, fever and hot flushes. Less frequently neutropenia (40% vs. 18%) and thrombocytopenia (15% vs. 7%) were observed, and the rate of grade 3–5 infections was 16% in the obinutuzumab group [14]. The most frequent grade 3, or higher, adverse events in patients from the group receiving obinutuzumab + chlorambucil, compared with chlorambucil monotherapy respectively, included infusion-related reactions (12% vs. 0%), neutropenia (35% vs. 16%), thrombocytopenia (11% vs. 4%) and anemia (5% vs. 4%).

For the group receiving obinutuzumab + chlorambucil in this study, compared with the group treated with rituximab + chlorambucil, the most frequently developing grade 3, or higher, adverse reactions respectively included neutropenia (33% vs. 28%), infections (12% vs. 14%; including pneumonia in 4% vs. 5%, neutropenia with fever in 2% vs. 1%), infusion-related reactions (20% vs. 4%), thrombo-

cytopenia (10% vs. 3%), leucopenia (4% vs. 1%) and tumour lysis syndrome (2% vs. 0%). In summary, grade 3, or higher, adverse reactions occurred more frequently in the group treated with obinutuzumab + chlorambucil as compared with the group receiving rituximab + chlorambucil (70% vs. 55%). Deaths due to adverse reactions occurred more frequently in the group receiving obinutuzumab + chlorambucil than in the group on rituximab + chlorambucil (4% vs. 6%).

Ibrutinib

Ibrutinib is a strong, low molecular weight Bruton's tyrosine kinase inhibitor. It was approved in the European Union (EU) in October 2014 (in February 2014 by the FDA) for treating adult CLL patients, who were given at least one previous therapy, or treatment-naïve patients with 17p deletion or *TP53* mutation, in whom chemoimmunotherapy administration is not appropriate. The safety of use and effectiveness of ibrutininb in patients with CLL was assessed in one uncontrolled and one randomised trial with a control group.

An open-label, uncontrolled, multicentre study (PCYC-1102-CA) involved 51 patients with recurrent and drug-refractory CLL, who were given a 420 mg dose once daily and 34 patients who received 840 mg once daily [17]. Ibrutinib was administered until disease progression or loss of patient tolerance to treatment. The primary endpoint was the safety of using two treatment regimens, based on the incidence and intensity of adverse events. The secondary endpoints included: OS, PFS, pharmacodynamics and pharmacokinetics of the drug. The response assessment was carried out at the end of the 2^{nd}, 5^{th}, 8^{th}, 12^{th}, 15^{th} and 24^{th} treatment cycles. The median age of the study subjects was 68 years (range from 37 to 82 years), the median time after diagnosis — 80 months, and the median number of previous treatment lines — 4. At baseline, 39.2% of the patients were at clinical stage IV according to Rai, in 45.1% a bulky disease was found (tumour diameter ≥ 5 cm), in 35.3% the 17p deletion and in 31.4% the 11q deletion were both confirmed [18].

The overall response rate (ORR) was determined by the investigators and IRC according to IWCLL (International Workshop on CLL) 2008 criteria. After the follow-up period (median 16.4 months), the ORR in IRC assessment for 51 patients with recurrent/refractory disease was 64.7% (95% CI: 50.1%, 77.6%); all responses being partial (PR) [18]. Taking into account partial responses with lymphocytosis, the ORR was 70.6% (two complete responses and 34 partial responses) in the group receiving the 420 mg dose. Ten patients (20%) in that group achieved PR with persistent lymphocytosis.

The treatment with ibrutinib led to long term responses irrespectively of the dose administered. The estimated 26-month PFS rate was 75% and the estimated OS rate was 83%. During the follow-up period, disease progression was found in 11 patients (13%) [18].

