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IGHV mutational status and the choice of first-line therapy for patients with chronic lymphocytic leukaemia

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Abstract

Chronic lymphocytic leukaemia (CLL) is an incurable lymphoid malignancy with a heterogeneous clinical course varying from relatively indolent cases characterized by long survival to more aggressive and treatment-resistant ones. Findings from randomized clinical trials and long-lasting retrospective observations have shown that somatic hypermutation (SHM) status of the immunoglobulin heavy chain variable gene (IGHV) comprising the B cell receptor (BCR) plays a significant prognostic and predictive role in patients with CLL. According to the current international and Polish guidelines, assessment of IGHV mutational status should be mandatory at first-line treatment initiation in addition to p53 pathway defects and comorbidities for therapy allocation.

This review describes the rationale for IGHV mutational status assessment as well as discusses its prognostic role in patients with CLL in the first-line setting.

Key words: chronic lymphocytic leukaemia, ibrutinib, acalabrutinib, idelalisib, monoclonal antibodies, venetoclax, treatment, immunoglobulin heavy chain variable gene

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Introduction

Chronic lymphocytic leukaemia (CLL) is an incurable lymphoid malignancy characterized by clonal proliferation of small CD5/CD19-positive lymphocytes [1]. The median age at diagnosis is 72 years with an annual age-adjusted incidence rate of 3–5 per 100 000 persons [1, 2]. CLL is the most diagnosed leukaemia in the US and Europe [1, 2]. The clinical course of CLL is very heterogeneous varying from relatively indolent cases characterized by long survival to more aggressive and treatment-resistant ones [3]. During the past decade, the treatment armamentarium for CLL has been based on alkylating agents and purine analogues. However, significant progress in the recent years has led to the development of more selective and more efficient treatment options including anti-CD20 monoclonal antibodies (rituximab, obinutuzumab), Bruton's tyrosine

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kinase (BTK) inhibitors (ibrutinib, acalabrutinib and zanubrutinib), selective phosphatidylinositol-3-kinase (PI3K) inhibitors (idelalisib, duvelisib, umbralisib) and the first-in-class BCL-2 antagonist venetoclax [1, 4].

At first, the chemotherapy options were enriched by the approval of anti-CD20 antibodies [5, 6]. Nevertheless, in numerous clinical trials and retrospective studies poor efficacy of anti-CD20-based immunochemotherapy in patients with p53 pathway defects, e.g. 17p deletion and/or *TP53* mutation was demonstrated [7, 8]. A significant breakthrough in the treatment of this aggressive CLL subset was made with the introduction of ibrutinib in monotherapy and idelalisib combined with rituximab, which both have shown remarkable efficacy [9–11]. Venetoclax was the next significant milestone in CLL treatment due to its high efficacy in high-risk patients and the possibility of time-limited therapy as opposed to BTK and PI3K inhibitors [12, 13].

In line with the development of novel therapeutic options, significant progress in the understanding of CLL biology has been also made in terms of the identification of new prognostic and therapy predictive factors. Besides the clinical importance of Rai and Binet staging systems which have been used for risk stratification since the early 1980s, the importance of molecular targets in CLL biology and progression is increasing [14–17]. Next-generation sequencing (NGS) identified several recurrent mutations in genes which may be grouped by biological function e.g. response to DNA damage and cell cycle control (*TP53*, *ATM*, *RB1*, *BIRC3*), Notch signalling (*NOTCH1*, *NOTCH2*, *FBXW7*), inflammatory pathways (*MYD88*, *DDX3X*, *MAPK1*), RNA processing (*SF3B1*), and cytokine signalling (*NRAS*, *KRAS*, *BRAF*) [15–20]. From the above-mentioned list, only the p53 pathway status is currently reflected in the international guidelines [1, 21, 22].

