Current Treatment of Refractory/Relapsed Chronic Lymphocytic Leukemia: A Focus on Novel Drugs

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Keywords

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Abstract

Recently, the use of novel targeted drugs has changed the treatment paradigms in chronic lymphocytic leukemia (CLL). Among the several drugs used for the management of relapsed/refractory (R/R) CLL, Bruton tyrosine kinase inhibitors (ibrutinib and acalabrutinib), phosphatidylinositol 3-kinase inhibitors (idelalisib and duvelisib), B-cell lymphoma 2 inhibitor (venetoclax), and novel CD20 monoclonal antibodies have demonstrated the greatest improvements in survival among R/R CLL patients. However, patients with relapsed but asymptomatic CLL do not need immediate alternative treatment and should be observed until evident sign of progression. Among available approved treatments, venetoclax + rituximab for 24 months or ibrutinib as continuous therapy is recommended. Another, less recommended, option is idelalisib in combination with rituximab. The correct treatment selection depends on the type of prior therapy,

response to previous treatment and side effects, presence of comorbidities, and the risk of drug toxicity. Allogeneic hematopoietic stem cell transplantation and investigational therapies such as chimeric antigen receptor-T-cell therapy are promising treatment options for high-risk patients, including those progressing after 1 or more targeted therapies. The present review discusses current treatment strategies for patients with R/R CLL.

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Introduction

Chronic lymphocytic leukemia (CLL) is a heterogeneous lymphoproliferative disease and the commonest form of leukemia in Western countries. CLL typically occurs in elderly patients, with a median age at diagnosis of 72 years. The incidence of the disease is 4–5 cases per 100,000 population per year [1, 2]. In 2020, an estimated 32,270 new cases and 4,060 deaths were reported in the USA alone [3]. In approximately 1/3 of patients, the disease is progressive at diagnosis and has to be treated from the onset [2]. The World Health Organization (WHO) classifies small lymphocytic small B-cell lymphoma (SLL) as similar to non-Hodgkin lymphoma affecting B lym-

phocytes: the 2 demonstrate the same immunophenotype (CD5+/CD19+ and CD5+/CD23+) and morphology of mature lymphoid tumor cells. However, SLL does not involve the bone marrow. SLL is classified as a low-grade lymphoproliferative disease coupled as SLL/CLL. Therefore, in many clinical studies, CLL and SLL are included in the same group of malignancy.

Despite recent developments in therapeutic strategies in CLL, the disease remains incurable in most patients; most of them sooner or later relapse, and some are refractory to available treatment. According to the International Workshop Group on CLL (IWCLL) criteria, relapsed CLL should only be treated if symptomatic, similar to the first-line therapy [2]. The IWCLL guidelines define relapsed patients as those who have previously achieved a complete response (CR) or partial response (PR) but demonstrated evidence of disease progression after a period of 6 or more months [2]. Treatment-refractory CLL is defined as a disease without PR or CR or disease progression within 6 months following the last antileukemic therapy.

The response to second-line or subsequent treatment depends on a variety of factors, including clinical stage, adverse biological prognostic factors, and number of prior therapies, particularly those with purine analogs. However, the recent introduction of Bruton's tyrosine kinase (BTK) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and B-cell lymphoma 2 (BCL-2) antagonist venetoclax has changed the treatment landscape and horizon for patients with previously untreated and relapsed/refractory (R/R) disease, resulting in improved prognoses for both [4–8]. In addition, patients with particularly poor prognosis, especially those refractory to previous therapy with fludarabine-containing regimens and those with a 17p deletion/*TP53* mutation, were also treated. Currently, CLL patients have significantly better survival when treated with the novel targeted agents [2, 9–16]. The present review discusses a number of newly developed agents which are used in the therapy of R/R and have changed the treatment algorithm in CLL.

Inhibitors of BCR Pathways

Novel agents for R/R CLL act by blocking the pathways important for the survival of leukemic cells. The inhibition of BTK and PI3K has shown high clinical efficacy, even in poor-risk and chemo-refractory patients with CLL [17–20].

BTK Inhibitors

Inhibition of BTK is a breakthrough therapy for CLL [19]. BTK is a molecule positioned early within the B-cell antigen receptor (BCR) signaling cascade which regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival.

Ibrutinib Monotherapy

Studies concerning ibrutinib in monotherapy performed over several years have yielded successful results in R/R CLL patients at different time points [21–23]. Namely, in an initial phase 1b/2 study in patients with R/R CLL, ibrutinib was given at a daily dose of 420 or 840 mg until unacceptable toxicity or disease progression [21]. The ORR was found to be 71% in both groups [21]. An additional 20 and 15% of patients in the 2 dosing groups, respectively, demonstrated a PR with lymphocytosis. The responses observed were independent of clinical and genomic risk factors including del(17p) status. At 26 months, the estimated PFS rate was 75%, and the overall survival (OS) rate 83%. A phase 2 trial in CLL/SLL patients (PCYC-1102) examined the effect of ibrutinib monotherapy in therapy-naïve high-risk patients ($n = 31$) and patients with refractory or progressive disease earlier than 24 months after chemoimmunotherapy ($n = 101$) [22]. All participants received ibrutinib 420 or 840 mg/day p.o. until unacceptable toxicity or disease progression. For the R/R patients, the ORR was 90%, with 7% of patients achieving CR and 80% PR. Longer treatment with ibrutinib was associated with improved quality of response and durable remissions. Treatment-related, asymptomatic lymphocytosis was observed and mostly did not influence the duration of PFS and OS. Progression was rarely observed, with most cases being seen in patients with relapsed del(17)(p13.1) and/or del(11)(q22.3) disease. Additionally, analysis of the extension of the PCYC-1102 study has recently been reported (PCYC-1103; 23). After 8 years of follow-up, the ORR in the whole group was 89%, with similar rates in first-line (ORR 87%; CR 35%, respectively) and R/R settings (ORR 89%; CR 10%, respectively) (Table 1). Progression was observed in 41 patients, including Richter syndrome in 11 patients. Median PFS was not reached in the previously untreated patients with first-line ibrutinib; however, median PFS was 52 months in R/R patients but only 26 months in patients with chromosome 17p deletion. Estimated 7-year OS rates were 84% in the first-line and 55% in the R/R settings. Grade ≥ 3 adverse events (AEs) were observed in >15% of patients: hypertension (28%), pneu-