It is very significant that the ibrutinib-treated patients achieved a prolongation of the time to disease progression in spite of the genetic load of risk factors. In 28 patients with deletion of the short arm of chromosome 17 [del(17)(p13.1)] (a chromosome aberration linked with the poorest prognosis) — the estimated 26-month PFS rate was 57% and the estimated OS rate was 70%. The patients who discontinued ibrutinib treatment for reasons other than disease progression remained in the study and were followed up every three months until disease progression, starting another line of therapy, or death. After detecting disease progression or starting another line of antitumour treatment, the follow-up was limited only to survival status. A long term improvement of cytopenia during ibrutinib treatment was observed in 32 out of 41 (78%) patients with baseline thrombocytopenia, 27 out of 33 (82%) patients with anemia and 24 out of 31 (77%) patients with neutropenia [17].

Another study was a Phase 3 open-label, randomized, multicentre study of superiority type (PCYC-1112-CA, RESONATE study), comparing ibrutinib with ofatumumab [19]. Patients with recurrent and drug-refractory CLL (n = 391) were randomised in a 1:1 ratio into groups receiving ibrutinib or ofatumumab. Ibrutinib was administered in a 420 mg daily dose until disease progression or loss of tolerance, while ofatumumab was given in 12 doses (initial dose — 300 mg/week, then 2000 mg weekly). After disease progression, 57 patients in the ofatumumab arm were qualified by crossover to receive ibrutinib. The median age of the study subjects was 67 years (range from 30 to 88 years), 68% were males and 90% of the patients were Caucasians. All patients had a baseline fitness status of 0 or 1 according to ECOG. The median time to diagnosis was 91 months and the median number of previous therapies was 2. In 58% of the patients at least one leukemic tumor of diameter of 5 cm or more was found at baseline. In 32% of the patients a 17p deletion were found and in 31% a 11q deletion.

Table 2. Data on the effectiveness of treating patients with chronic lymphocytic leukemia with ibrutinib in the RESONATE study (source [19])

Tabela 2. Dane dotyczące skuteczności leczenia ibrutynibem chorych na przewlekłą białaczkę limfocytową w badaniu RESONATE (źródło [19])

Endpoint	Ibrutinib N = 195	Ofatumumab N = 196
Median PFS	Not reached	8.1 months
	HR = 0.215 (95% CI: 0.146–0.317)	
Median OS*	HR = 0.434 (95% CI: 0.238–0.789) HR = 0.387 (95% CI: 0.216–0.695)	
ORR acc. to IRC** p < 0.0001	42.6%	4.1%
ORR including PR with lymphocytosis (ORR acc. to IRC) p < 0.0001	62.6%	4.1%

*Overall survival (OS) medians had not been reached in both groups; **all, who developed partial response (PR); PFS — progression-free survival; HR — hazard ratio; ORR — overall response rate; IRC — independent review committee

Ibrutinib significantly prolonged disease progression-free survival time, however the median had not been reached before the preliminary results were published (median follow-up time was 9.4 months). The median disease PFS in the ofatumumab group was 8.1 months whereas the relative risk of disease progression or death in the ibrutinib-treated group was HR = 0.22 (95% CI: 0.15–0.32, p < 0.001). This means a reduced risk of disease progression or death in patients treated with ibrutinib by 78% compared with ofatumumab. After six months of treatment, 88% of patients in the ibrutinib group remained free of disease progression, compared with 65% in the ofatumumab group. The effect of ibrutinib on PFS was observed independently of the baseline characteristics of the patients.

In patients with deletion of the short arm of chromosome 17 deletion [del(17)(p13.1)], linked with the poorest prognosis, the median PFS was not attained by the ibrutinib group, compared with a median of 5.8 months in the ofatumumab group (relative risk for progression or death was: HR = 0.25; 95% CI: 0.14–0.45). After six months, 83% of patients with this aberration in the ibrutinib group still lived without disease progression, compared with 49% in the ofatumumab group.