Findings from randomized clinical trials and long-lasting observations showed that the somatic hypermutation (SHM) status of the immunoglobulin heavy chain variable gene (*IGHV*) comprising the BCR receptor has significant prognostic significance [1, 21, 22]. Somatic hypermutation is a physiological process occurring in B cells during their passage through lymph nodes. Malignant transformation might occur in the B cells before or after the SHM of the genes encoding the *IGHV* region of the leukemic BCR. Therefore, in CLL two types of varying B-cell clones may be distinguished based on the difference in *IGHV* mutational status compared to germline sequence [23]. Patients with mutated CLL (M-CLL) denote patients with a CLL clone whose IGHV is mutated ≥ 2% from the reference germline sequence, while the patients with unmutated IGHV (U-CLL) clones are characterized by sequences mutated < 2% from the germline sequence [23]. According to the current guidelines, the *IGHV* mutational status and designation of patients to M-CLL and U-CLL have both significant prognostic values. The U-CLL cases are characterized by a shorter response to classical chemotherapy and anti-CD20 based immunotherapy [7, 24, 25]. The U-CLL cases differ also in the biological features compared to M-CLL cases, with the accumulation of adverse prognostic mutations and increased BCR signalling activity [7, 24, 25].

The *IGHV* mutational status is determined routinely by Sanger sequencing. Due to its prognostic value, information should be determined at the time of the first-line treatment initiation. Mutational status does not change with time as opposed to mutational load due to clonal evolution [26]. Therefore, the assessment of *IGHV* status does not require repeated testing unlike the assessment of deletion 17p or *TP53* mutation. So far NGS based determination of *IGHV* mutational status has not been approved for clinical routine testing due to lack of standardization and ambiguous results, however, intensive efforts are being made to utilize implement this methodology in the CLL diagnosis and response monitoring by assessing the minimal residual disease (MRD) status and clonal evolution. At diagnosis and in early-stage disease, the U-CLL cases comprise around 50–60% of patients, however, this increases up to over 80% in the relapsed and refractory setting [26].

Considering the increasing significance of *IGHV* determination and its prognostic role regarding CLL treatment allocation, this review summarizes the current findings of phase II and III clinical trials in the context of *IGHV* mutational status in the treatment-naïve patients with CLL.

Outcomes of the therapies used in the treatment-naïve patients

Patients with CLL may be treated in the first-line setting with various agents ranging from anti-CD20 based immunotherapy, to BTK inhibitors, PI3K inhibitors and venetoclax in combination with anti-CD20 antibodies. Depending on the patient's age, eligibility for fludarabine treatment and comorbidities the above-mentioned treatments are implemented according to Polish and international guidelines [1, 21, 22]. Outcomes depending on ap-

plied treatment in CLL patients with M-CLL and U-CLL are summarized in Table 1.

Immunochemotherapy

As it was shown independently in clinical trials and confirmed in a meta-analytical approach, the use of fludarabine, cyclophosphamide and rituximab (FCR) in patients with M-CLL results in durable remissions as opposed to patients with U-CLL [7, 27, 43]. In the study of Thompson et al. [44] performed in the MD Anderson Cancer Centre, patients with M-CLL were characterized by durable remissions with a median PFS not reached and a median OS of 153.6 months. PFS and OS values in the U-CLL group were 50.4 and 112.8 months, respectively [44]. Similar results were reported in the CLL8 trial, where the median PFS and OS of patients with M-CLL were not reached, whereas in patients with U-CLL median PFS was 41.9 months and median OS was 84 months [7]. Also, in the CLL10 trial patients with M-CLL had longer median PFS after FCR immunochemotherapy as compared to U-CLL (not reached vs. 42.7 months, respectively) [32]. The effectivity of the FCR regimen in patients with M-CLL was also recently underlined by the results of the ECOG-1912 study which compared rituximab-ibrutinib with the FCR regimen [33]. At a median follow-up of 33.6 months, BTK inhibitor-treated cohort achieved significantly superior results in the terms of the 3-year PFS (89.4% vs. 72.9%) and OS rates (98.8% vs. 91.5%). Nevertheless, the subgroup analysis did not show a significant difference in the 3-year PFS in patients with M-CLL (87.7% in the ibrutinib-rituximab cohort vs. 88.0% in the FCR cohort) [33]. The worse outcome of patients with U-CLL was also observed in patients treated with other immunochemotherapy regimens. In the CLL10 trial in the subgroup receiving bendamustine-rituximab (BR), the median PFS was not reached in the patients with M-CLL, whereas in the U-CLL group median PFS was 33.6 months [32]. The superior outcome of patients with M-CLL compared to U-CLL was also observed in the ALLIANCE 041202 trial in patients treated with BR (median PFS 51 months vs. 39 months) [34]. A similar tendency of worse outcomes in response to obinutuzumab based immunochemotherapy in patients with U-CLL was also observed in the CLL14, ELEVATE-TN and GREEN trials (Table 1) [13, 37–39].