Table 1. Larger clinical trials with newer drugs in patients with R/R CLL

Study	Treatment	Patients, <i>n</i>	Median age	Previous regimens, ORR Me (range)	CR rate	PFS	OS
PCYC-1102/1103 Byrd et al. [23] * phase 1b/2 and extension study	Ibrutinib	101*	64*	4 (1–12)*	89%*	10%*	53 m* (estimated at 7 yrs 34%) Estimated at 7 yrs – 55%*
RESONATE (PCYC-1112) Byrd et al. [24, 25] phase 3	Ibrutinib versus ofatumumab	195 versus 196	67 yrs versus 67 yrs	3 (1–12) versus 2 (1–13)	42.6% versus 4.1%, <i>p</i> < 0.001	2% versus 1% <i>p</i> < 0.001	At 12 m – 90% versus 81%, <i>p</i> = 0.005
Burger et al. [44] phase 2	Ibrutinib versus Ibrutinib + rituximab	104 versus 104 (relapsed 181)	65 yrs versus 65 yrs	1 (0–7) versus 1 (0–10)	92% versus 92.3%	At 36 m, 86% versus 86.9%	At 36 m – 92% versus 89%
HELIOS Chanan-Khan et al. [45], Fraser et al. [46] phase 3	Ibrutinib + BR versus BR	289 versus 289	64 yrs versus 63 yrs	2 (1–11) versus 2 (1–9)	82.7% versus 67.8%, <i>p</i> < 0.0001	10.4% versus 2.8% <i>p</i> < 0.0001	nr versus nr, <i>p</i> = 0.0598
Byrd et al. [52] phase 1b/2	Acalabrutinib	134	66 yrs	2 (1–11)	94%	4%	Median nr (at 45 m 62%) nr
Furman et al. [68], Sharman et al. [6] phase 3	Idelalisib + rituximab versus rituximab	110 versus 110	71 yrs versus 71 yrs	3 (1–12) versus 3 (1–9)	81% versus 13%, <i>p</i> < 0.001	0 versus 0	At 12 m, 92% versus 80%, <i>p</i> = 0.02
Jones et al. [69] phase 3	Idelalisib + ofatumumab versus ofatumumab	174 versus 87	68 yrs versus 67 yrs	3 (2–4) versus 3 (2–5)	75.3% versus 18.4%, <i>p</i> < 0.0001	<1% versus 0	20.9 m versus 19.4 m, <i>p</i> = 0.27
Zelenetz et al. [70] phase 3	Idelalisib + BR versus BR	207 versus 209	62 yrs versus 64 yrs	Refractory 31% versus 29%	68% versus 45%	5% versus 0	nr versus nr, <i>p</i> = 0.008
DUO Flinn et al. [74] phase 3	Duvelisib versus ofatumumab	160 versus 159	69 yrs versus 69 yrs	2 (1/3 ≥3) versus 2 (1/3 ≥3)	73.8% versus 53%, <i>p</i> < 0.0001	0.6% versus 0.6% <i>p</i> < 0.0001	86% versus 86%
Roberts et al. [80] phase 1	Venetoclax	116**	66 yrs	3 (1–11)	79%	20%	At 15 m – 66% (for 400 mg/day expansion cohort) At 24 m – 84%
M13-982 trial Stiglbauer et al. [81] phase 2	Venetoclax	107	65 yrs	2 (91–4)	85%	8%	At 12 m – 86.7% 72%
MURANO Seymour et al. [89] phase 3	Venetoclax + rituximab versus BR	194 versus 195	65 yrs versus 65 yrs	2 (1 to ≥3) versus 2 (1 to ≥3)	92.3% versus 72.3%	8.2% versus 3.6%	At 12 m – 91.9% versus 86.6%

R/R CLL, refractory/relapsed chronic lymphocytic leukemia; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; nr, not reached; m, months; yrs, years; SLL, small lymphocytic lymphoma. * Data for cohort of R/R CLL/SLL patients are shown. ** Data on expansion cohort (dose 400 mg/day) – *n* = 60.

monia (24%), and neutropenia (18%). These grade ≥ 3 AEs generally declined over time, except hypertension. Hence, sustained responses and long-term tolerability of single-agent ibrutinib were observed both in treatment naïve and R/R CLL/SLL patients throughout the 8-year follow-up period [23].

The phase 3 RESONATE study compared ibrutinib with ofatumumab in 391 patients with R/R CLL [24–26]. Ibrutinib was found to significantly improve PFS and OS. The median follow-up was 65.3 months (range, 0.3–71.6) for the ibrutinib arm; the median PFS was 44.1 months for the ibrutinib arm and 8.1 months for the ofatumumab arm ($p < 0.001$). Among the patients with ibrutinib, the ORR was 91%, including 11% CR. The patients receiving ibrutinib also demonstrated longer OS, censored for crossover, than those on ofatumumab (HR: 0.639; 95% CI: 0.418–0.975). At a median follow-up of 41 months, all-grade hypertension was observed in 21% of patients on ibrutinib therapy and atrial fibrillation in 12%, while grade 3 was found in 9% and higher grades in 6%. In 16% of patients, ibrutinib was discontinued due to AEs [25]. The RESONATE findings indicate that ibrutinib treatment allowed greater improvements in disease symptoms and hematologic parameters compared to ofatumumab and significantly increased the quality of life of CLL/SLL patients [26].