Ibrutinib, in comparison to ofatumumab, significantly improved the patient OS (the relative risk of death in the ibrutinib group being: HR = 0.43; 95% CI: 0.24–0.79, p = 0.005), meaning that the risk of death was reduced by 57%. After 12 months the OS rate was 90% in the ibrutinib group and 91% in the ofatumumab group. Before publication of the preliminary results from the RESONATE study, 57 patients from the ofatumumab group were switched to ibrutinib by crossover after confirmation of disease progression.

The survival results were based on analysing the data that were censored during the crossover switch of the patients between the groups. After 12 months of the treatment the survival results were also analyzed in the non-censored analysis of susceptibility (relative risk of death: HR = 0.29, p = 0.001), in which OS rates were 90% in the ibrutinib group and 79% in the ofatumumab group. The advantage in effectiveness of ibrutininb over ofatumumab for OS was noted in all subgroups of the RESONATE study subjects.

The response rate, when measured independently, was significantly higher in the ibrutinib group, compared with the ofatumumab group (Table 2). Partial responses were confirmed in 43% of patients on ibrutinib and 4% in the group on ofatumumab (odds ratio [OR] = 17.4; 95% CI: 8.1–37.3, p < 0.01). In 20% of patients receiving ibrutinib a partial response with lymphocytosis was noted. Lymphocytosis was observed in 69% of patients treated with ibrutinib, in whom no disease progression was found. The response rates in the investigators' opinion were significantly higher; being respectively 68% and 21% [19, 20].

The effectiveness was similar in all studied subgroups, including patients with and without the 17p deletion; a predetermined stratification factor.

The treatment duration in the RESONATE study was longer in those patients receiving ibrutinib than in patients treated with ofatumumab (median treatment duration — 8.6 months [range from 0.2 to 16.1] vs. 5.3 months [range from 0 to 7.4]).

The most frequent non-hematological adverse events, developing in at least 20% of the patients, included: diarrhea, fatigue, fever and nausea in the group of ibrutinib, and fatigue, infusion-related reactions and coughing in the group on ofatumumab.

At least one adverse event of grade 3, or higher, was observed in 57% of the patients on ibrutinib and 47% of the patients from the ofatumumab group. The grade 3, or higher, adverse events developed significantly higher in the ibrutinib group which respectively included mainly diarrhoea (4% vs. 2%) and atrial fibrillation (3% vs. 0%). The adverse events bleeding-related (irrespective of the degree of severity) significantly developed more frequently in the group of ibrutinib (44% vs. 12%). Furthermore, marked bleedings (of degree ≥ 3) were only reported in 1% of patients from the ibrutinib group and in 2% of patients on ofatumumab. The remaining adverse events, which developed more frequently in the ibrutinib group, irrespectively of their severity, included: rash (8% vs. 4%), fever (24% vs. 15%) and vision disturbances (10% vs. 3%). Infections were seen more frequently in the group on ibrutinib (70% vs. 54%), whilst the infection rate of grade 3, or higher, was similar in both groups (24% vs. 22%). In the ofatumumab group, infusion-related reactions, peripheral sensory neuropathy, urticaria, nocturnal hyperhidrosis and pruritus were more frequent. Basocellular and squamous cell carcinoma were observed in 4% of patients on ibrutinib and 2% of patients in the ofatumumab group, whilst other malignancies were respectively found in 3% and 1% of the patients. Treatment discontinuation due to adverse events occurred in 4% of the study subjects in each group. The mortality rate due to the adverse events was 4% in the group of ibrutinib and 5% in the patients on ofatumumab. It should be stressed, however, that the incidence of adverse events did not take into account the longer exposure of patients to the drug in the ibrutinib group. As mentioned by the investigators, the significantly longer (by over three months) duration of ibrutinib treatment could have significantly contributed to higher rates of some adverse events in that group of patients.