Bruton's tyrosine kinase inhibitors

BTK inhibitors show high and durable activity in the first-line treatment of CLL patients both in monotherapy or in combination with anti-CD20 MoAbs, especially in patients unfit for FCR and BR immunochemotherapy [36, 37, 45, 46]. Therefore, the BTK inhibitors are the cornerstone in the treatment of unfit patients with CLL regardless of IGHV mutational status. BTK inhibitors' activity is similar in U-CLL and M-CLL. Ibrutinib monotherapy in the RESONATE-2 study resulted in high response rates in the patients with U-CLL (95%) and M-CLL (88%) and in both cohorts, the median PFS was not reached [41]. A similar observation was made in the PCYC-1102 study where patients with U-CLL had a similar response rate to patients with M-CLL (87% vs. 81%, respectively). Ibrutinib combined with rituximab (ALLIANCE 041202 study and ECOG-1912 study) or with obinutuzumab (iLLUMINATE study) is characterized by durable remissions. In the long-term follow-up, the median PFS was not reached so far in both U-CLL and M-CLL cohorts [33, 34, 36]. Similar high response rates and durable responses were observed for acalabrutinib in the ELEVATE-TN trial [37, 46]. The updated results of the ELEVATE-TN trial showed the superiority of acalabrutinib in monotherapy or combined with obinutuzumab over chlorambucil combined with obinutuzumab (O-Clb) in patients with mutated and unmutated *IGHV* status. The above-mentioned combinations were characterized by 81%, 89% and 62% 4-year PFS rates in M-CLL cases. In the U-CLL group, it was slightly lower for acalabrutinib (77%) and acalabrutinib-obinutuzmab (86%), significantly lower in the patients treated with O-Clb (4%; with a median PFS of 22.2 months) [37]. Based on the results of the randomized clinical trials performed in the first-line setting, BTK inhibitors are a treatment of choice in patients with U-CLL. In unfit patients, BTKi is preferred over less intensive immunochemotherapy (BR and chlorambucil in monotherapy and combinations with anti-CD20 antibodies) both in patients with U-CLL and M-CLL due to significantly better outcomes.

Venetoclax

The CLL14 trial compared venetoclax-obinutuzumab to the previous standard O-Clb immunochemotherapy in unfit patients with CLL. After a median follow-up of 28.1 months, the percentage of patients with a 2-year PFS rate was significantly higher in the venetoclax-obinutuzumab group than in the O-Clb group (88.2% vs. 64.1%) [13]. At a median follow-up of 52.4 months even higher differences were reported by Al-Sawaf et al. [35]. Significant PFS improvement was observed in the venetoclax-obinutuzumab arm compared

Table 1. Phase II and III clinical trials in first-line treatment in patients with chronic lymphocytic leukaemia regarding somatic hypermutation (SHM) status of the immunoglobulin heavy chain variable gene (*IGHV*)