A recent study evaluated the outcomes of 271 ibrutinib-treated patients in prior lines of therapy [27]. The analyzed data were collected from 2 randomized studies: the RESONATE study performed with R/R patients and RESONATE-2 with previously untreated patients without del(17p); median follow-up times were 36 months for the treatment-naïve patients and 44 months for the R/R patients. The ORR was 92% in the treatment-naïve patients and 92% in the R/R patients. Median PFS was not reached for patients with 1 or 2 prior therapies, or without, and 40.6 months for patients with 3 or more therapies, and median OS was not reached in all subgroups. The poorest results were obtained in patients with both R/R and del(17p)/TP53 mutation. An analysis performed by Jones et al. [28] in 230 CLL patients yielded an ORR of 85% and estimated 30-month PFS and OS scores of 57 and 69%, respectively. Sustained hematological improvements in hemoglobin, platelet count, and absolute neutrophil count were observed in 61, 67, and 70% of previously cytopenic patients.

The results in 2 pivotal studies (RESONATE, RESONATE-2, and 2 PCYC-1102) regarding the long-term safety of ibrutinib monotherapy in 465 patients with CLL have recently been reported [29]. The most common

grade AEs were diarrhea (52%) and fatigue (36%). The most common grade 3/4 AEs were neutropenia (18%) and pneumonia (12%). Another recent report based on several studies found early common grade AEs of ibrutinib to include diarrhea (50–60%), cytopenias (50–60%), nausea (40–50%), fatigue (30–40%), muscle spasms or myalgias (30–40%), increased risk of infections (30–35%), pyrexia (20–25%), skin rash (20–25%), headaches (10–14%), and bleeding (10–14%) [30]. Most of these AEs were self-limiting grade 1 or 2, without the need for drug interruption or reduction. The most common serious side effects included neutropenia (10–15%), thrombocytopenia (5–8%), anemia (6–8%), bleeding (3–5%), and atrial arrhythmias, mainly atrial fibrillation (5–8%).

The most common reason for ibrutinib discontinuation is toxicity [31, 32]. The most common AEs in ibrutinib-treated CLL patients leading to treatment interruption or discontinuation are atrial fibrillation, infections, and cytopenias as well as joint/bone pain, muscle cramps, or hypertension. Bleeding is a less common but potentially serious side effect, especially if the treatment is applied concurrently with antiplatelet drugs or anticoagulants [33]. A study of 308 patients at a median follow-up of 20 months found that 76 (25%) had discontinued therapy, including 31 due to disease progression and 45 for other reasons; the cumulative incidence of progression at 4 years was 19% [34]. An analysis of the cumulative incidence of ibrutinib discontinuation found that most events occurred within the first 2 years of ibrutinib therapy [35, 36]. Treatment discontinuation due to toxicity is more common in elderly patients with comorbidities and/or an ECOG PS > 1 [31, 37–42]. In addition, atrial fibrillation is more common in older patients with previous arterial hypertension and pre-existing cardiologic diseases.

Ibrutinib Combined with Other Drugs

The efficacy of ibrutinib combined with rituximab alone or rituximab plus bendamustine has been investigated in R/R CLL patients [43–46]. A randomized trial of ibrutinib versus ibrutinib plus rituximab enrolled 208 CLL patients requiring therapy: 181 with relapsed CLL and 27 treatment-naïve patients with high-risk disease (del17p or TP53 mutation) [44]. Rituximab added to ibrutinib in relapsed and treatment-naïve high-risk CLL patients failed to improve PFS. However, patients treated with ibrutinib plus rituximab reached their remissions faster and achieved significantly lower residual disease levels [44].

Ibrutinib combined with bendamustine and rituximab (BR) was compared with BR in previously treated CLL in a randomized, double-blind, phase 3 study (HELIOS)

[45, 46]. ORR was significantly higher in the group treated with ibrutinib + BR (87.2%) than BR (66.4%) with continuous improvement observed over time in the ibrutinib arm. This study also showed superior PFS and OS for ibrutinib + BR compared to BR [45, 46]. It was found that 70.2% of patients who received BR plus ibrutinib achieved 36-month PFS in comparison with 15.5% who received BR plus placebo [46].

An indirect comparison of the RESONATE and HELIOS studies found ibrutinib to be more effective than a BR regimen. Ibrutinib and ibrutinib + BR were found to have similar PFS and OS scores. However, a longer-term follow-up is needed to understand whether the deeper responses observed for ibrutinib + BR will translate to improved PFS and OS [47]. Single-agent ibrutinib showed superiority to ibrutinib + BR for PFS and OS in patients with R/R CLL. Thus, the addition of bendamustine or/and rituximab to ibrutinib does not appear to improve the efficacy of ibrutinib in monotherapy but increases the toxicity of the combined treatment [47]. Certainly, this should be confirmed by direct comparison of ibrutinib monotherapy with a combined ibrutinib plus BR regimen; however, such study is currently difficult to construct and develop.

New BTK Inhibitors

The next generation of BTK inhibitors, such as acalabrutinib, zanubrutinib, tirabrutinib, vecabrutinib, and fenebrutinib, is currently under evaluation in ongoing clinical trials or just reported as phase 1 study [48–50]. The most advanced BTK inhibitors apart from ibrutinib are acalabrutinib and zanubrutinib; both agents have been approved for the treatment of mantle cell lymphoma (MCL), and acalabrutinib has been also approved for the treatment of CLL. While acalabrutinib may be an option for ibrutinib-resistant CLL patients, other new BTK inhibitors may also limit off-target toxicities. However, it has to be stressed that CLL trials of the agents based on a head-to-head comparison are needed to identify improved efficacy and better safety profiles.