In the registration study, about 3/4 of the patients with CLL treated with ibrutinib demonstated a reversible increase in the lymphocyte count after therapy initiation (increase by ≥ 50% compared with the baseline value and exceeding the value of 5000/μl), frequently observed with a reduction of lymphadenopathy. It was found that lymphocytosis was a pharmacodynamic effect and should not have been regarded as disease progression in the absence of other clinical data. Lymphocytosis usually occurred during the first several weeks of ibrutinib administration and usually regressed with time (median value 18.7 weeks in CLL patients) [18].

In September 2014, an one-arm Phase 2 study was published, conducted at the MD Anderson Cancer Center in Houston USA, which suggests that the combination of ibrutinib with rituximab may be an effective and well tolerated therapeutic option for CLL patients with unfavourable prognostic factors [21]. In all, 40 patients with symptomatic CLL were enrolled into the study 20 out of whom had the 17p deletion or the *TP53* mutation (16 patients were previously treated and four were treatment-naïve). In 13 cases, recurrent CLL with the 11q deletion were observed. The remaining seven patients were previously subjected to first-line chemoimmunotherapy (median PFS < 36 months).

Subjects were given 420 mg ibrutinib once daily in 28-day cycles, in combination with rituximab administered once weekly in the first cycle and then once per cycle for another five cycles. The primary endpoint of the study was PFS in the ITT group.

In the 18th month of the study, the patient rates without disease progression were estimated at 78% (95 CI: 60.58–88.45). In patients with the 17p deletion or *TP53* mutation, the rate became 72% (95% CI: 45.56–87.55). Furthermore, in month 18, 84% of the study subjects were still alive (95% CI: 67.22–92.39). The patient rate in the subgroup with the 17p deletion or *TP53* mutation was 78% (95% CI: 51.99–91.36). When comparing differences in health-related quality of life at the study beginning and during treatment, patients treated with ibrutinib in combination with rituximab, reported a significant improvement in their general health and quality of life after six and 12 months, with simultaneous and significant body mass gain. The toxicity of this treatment regimen, in most cases, was limited to adverse events of grade 1–2. 25% of the patients developed diarrhoea, 35% developed bleeding events, in 37.5% nausea and in 17.5% suffered fatigue. Grade 3 infections occurred in 10% of the patients.

This study reports promising observations concerning the effectiveness and safety of ibrutinib combined with rituximab in the treatment of CLL patients with a poor prognosis. They, however, require confirmation in randomised studies on a greater number of patients. The possibility seen here of effective drug use, even in patients with *TP53* gene disorders, seems particularly significant.

Idelalisib

Idelalisib — an oral, selective inhibitor of phosphatidylinositiol p110δ 3-kinase (PI3kδ) is the third drug granted breakthrough therapy status by the FDA and was approved in the USA in 2014 for treating CLL patients. This kinase is hyperactive in B-cellular malignancies and is of key importance for many signalling pathways that regulate the proliferation, survival and accumulation of malignant cells in lymphoid tissues and bone marrow. Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B cells and in primary tumour cells.

Idelalisib in 2014 was approved in the EU for use as a therapy combined with rituximab in the treatment of those adult patients with CLL as follows:

- who had previously received at least one therapy, or
- as a first-line therapy in the case of 17p deletion or *TP53* mutation in patients, for whom no chemoimmunotherapy could be used.

The marketing authorisation holder has been obliged to submit periodical idelalisib safety reports and to submit, by the end of 2017, the final report on the Phase 3 GS-US-312-0116 study assessing the effectiveness and safety of idelalisib use in combination with rituximab in patients with previously treated CLL, together with the final data on the extension of the GS-US-312-0117 study.

The randomised, double blind and placebo-controlled Phase 3 study (GS-US-312-0116) was the main one serving as the basis for drug approval [22]. The study randomised 220 subjects in a 1:1 ratio of the group receiving idelalisib in 150 mg dose twice daily in combination with rituximab, or to the group treated with placebo and rituximab. In most patients, unfavourable cytogenetic prognostic factors were present (in 43.2% — the 17p deletion and/or the *TP53* mutation; in 83.6% — non-mutated IgVH genes). The median number of previous therapies was 3. All subjects were given rituximab intravenously in an initial dose of 375 mg/m^2 body surface area and then 500 mg/m^2 body surface area (eight infusions in total). The patients in idelalisib group, for whom disease progression was confirmed, could be given a higher drug dose (300 mg twice daily). The disease PFS was the primary endpoint of the study.