Trial	Phase	Median FU	U-CLL				M-CLL				Reference
			Number of cases	ORR	mPFS	mOS	Number of cases	ORR	mPFS	mOS	
FCR											
Tam et al.	II	153.6	126	NA	50.4	112.8	88	NA	NR	NR	[27, 28]
CLL8	III	70.8	197	91%	41.9	84.0	NA	93%	NR	NR	[8, 29, 30]
Rossi et al.	II	70.0	216	NA	48.2	NA	120	NA	NR	NA	[31]
CLL10	III	37.4	155	95%	42.7	NA	196	95%	NR	NA	[32]
ECOG-1912	III	33.6	71	NA	NR	NA	44	NA	NR	NA	[33]
BR											
CLL10	III	36.0	108	95%	33.6	NA	86	97%	55.4	NA	[32]
ALLIANCE 041202	III	38	71	NA	39.0	NR	52	NA	51.0	NR	[34]
O–chlorambucil											
CLL14	III	52.4	123	63%	26.9	NA	83	85%	54.5	NA	[13, 35]
iLLUMINATE	III	31.3	57	NA	14.6	NA	50	NA	NR	NA	[36]
ELEVATE-TN	III	46.9	116	NA	22.2	NA	61	NA	NR	NA	[37, 38]
GREEN	III	43.7	33	75.8%	26	NR	20	90%	34	NA	[39]
O–venetoclax											
CLL14	III	52.4	121	84%	57.3	NA	76	85%	NR	NA	[13, 35]
Ibrutinib											
PCYC-1102	II	35.2	15	87%	NA	NA	16	81%	NA	NA	[40]
RESONATE-2	III	60	42	95%	NR	NR	40	88%	NR	NR	[41]
ALLIANCE 041202	III	38	77	NA	NR	NR	52	NA	NR	NR	[34]
R–ibrutinib											
ECOG-1912	III	33.6	210	NA	NR	NA	70	NA	NR	NA	[33]
ALLIANCE 041202	III	38	70	NA	NR	NR	45	NA	NR	NR	[34]
O–ibrutinib											
iLLUMINATE	III	31.3	66	NA	NR	NA	41	NA	NR	NA	[36]
Acalabrutinib											
ELEVATE-TN	III	46.9	119	NA	NR	NA	60	NA	NR	NA	[37, 38]
O–acalabrutinib											
ELEVATE-TN	III	46.9	103	NA	NR	NA	76	NA	NR	NA	[37, 38]
R–idelalisib											
101-08	II	36.4	37	97.3%	NR	NR	37	95.7%	NR	NR	[42]

BR — bendamustine, rituximab; FCR — fludarabine, cyclophosphamide, rituximab; FU — follow-up; O — obinutuzumab; M-CLL — patients with mutated chronic lymphocytic leukaemia; mPFS — median progression-free survival; mOS — median overall survival; NA — not available; NR — not reached; ORR — overall response rate; R — rituximab; U-CLL — patients with unmutated chronic lymphocytic leukaemia

with O-Clb (median not reached vs. 36.4 months) with an estimated 4-year PFS rate of 74.0% in the venetoclax-obinutuzumab and 35.4% in the O-Clb arm [35]. Outcome analysis regarding *IGHV* mutational status showed a significantly longer PFS in venetoclax-obinutuzumab than with O-Clb treated patients in both groups. In the M-CLL cohort, the median PFS was not reached with venetoclax-obinutuzumab and was 54.5 months with O-Clb. In the U-CLL group, the median PFS was 57.3 months compared to 26.9 months. In both arms, PFS was significantly longer for patients with mutated *IGHV* compared with unmutated *IGHV* [35]. Based on the results of this clinical trial the combination of venetoclax and obinutuzumab should be considered over the O-Clb immunochemotherapy for treatment of U-CLL and M-CLL patients with coexisting comorbidities.

Selection of first-line treatment

In the choice of the first-line therapy three major elements should be taken into consideration i.e. patient's age and comorbidities, p53 pathway aberration and *IGHV* mutational status. The above-mentioned traits are the main basis for a proper treatment allocation according to Polish and international guidelines [1, 21, 22]. Assessment of p53 status and *IGHV* mutational status is of utmost importance as patients with del17p, *TP53* mutation or unmutated *IGHV* gene (U-CLL) should not be treated with immunochemotherapy but should be qualified for the therapy with BTK inhibitors or BCL2 antagonist. The role of PI3K inhibitors due to their toxicity profile, especially in the first-line setting, should be reserved for cases where treatment with BTK inhibitors and venetoclax is not available and should be restricted rather to older patients due to their poor tolerability in younger patients with CLL [47, 48].