Acalabrutinib

Acalabrutinib (ACP-196) is an oral, highly selective, second-generation irreversible BTK inhibitor with higher selectivity than ibrutinib [51]. A phase 1b/2 study of acalabrutinib in 134 patients with R/R CLL found ORR to be 94%, independent of genetic abnormalities or heavy-chain immunoglobulin mutational status [52, 53]. The es-

timated 45-month PFS was 62%, but the median duration of PFS has not been reached. Most common all-grade AEs were diarrhea (52%) and headache (51%). The grade 3 and higher AEs were neutropenia (14%), pneumonia (11%), hypertension (7%), anemia (7%), and diarrhea (5%). Awan et al. [54] evaluated the safety and efficacy of acalabrutinib at a dose of 200 mg daily in 33 ibrutinib-intolerant patients. With a median observation of 19.0 months, ORR was 76%, including 1 CR and 24 PR. Among the 25 responders, the median duration of response and median PFS were not reached. Acalabrutinib was well tolerated, and no drug dose reductions were needed. The most frequent AEs included diarrhea (58%), headache (39%), and coughing (33%). Grade 3/4 AEs occurred in 58% of patients, with the most common ones being neutropenia (12%) and thrombocytopenia (9%).

The randomized phase 2 study (NCT02337829) by Sun et al. [55] investigated the safety, efficacy, and pharmacodynamics of acalabrutinib administered at 100 mg twice daily or 200 mg once daily in 48 patients with R/R or high-risk naïve CLL. With twice-daily dosing, acalabrutinib was well tolerated. ORR, with PR or better, was 95.8%, and the estimated PFS at 24 months was 91.5%. With once-daily dosing, the ORR was 79.2%, and the estimated PFS at 24 months was 87.2%. In addition, twice-daily dosing of acalabrutinib was also found to demonstrate greater potency regarding BTK pathway inhibition [54]. A subsequent phase 3 ASCEND study found that acalabrutinib monotherapy improved efficacy and tolerability over standard-of-care treatments, that is, the investigator's choice of rituximab + idelalisib (IdR) or bendamustine (BR) [56]. At a median follow-up of 16.1 months, acalabrutinib significantly prolonged PFS compared to IdR/BR (median NR vs. 16.5 months). Discontinuation due to AEs occurred in 11% of patients on acalabrutinib versus 49% on IdR/BR, indicating that acalabrutinib monotherapy also has a more tolerable safety profile versus IdR/BR in R/R CLL patients. Fewer classic BTK-associated toxicities, such as bleeding or atrial fibrillation events, are observed compared to the ibrutinib-treated patients. However, headache is more commonly observed in acalabrutinib treatment. Currently, a phase 3 study (NCT02477696) directly comparing acalabrutinib with ibrutinib in previously treated and untreated patients is ongoing [57]. Acalabrutinib received an accelerated US FDA approval for patients with R/R MCL in 2017 and in 2019 for the treatment of CLL. However, it was not approved by the European Medicines Agency (EMA) yet.

Woyach et al. [58] assessed combination of acalabrutinib with obinutuzumab in a phase 1b/2 study of 19 pa-

tients with not-treated CLL and 26 with R/R CLL. Acalabrutinib was administered at a dose of 100 mg twice daily, until progression, and obinutuzumab in sequentially increased doses from 100 to 1,000 mg/day, up to 6 cycles. ORR was 95% in treatment-naïve and 92% in RR patients, with CR achieved in 32 and 8% of patients and PFS at 36 months in 94 and 88%, respectively. The regimen had acceptable tolerability, with grade 3/4 AEs occurring in 71% of patients.

Zanubrutinib

Zanubrutinib is a next-generation irreversible BTK inhibitor with minimal off-target effects and sustained BTK occupancy in malignant cells from patients with B-cell malignancies [59]. Inhibition of BTK and several connected pathways may be responsible for side effects like diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, or fatigue [60, 61].

A phase 1 study by Tam et al. [60] examined 78 patients with CLL/SLL treated with zanubrutinib monotherapy [58]. After a median follow-up of 13.7 months, ORR was 96.2% (75/78), including 2 patients (2.6%) demonstrating CR and 63 (80.8%) with PR. Zanubrutinib demonstrated off-target effects such as diarrhea and rash, which were observed in approximately 20% of patients (all grade 1 or 2 events).

A safety analysis of pooled data from 6 zanubrutinib monotherapy trials showed that zanubrutinib is generally well tolerated in patients across various B-cell malignancies [61]. A total of 682 patients with non-Hodgkin lymphoma, CLL/SLL, Waldenström macroglobulinemia, hairy cell leukemia, and Richter's transformation were included. The most common AEs of grade 3 or higher were decreased neutrophil count (14%), anemia (8%), pneumonia (5%), decreased platelet count (4%), lung infection (4%), hypertension (3%), atrial fibrillation (1.9%), grade ≥ 3 hemorrhage (2.1%), and grade ≥ 3 diarrhea (0.9%). Myalgias or arthralgias occurred in <10% of patients. After initial promising results, further studies of zanubrutinib as a single agent or as part of combination therapy are ongoing. A phase 2 study has been planned to assess the safety of zanubrutinib in CLL patients intolerant to ibrutinib (NCT04116437). A head-to-head phase 3 study (ALPINE) comparing the efficacy and safety of zanubrutinib with those of ibrutinib in patients with CLL/SLL in the R/R patients is also ongoing [62].