In week 24, the patient rate with no progression was 93% in the idelalisib group and 46% in the placebo (the corrected risk ratio for disease progression or death in the idelalisib group was: HR = 0.15 (95% CI: 0.08–0.28, p < 0.001). Disease progression occurred in 12 patients in the idelalisib group and 53 patients receiving placebo. The median PFS in the idelalisib group was not reached, whilst being 5.5 months in the placebo group (Table 3). The therapeutic effect of idelalisib was demonstrated in all predefined subgroups in-

Table 3. Results of idelalisib effectiveness in patients with treating chronic lymphocytic leukemia obtained in the 312-0116 study, according to an independent review committee assessment (source [22])

Tabela 3. Wyniki skuteczności idelalisibu w leczeniu chorych na przewlekłą białaczkę limfocytową uzyskane w badaniu 312-0116 według opinii niezależnej komisji (źródło [22])

		Idelalisib + rituximab N = 110	Placebo + rituximab N = 110
PFS	Median (95% CI)	NR (10.7; NR) months	5.5 (3.8; 7.1) months
	HR (95% CI)	0.18 (0.1; 0.32)	
	P value	< 0.0001	
ORR	Patient responding rates (95% CI)	74.5%	14.5%
	Odds ratio (95% CI)	17.28 (8.66; 34.46)	
	P value	< 0.0001	
LNR*	Patient responding rates, (95% CI)	92.2% (85.1; 96.6)	5.9% (2.2; 12.5)
	Odds ratio (95% CI)	165.5 (52.17; 524.98)	
	P value	< 0.0001	
OS	Median (95% CI)	NR (NR; NR)	NR (12.8; NR)
	HR (95% CI)	0.28 (0.11; 0.69)	
	P value	0.03	

*LNR — lymph node response defined as obtained reduction by ≥ 50% of the sum of the products of the greatest perpendicular diameters of changes selected as indices; PFS — progression-free survival; CI — confidence interval; NR — not reached; HR — hazard ratio (relative risk); ORR — overall response rate; OS — overall survival

cluding those stratified according to the presence of the 17p deletion or *TP53* or *IgVH* mutations.

In month 12 it was found that OS in the idelalisib group was significantly greater than that in the placebo group (92% vs. 80%). The corrected death risk ratio was; HR = 0.28 (95% CI: 0.09–0.86, p = 0.02). Before publishing the preliminary study results, the median OS was not reached in any group. Before the survival analysis was made, 16 patients died; four in the idelalisib group and 12 in the placebo group. The ORR was 81% (95% CI: 71–88) in the group of idelalisib and 13% (95% CI: 6–21) in the placebo group (OR = 29.92, p < 0.001). All responses were partial.

The assessment carried out by the IRC demonstrated that the patient rate, in whom at least a 50% reduction of lymphadenopathy occurred, was significantly higher in the idelalisib group, i.e. 93% (95% CI: 85–97) compared with 4% (95% CI: 1–10) in the placebo group (OR = 264, p < 0.001).

Compared with rituximab and placebo, the treatment with idelalisib combined with rituximab led to a statistically and clinically significant improvement in the physical state, social functioning and functional fitness assessed by the patients with a standardized FACT-LEU (Functional Assessment of Cancer Therapy — Leukemia) questionnaire, along with a significant improvement in anxiety, depression and common activities as measured according to the EQ-5D (EuroQoL Five-Dimensions) scale.