Based on the observations of phase II and III clinical trials the FCR regimen should be restricted to young patients (< 65 years old) eligible for fludarabine treatment, lacking p53 pathway aberrations and with a mutated *IGHV* status. In these patients, time-limited therapy with 6 cycles of FCR may result in long-term remissions, however, the use of BTK inhibitors remains an equivocal treatment option for this group. The BR protocol, according to international guidelines, loses its importance since it does not result in such long remissions as FCR, and results in a significantly worse outcome than ibrutinib in the first-line therapy of unfit patients with CLL [34]. Nevertheless, the use of the BR regimen in patients older than 65 years without significant comorbidities in the context of limited access to BTK inhibitors (ibrutinib and acalabrutinib) poses a viable treatment option in the first-line setting in Poland [22].

In the case of comorbid patients, regardless of p53 or *IGHV* mutational status BTK inhibitors or venetoclax combined with obinutuzumab are preferred over immunochemotherapy due to their better tolerability in older patients and clinical efficiency in high-risk diseases [1, 21, 22]. Based on the long-term observation of the CLL14 study, time-limited venetoclax-obinutuzumab therapy is slightly more efficient in patients with M-CLL compared to patients with U-CLL. A similar observation, but more prominent, was noted regarding p53 aberrations, as patients with p53 pathway defects lose response much faster as compared to patients without 17p deletion or *TP53* mutation [35]. Although venetoclax-obinutuzumab treatment enables the achievement of deep responses with undetectable minimal residual disease (MRD), the indefinite therapy with BTK inhibitors (ibrutinib and acalabrutinib) and their constant pressure on leukemic cells enable more durable disease control [37, 41, 49]. Although U-CLL cases should be treated with targeted therapies, current knowledge based on clinical trials does not point to a specific regimen, which should be preferred in the treatment-naïve patients [1, 21, 22].

In most comorbid patients, the use of targeted agents is warranted, as BTK inhibitors, as well as venetoclax-obinutuzumab, showed remarkable activity and tolerability compared to the so far used standard treatment with chlorambucil-obinutuzumab [1, 21, 22]. Venetoclax-obinutuzumab is reimbursed in Poland since 2021 for comorbid patients with CLL.

Considering the current clinical guidelines, fit patients with CLL with poor prognostic factors (p53 aberrations and/or unmutated *IGHV* status) cannot be treated properly as BTK inhibitors are not reimbursed in Poland in the treatment-naïve patients and venetoclax use is restricted within the therapeutic program of Ministry of Health only for unfit patients. The so far published clinical trials (Table 1) underline the importance of BTK inhibitors and venetoclax in patients with CLL with high-risk features [1, 21, 22].

Ibrutinib, acalabrutinib, zanubrutinib and venetoclax have not been compared head-to-head in a randomized clinical trial. Such a trial would be interesting in the view of proper patient treatment allocation due to different compound mechanisms

Table 2. Comparison of pros and cons of registered novel agents in the first-line therapy of patients with chronic lymphocytic leukaemia

	Ibrutinib	Acalabrutinib	Venetoclax	Idelalisib
Pros	• Durable remission in p53 aberrant disease • Longest follow-up • The only agent compared to immunochemotherapy (FCR, BR) • Administered once daily • Effective in autoimmune cytopenia (AIHA, ITP)	• Durable remission in p53 aberrant disease • More selective than ibrutinib therefore fewer off-target toxicities	• Time-limited therapy • High CR and undetectable MRD rate • May be used safely in cardiological patients	• Effective agent in high-risk disease
Cons	• Indefinite therapy time • Rarely achieves CR and undetectable MRD • Cardiologic adverse event profile (atrial fibrillation, hypertension) • Bleeding risk	• Indefinite therapy time • Rarely achieves CR and undetectable MRD • Contraindicated with the use of proton-pump inhibitors • Twice-daily dosing	• Increased TLS, especially in patients with impaired renal function • Concomitant use with obinutuzumab • Loss of response in p53 aberrant cases • Neutropenia • Use of warfarin in the round-up patients is contraindicated	• Safe administration most possible in an elderly population • Immunological adverse events (transaminitis, pneumonitis, colitis) • Risk of opportunistic infections

AIHA – autoimmune haemolytic anaemia; BR – bendamustine, rituximab; CR – complete remission; FCR – fludarabine, cyclophosphamide, rituximab; ITP – immune thrombocytopenic purpura; MRD – minimal residual disease; TLS – tumour lysis syndrome

of action and specific adverse events profiles. More selective BTK inhibitors (acalabrutinib and zanubrutinib) maintain their efficiency while minimizing the occurrence of adverse event profiles [37, 50]. The pros and cons of novel agent therapies in the first-line setting are summarized in Table 2.