Tirabrutinib

Tirabrutinib (GS-4059/ONO-4059) is another second-generation, selective, irreversible BTK inhibitor un-

der investigation in CLL and other B-cell lymphoid malignancies. The first phase 1 trial of tirabrutinib included 90 patients with R/R CLL and other B-cell malignancies [63]. The most common AE was found to be mild-grade diarrhea, occurring in 18% of cases. In the CLL cohort, 14.3% of patients experienced a drug-related grade 3 or 4 AE, most commonly a hematological toxicity. Objective responses within the first 3 months of therapy were 96% (24/25). Further studies of tirabrutinib with other targeted agents are ongoing. Currently, a prospective, randomized, open-label, multicenter, phase 2 trial evaluating the safety and efficacy of the combination of tirabrutinib and entospletinib, with or without obinutuzumab, is underway in R/R CLL patients (NCT02983617).

Other BTK Inhibitors

Clinical studies of other BTK inhibitors are in the early stages, and it remains to be seen whether this class of compounds may provide a further progress in treating patients with CLL, especially those who have acquired resistance to ibrutinib by Cys481 mutation. Most of these agents are reversible BTK inhibitors which do not interact with Cys481 and inhibit BTK through noncovalent binding [64].

Fenebrutinib (GDC-0853) is a selective BTK inhibitor currently under clinical development, mainly in autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus [49]. However, it has also been evaluated in 24 patients with R/R B-cell malignancies including 14 CLL patients [65]. The most common AEs were fatigue (38%), nausea (33%), diarrhea (29%), thrombocytopenia (25%), and headache (21%). Among the 14 patients with CLL, 7 achieved an objective response, with a mean duration of 2.5 months. Vecabrutinib (formerly SNS-062) is also a selective BTK inhibitor with noncovalent binding. The drug is under investigation in a phase 1b/2 trial in patients with R/R B-cell malignancies including CLL (NCT03037645) [66]. LOXO-305 (formerly RXC-005) is another highly selective, noncovalent, next-generation BTK inhibitor that may overcome acquired resistance to covalent BTK inhibitors associated with BTK C481 mutations [67]. A phase 1/2 trial is currently ongoing in CLL and other R/R B-cell neoplasms (NCT03740529).

PI3K Pathway Inhibitors

Constitutive PI3K activation resulting from aberrant regulation of BCR signaling plays a crucial role in CLL cell proliferation and survival [18, 19]. Blockade of the BCR

signaling cascade by inhibition of either BTK or PI3K δ causes profound inhibition of proliferative signaling from CLL cell-host interactions and results in significant improvement of outcomes in patients with R/R CLL/SLL, including both PFS and OS. During recent years, several PI3K inhibitors have been investigated in CLL patients.

Idelalisib

Idelalisib is the first-in-class, oral PI3K δ -isoform-selective inhibitor promoting apoptosis in CLL cells [18]. The activity of idelalisib + rituximab was compared with that of rituximab alone in previously treated CLL patients in a phase 3, randomized, double-blind, placebo-controlled study [6, 67]. The ORR was found to be 81% for idelalisib + rituximab and 13% for rituximab monotherapy ($p < 0.001$). The median PFS was not reached for idelalisib + rituximab and 5.5 months for rituximab alone; similarly, OS at 12 months was 92% for idelalisib + rituximab versus 80% for rituximab ($p = 0.02$) [6, 68]. Based on the results of this study, idelalisib + rituximab was approved for patients with R/R CLL who are unfit for receiving chemotherapy. Based on these study results, the long-term efficacy and safety of idelalisib has been recently reported: median OS was found to be 40.6 months for idelalisib + rituximab and 34.6 months for rituximab alone [6].

The effectiveness of combined idelalisib and ofatumumab was compared with that of ofatumumab monotherapy in patients with relapsed CLL [69]. Median PFS was found to be 16.3 months in the idelalisib + ofatumumab group and 8.0 months in the ofatumumab arm ($p < 0.0001$). In addition, the combination of idelalisib with bendamustine + rituximab (IBR) resulted in improved PFS compared with bendamustine + rituximab alone (BR) in patients with R/R CLL [70].

During phase 2 and 3 studies, several serious AEs were observed in patients treated with idelalisib. Grade 3 or 4 neutropenia was reported in around 30% of patients treated with idelalisib across clinical trials. Infections, including PCP infection and CMV reactivation, were also observed, as well as immune complications including colitis and transaminitis [71, 72]. This poor safety profile is the reason why idelalisib is not used in CLL. Our own meta-analysis performed in R/R CLL did not identify any statistically significant difference in terms of efficacy or tolerability between ibrutinib and idelalisib-based regimens. In comparison with standard immunochemotherapy, both BCR inhibitors demonstrate remarkable efficacy in R/R CLL; however, the 2 are associated with a high risk of serious AEs. Specifically, BCR inhibitors increase the risk of diarrhea, pyrexia, neutropenia, arthralgia, and rash [73].

Duvelisib

Duvelisib (IPI-145) is a second-generation oral, dual inhibitor of PI3K- δ and PI3K- γ [19]. It demonstrated clinical activity and acceptable safety in CLL/SLL patients in a phase 1 study [74]. It was also compared with ofatumumab monotherapy in patients with R/R CLL/SLL in the phase 3 randomized DUO trial [75]. The duvelisib arm demonstrated significantly higher ORR (74%) than the ofatumumab arm (45%; $p = 0.0001$) and improved PFS (median 13.3 months) compared with ofatumumab (median 9.9 months; $p < 0.0001$). The most common AEs were diarrhea, neutropenia, pyrexia, nausea, anemia, and coughing on the duvelisib arm and neutropenia and infusion reactions on the ofatumumab arm. These data indicate that duvelisib may be an effective and well-tolerated treatment for patients with R/R CLL/SLL. Duvelisib was approved by the FDA for the treatment of patients with R/R CLL or SLL in September 2018 and for the treatment of patients with R/R CLL/SLL after at least 2 prior therapies in the same year [76].

Other PI3K Inhibitors

Several newer PI3K inhibitors are under development in R/R CLL [76]. Among them, umbralisib, acalisib, buparlisib, parsacalisib, and YY-20394 are the most advanced in clinical development. These agents seem to be more potent and better tolerated than idelalisib.