In over 90% of patients, at least one adverse event occurred. In the idelalisib group, the following were respectively reported more frequently than in the placebo group; neutropenia (55% vs. 49% abnormal laboratory test results), increased aminotransferase activity (35% vs. 19% abnormal laboratory test results), fever (29% vs. 16%), nausea (24% vs. 21%), chills (22% vs. 16%), diarrhea (19% vs. 14%). In the idelalisib group the following were respectively less frequently observed: anemia (25% vs. 30% abnormal laboratory test results), fatigue (24% vs. 27%), infusion-related reactions (15% vs. 28%), thrombocytopenia (17% vs. 26% abnormal laboratory test results), cough (15% vs. 25%) and dyspnea (11% vs. 19%). The adverse events in both groups were usually mild or moderately intense.

In 40% of the patients on idelalisib, at least one serious adverse event occurred, compared with 35% in the placebo group. The most frequently reported serious adverse events in both groups respectively included; pneumonia (6% vs. 8%), fever (6% vs. 3%), neutropenic fever (5% vs. 6%) and sepsis (5% vs. 3%). Treatment discontinuation due to adverse events became necessary in 8% of the patients receiving idelalisib and 10% of the patients in the placebo group.

Discussion

The improvements in treatment outcomes for CLL patients, due to the marketing of the most modern molecularly-directed drugs, (in Poland, such drugs are not publicly reimbursed), has attracted the attention of not just hematologists or oncologists, but the wider medical community; especially as such changes may also lead in the near future to similar approaches for treating of other diseases. A vital aspect of this progress benefits those patients with highly unfavourable prognostic factors like *TP53* gene disorders and the elderly who suffer from many comorbidities. In the past, for safety reasons, these patients did not usually qualify for clinical trials despite constituting a sizeable proportion of those suffering with CLL.

Another promising aspect is an acquirement more detailed knowledge of the B cell antigen receptor's role in the pathogenesis of CLL, thereby leading to the development of several low-molecular-weight inhibitors of important signalling pathways, which in turn, has opened a new era for targeted therapy in CLL.

Progress in CLL research, with confirmed scientific evidence, has suggested that significant improvements can be made in treating this condition, particularly regarding the clinically significant endpoints as when compared to current therapy standards. This has contributed to the FDA granting such drugs 'breakthrough therapy status' so as to hasten the drug registration process.

It should however be kept in mind that early stages of drug approval requires additional monitoring of adverse events because of an insufficiently known safety profile [23]. In order to offer patients the highest level of protection in everyday clinical practice conditions, obinutuzumab, ibrutinib and idelalisib have been placed by the EMA on the European list of drugs that are included into the additional safety monitoring system [24].

Setting an official price for a medicinal product can be controversial with an adequate therapeutic benefit expressed in quality-adjusted life years (QALY). Polish legal regulations about the cost of obtaining a quality-adjusted life year require the manufacturer to estimate the so-called threshold price ie. threshold value of the drug price at which the ratio of the cost to the obtained health effects is not higher than the cost-effectiveness threshold

stipulated by the Agency for Health Technology Assessment and Tariff System. This may be controversial in a situation when no final data on patient OS are available.

Obinutuzumab, ibrutinib and idelalisib supplement the drug armamentarium hitherto used for treating CLL. Ibrutinib and idelalisib are a new alternative for patients with refractory/recurrent disease and also for treatment-naïve patients with the 17p deletion or *TP53* mutation, in whom administration of chemoimmunotherapy is not indicated because of predicted poor effectiveness. These drugs enable a better control of disease progression and the quality of life to be achieved. The most serious adverse effects are also reduced as compared with traditional chemotherapy regimens. Moreover, obinutuzumab combined with chlorambucil offers additional therapeutic benefits to patients previously treated for CLL and may be a valuable first-line therapeutic option in elderly CLL patients with comorbidities.