Summary

The low response rate and short remission duration following immunochemotherapy in patients with high-risk CLL defined as patients with *TP53* deletion/mutation or/and unmutated *IGHV* status underlie the necessity of the use of novel and selective agents in this population. The BTK inhibitors and venetoclax-based treatment are the most viable therapy options in such patients based on the so-far published clinical trial results.

Author's contributions

All authors wrote and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

BP served as a consultant for Abbvie, Roche and Pfizer and received honoraria and research funding from Abbvie, Gilead, Celgene and Janssen. KJ received research funding from Janssen, AbbVie, and honoraria from Abbvie, Amgen, AstraZeneca, Bei-Gene, Janssen, Sanofi-Genzyme, Sandoz, Novartis, Takeda, Roche, GSK, Gilead, Pfizer, Teva. TW received served as a consultant and received research funding and honoraria from Abbvie, Amgen, AstraZeneca, Bei-Gene, GSK, Gilead, Janssen, Sanofi-Genzyme, Sandoz, Novartis, Roche, Pfizer, Takeda, Teva. KG received served as a consultant and received research funding and honoraria from Abbvie, Amgen, AstraZeneca, Bayer, Bei-Gene, Janssen, Sanofi-Genzyme, Sandoz, Novartis, Takeda, Roche, Karyopharm, GSK, Gilead, TG Therapeutics, Pfizer, Teva. IH served as a consultant for Roche, Janssen, Abbvie, Bei-Gene, AstraZeneca, Gilead, and received honoraria and research funding from Roche, Janssen, Abbvie, Bei-Gene and AstraZeneca.

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References

1. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018; 131(25): 2745–2760, doi: 10.1182/blood-2017-09-806398, indexed in Pubmed: 29540348.
2. Redaelli A, Laskin BL, Stephens JM, et al. The clinical and epidemiological burden of chronic lymphocytic leukaemia. Eur J Cancer Care (Engl). 2004; 13(3): 279–287, doi: 10.1111/j.1365-2354.2004.00489.x, indexed in Pubmed: 15196232.
3. Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the di-