Umbralisib (TGR-1202) is a novel next-generation inhibitor of PI3K isoform p110 δ (PI3K δ) and casein kinase-1 ϵ , a major regulator of protein translation. Umbralisib is better tolerated than idelalisib due to reduced inhibitory activity on T regulatory cells and appears to be less associated with the development of pneumonitis, transaminitis, and colitis [77]. In a phase 1 study, umbralisib was found to possess a favorable safety profile and high clinical activity in patients with lymphoid malignancies, including CLL, with no cases of grade 3 hepatotoxicity or colitis being observed [78]. A phase 1/1b study examining the effect of umbralisib + ibrutinib treatment in patients with R/R CLL or MCL [79] recorded serious AEs in 12 (29%) patients; these AEs included lipase elevation, AF, hypophosphatemia, adrenal insufficiency, transaminitis, and infections [76]. The ORR was found to be 90% in the CLL patients, which was similar to the ORR observed for ibrutinib monotherapy in previous studies; however, the CR for umbralisib + ibrutinib was 29%, which is substantially higher than for each drug alone. PFS was also found to be 90% at 2 years, which is also promising.

BCL-2 Inhibitors – Venetoclax

Venetoclax is a selective BH3 mimetic that targets the BCL-2, an antiapoptotic protein highly expressed in CLL cells [19, 20]. Upregulation of BCL-2 protein expression is one factor that bestows a survival advantage on CLL cells [80]. In the first-in-human phase 2 trial, venetoclax induced objective responses in 77% of patients with R/R CLL/SLL including del(17p), 16–20% of whom demonstrate CR [81]. At a median follow-up of 12.1 months, the ORR was 79%. The most common grade 3–4 AEs were neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%).

Most CLL patients treated with venetoclax demonstrate rapid reductions in tumor burden in the blood, nodes, and bone marrow, with improvement increasing over time. Venetoclax increases the risk of tumor lysis syndrome (TLS), but this complication is rarely observed at the currently tested doses and is mainly observed in laboratory form. TLS rates were high with initial 100- or 200-mg doses [20], and they were moderated at 50 mg [82]; after an analysis of risk factors, the current recommended initial dosing is 20 mg with weekly ramp-up [82, 83]. Some patients with CR demonstrated minimal residual disease (MRD) negativity, as identified by flow cytometry analysis of the bone marrow. Similar response rates were observed in patients with previously negative prognostic factors, including older age, disease refractoriness to fludarabine, unmutated *IGHV*, and del(17p).

Most importantly, venetoclax demonstrates high activity and good tolerability in patients with CLL refractory to ibrutinib or idelalisib or who may be progressing during or after treatment [84, 85]. A phase 2 trial examined 127 patients with R/R disease following previous treatment with a BCR signaling pathway agent, including 91 patients previously treated with ibrutinib [84]. The patients were treated with venetoclax, starting with a dose of 20 mg per day, which was ramped stepwise over 5 weeks to 400 mg per day. At median follow-up (14 months), the ibrutinib-treated group demonstrated 65% objective response, with 17 (19%) patient deaths, including 7 due to disease progression [80]. Elsewhere, an ORR of 67% including 8% CR was observed among a group of 36 patients with CLL who had progressed during or after idelalisib and who had received venetoclax for a median time of 14 months [85].

A real-world retrospective cohort analysis of 141 R/R patients with CLL demonstrated similar ORR (72.1%) to that previously reported in a clinical trial [86]. Venetoclax in monotherapy was approved in 2016 by the FDA for the

treatment of patients with CLL/SLL and a 17p deletion (del[17p]) who had received at least 1 prior therapy. In 2012, the drug was also granted approval by the European Medicine Agency (EMA) for the treatment of CLL [87].

The combination of venetoclax with rituximab (VenR) is an effective and safe combination in R/R CLL patients. Importantly, in contrast to venetoclax monotherapy, VenR is given for a limited time of 2 years. A phase 1b (M13-365) dose-escalation study evaluated VenR in a group of 49 R/R CLL patients [88]. The ORR was 86%, with approximately half achieving CR. MRD negativity in the bone marrow was noted in 13/20 (65%) patients with CR. The median time to first response was 2.9 months, and CR was achieved after a median of 9.2 months. Fixed-duration treatment with VenR for 24 months was also investigated in the MURANO trial [89, 90]. In this randomized, phase 3 study, patients were randomly assigned to 6 cycles of either the VenR or BR regimen. With a median follow-up of 36 months, VenR demonstrated superior PFS and OS rates than BR ($p < 0.001$ and $p = 0.0093$) [85]. Patients treated with VenR had a significantly higher rate of undetectable MRD, defined as $<10^{-4}$ in peripheral blood, compared to BR. Furthermore, PFS was significantly longer in cases with MRD negativity at the end of combination therapy. The VenR group also reported a higher percentage of all grade 3–4 AEs (67%) than the BR group (53.3%). The most common AE of any grade in both the VenR- and BR-treated groups was neutropenia (57.7 vs. 38.8%). On the basis of this study, the FDA and EMA approved VenR for adult patients with CLL/SLL, with or without 17p deletion, who have received at least 1 prior therapy.

In the phase 2 CLARITY study, 53 R/R patients were treated with ibrutinib + venetoclax [91]. Due to the risk of occurrence of TLS, venetoclax was administered 8 weeks after starting ibrutinib. After 12 months, MRD was achieved in the blood of 28 patients (53%) and the bone marrow of 19 (36%). Importantly, the depth of response was improved after 12 months of combined therapy. This treatment was well tolerated, with only a single case of laboratory TLS, and neutropenia or GI events were observed most commonly [91].