An optimal sequential therapy with the afore-discussed drugs has not yet been established. Further studies on B cell receptors and inhibition of signalling pathways generated by these receptors could be a promising source of new data. This would thereby significantly change the current paradigm for treating these CLL patients. Undoubtedly in the nearest future, clinicians treating CLL patients will face a significant challenge of treatment individualisation, defining optimal therapy regimens and their sequence along with establishing molecular biomarkers of predictive importance. However, the true availability of the new treatment regimens for patients will depend in the first place on future reimbursement regulations.

References

1. Expanded access to investigational drugs for treatment use. Fed. Regist. 2006; 71: 75148.
2. Shulman S.R., Brown J.S. The Food and Drug Administration's early access and fast-track approval initiatives: how have they worked? Food Drug Law J. 1995; 50: 503–531.
3. Food and Drug Administration. FY 2012 Innovative drug approvals. Silver Spring, FDA, December 2012. Avaible on: www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ /ucm330859.pdf. Data access: 30.09.2015.
4. Steenburg C. The Food and Drug Administration's use of post--marketing (phase IV) study requirements: exception to the rule? Food Drug Law J. 2006; 61: 295–383.
5. Avaible on: http://www.fda.gov/forconsumers/byaudience/for--patientadvocates/speedingaccesstoimportantnewtherapies/ /ucm128291.htm. Data access: 30.09.2015.
6. Avaible on: http://www.fda.gov/forpatients/approvals/fast/ucm405397.htm. Data access: 30.09.2015.
7. Avaible on: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/ /pdf/BILLS-112s3187enr.pdf. Data access: 30.09.2015.
8. Avaible on: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf. Data access: 30.09.2015.
9. Avaible on: http://www.fda.gov/regulatoryinformation/legislation/ /federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm329491.htm. Data access: 30.09.2015.
10. Robak P., Smolewski P. Współczesne poglądy na leczenie przewlekłej białaczki limfocytowej. Acta Haematol. Pol. 2011; 42: 53–62.
11. National Cancer Institute, Surveillance Epidemiology and End Results. SEER Stat Facts Sheets: chronic lymphocytic leukemia. Avaible on: http://seer.cancer.gov/statfacts/html/clyl.html. Data access: 30.09.2015.
12. Robak T., Jamroziak K., Robak P. Current and emerging treatments for chronic lymphocytic leukemia. Drugs 2009; 69: 2415–2449.
13. Robak T., Hus I., Błoński J. et al. Rekomendacje diagnostyczne i terapeutyczne dla przewlekłej białaczki limfocytowej w 2014 r. — raport Grupy Roboczej PTHiT oraz PALG-CLL. Acta Haematol. Pol. 2014; 45: 221–239.
14. Charakterystyka Produktu Leczniczego — Gazyvaro.
15. Goede V., Fischer K., Busch R. et al. Chemoimmunotherapy with GA101 plus chlorambucil in patients with chronic lymphocytic leukemia and comorbidity: results of the CLL11 (BO21004) safety run-in. Leukemia 2013; 27: 1172–1174.
16. Goede V., Fischer K., Busch R. et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N. Engl. J. Med. 2014; 370: 1101–1110.
17. Byrd J.C., Furman R.R., Coutre S.E. et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N. Engl. J. Med. 2013; 369: 3 2–42.
18. Charakterystyka Produktu Leczniczego — Imbruvica.
19. Byrd J.C., Brown J.R., O'Brien S. et al.Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N. Engl. J. Med. 2014; 371: 213–223.
20. Hallek M., Cheson B., Catovsky D. et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. Blood 2012 June 4.
21. Burger J.A., Keating M.J., Wierda W.G. et al. Ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. Lancet Oncol. 2014; 15: 1090–1099.
22. Furman R.R., Sharman J.P., Coutre S.E. et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N. Engl. J. Med. 2014; 370: 997–1007.
23. Avaible on: http://www.ema.europa.eu/ema/index.jsp?curl=pages/ /special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff. Data access: 30.09.2015.
24. Avaible on: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142453.pdf. Data access: 30.09.2015.