agnosis 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. 2008; 111(12): 5446–5456, doi: 10.1182/blood-2007-06-093906, indexed in Pubmed: 18216293.
4. Jamroziak K, Puła B, Walewski J. Current treatment of chronic lymphocytic leukemia. Curr Treat Options Oncol. 2017; 18(1): 5, doi: 10.1007/s11864-017-0448-2, indexed in Pubmed: 28185174.
5. Wierda WG, Kipps TJ, Mayer J, et al. Hx-CD20-406 Study Investigators. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010; 28(10): 1749–1755, doi: 10.1200/JCO.2009.25.3187, indexed in Pubmed: 20194866.
6. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014; 370(12): 1101–1110, doi: 10.1056/NEJMoa1313984, indexed in Pubmed: 24401022.
7. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016; 127(2): 208–215, doi: 10.1182/blood-2015-06-651125, indexed in Pubmed: 26486789.
8. Hallek M, Fischer K, Fingerle-Rowson G, et al. International Group of Investigators, German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010; 376(9747): 1164–1174, doi: 10.1016/S0140-6736(10)61381-5, indexed in Pubmed: 20888994.
9. Pula B, Iskierka-Jazdzewska E, Długosz-Danecka M, et al. Long-term efficacy of ibrutinib in relapsed or refractory chronic lymphocytic leukemia: results of the Polish Adult Leukemia Study Group Observational Study. Anticancer Res. 2020; 40(7): 4059–4066, doi: 10.21873/anticanres.14403.
10. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019; 133(19): 2031–2042, doi: 10.1182/blood-2018-08-870238, indexed in Pubmed: 30842083.
11. Sharman JP, Coutre SE, Furman RR, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013; 369(1): 32–42, doi: 10.1056/NEJMoa1215637, indexed in Pubmed: 23782158.
12. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. J Clin Oncol. 2019; 37(4): 269–277, doi: 10.1200/JCO.18.01580, indexed in Pubmed: 30523712.
13. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019; 380(23): 2225–2236, doi: 10.1056/NEJMoa1815281, indexed in Pubmed: 31166681.
14. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med. 2011; 365(26): 2497–2506, doi: 10.1056/NEJMoa1109016, indexed in Pubmed: 22150006.
15. Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. Nat Genet. 2011; 44(1): 47–52, doi: 10.1038/ng.1032, indexed in Pubmed: 22158541.
16. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature. 2011; 475(7354): 101–105, doi: 10.1038/nature10113, indexed in Pubmed: 21642962.
17. Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood. 2012; 119(2): 521–529, doi: 10.1182/blood-2011-09-379966.
18. Balatti V, Bottoni A, Palamarchuk A, et al. NOTCH1 mutations in CLL associated with trisomy 12. Blood. 2012; 119(2): 329–331, doi: 10.1182/blood-2011-10-386144, indexed in Pubmed: 22086416.
19. Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell. 2013; 152(4): 714–726, doi: 10.1016/j.cell.2013.01.019, indexed in Pubmed: 23415222.
20. Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations driving CLL and their evolution in progression and relapse. Nature. 2015; 526(7574): 525–530, doi: 10.1038/nature15395, indexed in Pubmed: 26466571.
21. Eichhorst B, Robak T, Montserrat E, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(1): 23–33, doi: 10.1016/j.annonc.2020.09.019, indexed in Pubmed: 33091559.
22. Hus I, Giannopoulos K, Jamroziak K, et al. Diagnostic and therapeutic recommendations of the Polish Society of Haematologists and Transfusiologists and Polish Adult Leukemia Group-CLL for chronic lymphocytic leukemia in 2021. Acta Haematol Pol. 2021; 52(5): 455–482, doi: 10.5603/ahp.a2021.0087.
23. Ghia P, Stamatopoulos K, Belessi C, et al. European Research Initiative on CLL. ERIC recommendations on IGHV gene mutational status analysis in chronic lymphocytic leukemia. Leukemia. 2007; 21(1): 1–3, doi: 10.1038/sj.leu.2404457, indexed in Pubmed: 17167526.
24. Lin KI, Tam CS, Keating MJ, et al. Relevance of the immunoglobulin VH somatic mutation status in patients with chronic lymphocytic leukemia treated with fludarabine, cyclophosphamide, and rituximab (FCR) or related chemoimmunotherapy regimens. Blood. 2009; 113(14): 3168–3171, doi: 10.1182/blood-2008-10-184853, indexed in Pubmed: 19050308.
25. Oscier DG, Gardiner AC, Mould SJ, et al. Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. Blood. 2002; 100(4): 1177–1184, indexed in Pubmed: 12149195.
26. Rosenquist R, Ghia P, Hadzidimitriou A, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations. Leukemia. 2017; 31(7): 1477–1481, doi: 10.1038/leu.2017.125, indexed in Pubmed: 28439111.
27. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016; 127(3): 303–309, doi: 10.1182/blood-2015-09-667675, indexed in Pubmed: 26492934.
28. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008; 112(4): 975–980, doi: 10.1182/blood-2008-02-140582, indexed in Pubmed: 18411418.