Rogers et al. [92] evaluated the activity of combined obinutuzumab, ibrutinib, and venetoclax therapy in 12 patients with R/R CLL. Due to risk of TLS, the agents were using sequentially, starting with obinutuzumab. Ibrutinib was added in the second cycle and venetoclax in the third cycle. The ORR was 92%, and 24-month PFS was 92%. All patients had undetectable MRD in the peripheral blood and/or bone marrow.

Venetoclax is generally well tolerated, with the most common AE being neutropenia. In patients with severe neutropenia, it is recommended to employ G-CSF administration or dose reduction. Other observed side effects include mild diarrhea, upper respiratory tract infection, nausea, anemia, thrombocytopenia, and neutropenic fever [80, 81, 84, 88]. TLS without clinical manifestation (only laboratory) was observed when the venetoclax dose was initiated as a stepwise ramp-up over 5 weeks. Less common complications were pneumonia, abdominal pain, hyponatremia, hypertension, hyperglycemia, hypokalemia, hypoxia, hypo/hypercalcemia, cellulitis, fall, cataract, hypoalbuminemia, autoimmune hemolytic anemia, increased aspartate aminotransferase, syncope, and dyspnea. Neutropenia and thrombocytopenia have been observed more frequently when venetoclax is administered in combination with other agents [80, 81, 84].

An indirect comparison of the efficacy of ibrutinib and venetoclax $\pm$ anti-CD20 was first reported by Eyre et al. [93]. Venetoclax treatment yielded higher CR rates and higher PFS over ibrutinib, but no OS advantage was observed. Dose reductions or treatment interruptions are more pronounced in ibrutinib-treated patients; however, randomized trials are necessary.

A recent systematic review and network meta-analysis compared VenR and BCRi in patients with R/R CLL. Both ibrutinib-BR and VenR demonstrated significant reductions in the risk of progression compared to idelalisib-BR. However, no difference was found between ibrutinib-BR and VenR in terms of PFS. As the PFS between the ibrutinib-based and venetoclax-based therapies is similar, the selection of proper treatments in routine clinical practice should be directed by side effect profile, cost, drug availability, and patient choice [94].

In R/R CLL patients, venetoclax can be used prior to BTKi. Mato et al. [95] report that 40% ($n = 130$) of patients who received a median of 3 therapies prior to venetoclax were BTKi naïve. ORR to BTKi was 84% among BTKi-naïve patients compared to 54% in those previously treated with BTKi. Hence, it appears that subsequent use of BTKi can induce high ORR and durable remissions in BTKi-naïve R/R patients, previously treated with venetoclax. Also, Lin et al. [96] examined 23 consecutive patients with R/R CLL who received ibrutinib ($n = 21$) or zanubrutinib ($n = 2$) after excluding from venetoclax; median PFS and OS were 34 and 42 months, respectively. In addition, BTKi therapy achieved durable benefit among patients with the Gly101Val mutation.

Allogeneic Stem Cell Transplantation and Cellular Therapies

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is currently believed to be the only curative therapy of CLL. However, several long-term FCR-treated survivors may also be cured. In addition, the role of allo-HCT in the management of high-risk CLL has also decreased following the introduction of BCR inhibitors and venetoclax [1, 2, 97]. Allo-HCT should be considered in patients with *TP53* dysfunction refractory to 2 previous lines of therapy and obtaining an objective response to BCR inhibitors or venetoclax [98]. Allo-HCT is also indicated for patients who did not achieve response or who progressed after BCR inhibitor therapy but received BCL-2 inhibitors, regardless of whether objective response is achieved. Moreover, patients with Richter's transformation in remission after therapy and clonally related to CLL should be considered for treatment with allo-HCT. Reduced-intensity conditioning (RIC) is recommended in the majority of CLL patients, that is, whenever possible. This therapy leads to sustained disease control in most patients with high-risk CLL, independently of *TP53* status.

Krämer et al. [99] report the results of the multicenter CLL3X trial by the German CLL Study Group (GCLLSG) which evaluated RIC allo-HCT in 90 patients with high-risk CLL. Blood stem cells from related donors were used in 40% of patients and from unrelated donors in 60%. Refractory disease at allo-HCT was observed in 24% and *TP53* deletion and/or mutation in 35%. The patients who achieved undetectable MRD 1 year after allo-HCT had an 87% probability of remaining disease free for at least 10 years. At the 6-year follow-up, 39 out of 90 transplanted patients demonstrated CLL recurrence after transplant, and 37 (41%) patients died. These findings indicate that RIC allo-HCT can induce disease control in a significant proportion of patients with high-risk CLL independent of *TP53* status. Among relapsed patients, agents that modulate the BCR pathway can be effective in those who are ibrutinib sensitive. However, allo-HCT is not feasible in many cases due to unsuitable patient age or fitness level, the presence of comorbidities, or the lack of a matching donor.

Some observation indicates that previous treatment with at least 5 cycles of ibrutinib enhances chimeric antigen receptor (CAR) engineered T-cell function; T-cell collection improved ex vivo and in vivo CTL019 expansion, which correlated positively with clinical response. Importantly, ibrutinib does not impair CAR-T-cell func-

tion in vitro and improves CAR-T-cell engraftment, tumor clearance, and survival in human xenograft models of CLL [100].

The results of clinical trials suggest that treatment with CAR-T offers promise. One such trial was based on 24 CLL patients treated with CD19-specific CAR-T cells after failure of ibrutinib [101]. Of the 24 patients, 19 demonstrated disease progression on ibrutinib, 3 were ibrutinib intolerant, 6 were venetoclax refractory, and 23 had complex karyotype and/or 17p deletion. ORR 4 weeks after infusion was 74%, including CR 21% and PR 53%. In the study group, 15/17 patients (88%) with marrow disease before CAR-T treatment demonstrated no disease after treatment, as indicated by flow cytometry. Moreover, 12/17 (70%) patients underwent deep IGH sequencing and 7 (58%) had no malignant IGH sequences detected in the marrow. In patients without the malignant IGH clone in the marrow, PFS and OS were 100% at a median 6.6-month follow-up [102]. Cytokine release syndrome developed in 20 patients (83%); in addition, neurotoxicity was observed in 8 patients (33%), 7 of which was reversible. One patient died. Although CAR-T therapy demonstrated lower nonrelapse mortality than allo-HCT in CLL [101, 103], less data are available regarding CAR-T therapy in CLL than allo-HCT, and its long-term curative potential needs to be determined in future clinical trials.