29. Fink AM, Böttcher S, Ritgen M, et al. Prediction of poor outcome in CLL patients following first-line treatment with fludarabine, cyclophosphamide and rituximab. Leukemia. 2013; 27(9): 1949––1952, doi: 10.1038/leu.2013.190, indexed in Pubmed: 23787395.
30. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014; 123(21): 3247–3254, doi: 10.1182/blood-2014-01-546150, indexed in Pubmed: 24652989.
31. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. Blood. 2015; 126(16): 1921–1924, doi: 10.1182/blood-2015-05-647925, indexed in Pubmed: 26276669.
32. Eichhorst B, Fink AM, Bahlo J, et al. international group of investigators, German CLL Study Group (GCLLSG). 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. 2016; 17(7): 928–942, doi: 10.1016/S1470-2045(16)30051-1, indexed in Pubmed: 27216274.
33. Shanafelt TD, Wang XV, Hanson CA, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019; 381(5): 432–443, doi: 10.1056/NEJMoa1817073, indexed in Pubmed: 31365801.
34. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018; 379(26): 2517–2528, doi: 10.1056/NEJMoa1812836, indexed in Pubmed: 30501481.
35. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off--treatment follow-up from the randomized CLL14 study. J Clin Oncol. 2021; 39(36): 4049–4060, doi: 10.1200/JCO.21.01181, indexed in Pubmed: 34709929.
36. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019; 20(1): 43–56, doi: 10.1016/S1470-2045(18)30788-5, indexed in Pubmed: 30522969.
37. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia. 2022; 36(4): 1171–1175, doi: 10.1038/s41375-021-01485-x, indexed in Pubmed: 34974526.
38. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020; 395(10232): 1278–1291, doi: 10.1016/S0140-6736(20)30262-2, indexed in Pubmed: 32305093.
39. Stilgenbauer S, Bosch F, Ilhan O, et al. Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study. Lancet Haematol. 2017; 4(10): e475–e486, doi: 10.1016/S2352-3026(17)30171-0, indexed in Pubmed: 28916311.
40. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015; 125(16): 2497–2506, doi: 10.1182/blood-2014-10-606038, indexed in Pubmed: 25700432.
41. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020; 34(3): 787–798, doi: 10.1038/s41375-019-0602-x, indexed in Pubmed: 31628428.
42. O'Brien SM, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib plus rituximab in treatment-naïve older patients with chronic lymphocytic leukemia. Blood. 2015; 126(25): 2686–2694, doi: 10.1182/blood-2015-03-630947, indexed in Pubmed: 26472751.
43. Chai-Adisaksopha C, Brown JR. FCR achieves long-term durable remissions in patients with -mutated CLL. Blood. 2017; 130(21): 2278–2282, doi: 10.1182/blood-2017-07-731588, indexed in Pubmed: 29025740.
44. Thompson PA, Stingo F, Keating MJ, et al. Outcomes of patients with chronic lymphocytic leukemia treated with first-line idelalisib plus rituximab after cessation of treatment for toxicity. Cancer. 2016; 122(16): 2505–2511, doi: 10.1002/cncr.30069, indexed in Pubmed: 27182988.
45. Burger JA, Tedeschi A, Barr PM, et al. RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015; 373(25): 2425–2437, doi: 10.1056/NEJMoa1509388, indexed in Pubmed: 26639149.
46. Ghia P, Dlugosz-Danecka M, Scarfò L, et al. Acalabrutinib: a highly selective, potent Bruton tyrosine kinase inhibitor for the treatment of chronic lymphocytic leukemia. Leuk Lymphoma. 2021; 62(5): 1066–1076, doi: 10.1080/10428194.2020.1864352, indexed in Pubmed: 33427570.
47. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front--line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. Blood. 2016; 128(2): 195–203, doi: 10.1182/blood-2016-03-707133, indexed in Pubmed: 27247136.
48. Hus I, Puła B, Robak T. PI3K Inhibitors for the treatment of chronic lymphocytic leukemia: current status and future perspectives. Cancers (Basel). 2022; 14(6), doi: 10.3390/cancers14061571, indexed in Pubmed: 35326722.
49. Puła B, Jamroziak K. Rola wenetoklaksu w leczeniu chorych na przewlekłą białaczkę limfocytową. Hematologia. 2017; 8(1): 20–32, doi: 10.5603/hem.2017.0003.
50. Robak T, Witkowska M, Smolewski P. The role of Bruton's kinase inhibitors in chronic lymphocytic leukemia: current status and future drections. Cancers (Basel). 2022; 14(3), doi: 10.3390/cancers14030771, indexed in Pubmed: 35159041.