Frey et al. [104] report the long-term outcomes of anti-CD19 CAR-T cells in 38 patients with R/R CLL, treated with a low (5×10^7) or high (5×10^8) dose of anti-CD19 CAR-T cells (CART-19) and followed for a median of 31.5 months (range, 2–75 months). Median OS for all patients was 64 months, and no significant differences were observed between low- and high-dose groups, with comparable cytotoxicity. Achievement of CR after CART-19 was associated with longer OS and PFS in patients with R/R CLL. Thus, a 5×10^8 dose of CART-19 may be more effective than 5×10^7 CART-19 at inducing CR without excessive toxicity.

Most recently, Gauthier et al. [105] examined the efficacy of CAR-T cells and performed a long-term follow-up study of 29 patients with R/R or transformed follicular lymphoma (tFL) patients. They were treated with cyclophosphamide and fludarabine for a decrease in lymphocyte level and then by infusion of CD19-CAR-T cells. CR rates were 88% for patients with R/R FL and 46% for tFL patients. All patients with R/R FL who achieved CR remained in remission at a median follow-up of 24 months, whereas the median duration of response for patients with tFL was 10.2 months (at a median follow-up of 38 months). No grade 3 or higher AEs were observed. There-

fore, CD19 CAR-T cells seem to be effective immunotherapy, inducing durable remission both in patients with R/R FL without transformation as well as those with tFL.

Recommendations and Conclusions

Novel targeted drugs, especially BTK and PI3K inhibitors, BCL-2 inhibitors, and monoclonal antibodies, have improved the prognosis of previously untreated and R/R CLL patients. More specific BTK inhibitors, including acalabrutinib and zanubrutinib, demonstrate greater selectivity than ibrutinib, with minimal off-target activity and better expected safety profiles. Second-generation PI3K inhibitors in development, including duvelisib and umbralisib, have shown preliminary activity and acceptable safety profiles in CLL. Several small-molecule inhibitors of BCL-2, especially venetoclax, are highly active in CLL and have great therapeutic potential. The combination of novel targeted agents can increase efficacy, decrease the risk of resistance, and reduce toxicity. In addition, combined treatment induces deeper response and can be used for a limited time; however, currently, only the combination of venetoclax and rituximab is approved for a fixed duration schedule in R/R CLL. Recently, Soumerai et al. [106] developed a validated prognostic model for OS in patients with R/R CLL to identify high-risk patients who do not achieve a good outcome with available targeted therapies. A total of 2,475 patients with CLL were treated in 6 randomized trials of ibrutinib, idelalisib, and venetoclax. The score in an internal-validation dataset ($n = 242$) of patients treated with ibrutinib or chemoimmunotherapy and 3 external-validation datasets (idelalisib or chemoimmunotherapy dataset, $n = 897$; venetoclax or chemoimmunotherapy dataset, $n = 389$; and the Mayo Clinic CLL Database [MCCD; $n = 220$]) was assessed. The obtained model consisted of 4 factors: serum β_2 -microglobulin ≥ 5 mg/dL, lactate dehydrogenase $>$ upper limit of normal, hemoglobin <110 g/L for women or <120 g/L for men, and time from initiation of last therapy <24 months; these criteria were used to separate patients into low- (score 0–1), intermediate- (score 2–3), and high-risk (score 4) groups. A single factor was calculated as 1 point. The risk score was prognostic for OS in all examined cohorts.

Currently, novel targeted drugs, especially BTK and PI3K inhibitors, BCL-2 inhibitors, and monoclonal antibodies, are recommended for use in the vast majority of R/R CLL patients. However, patients with relapsed but asymptomatic CLL do not need immediate alternative

treatment and should be observed until evident sign of progression.

Recent guidelines indicate kinase inhibitor therapy before repeat chemotherapy or chemoimmunotherapy in all patient subgroups [1, 2, 106–109]. Among currently available approved treatments, venetoclax plus rituximab for 24 months or ibrutinib or acalabrutinib as continuous therapy is recommended in most patients. Other less-recommended options include idelalisib in combination with rituximab. Correct treatment selection depends on the type of prior therapy, response to previous treatment and side effects, comorbidities, and the risk of drug toxicity.

Resistance to BTK inhibitors or BCL-2 inhibitors is a common problem in RR CLL patients. More than 80% of CLL patients develop resistance to ibrutinib due to a cysteine mutation at the site covalently bound by ibrutinib (C481S); this is connected with poor outcome. However, novel agents under investigation can be active also in these patients. Buhimschi et al. [110] developed a PROteolysis TArgeting Chimera (PROTAC), MT-802, triggering BTK ubiquitination and degradation by the proteasome. This agent requires further preclinical study in CLL with C481S mutation. Acquired resistance to venetoclax is also observed in some patients. Blombery et al. [111] report a new mutation (Gly101Val) that significantly reduces the affinity of BCL-2, thus reducing the binding of venetoclax. Interestingly, the mutation occurred during disease progression. Hence, Gly101Val may be a potential biomarker of clinical relapse in CLL. Most recently, acquired novel multiple BCL-2 mutations inhibiting venetoclax activity were reported, with the BCL-2 Asp103Glu mutation occurring in parallel with BCL-2 Gly101Val during venetoclax therapy [112].

Retreatment with purine analogs combined with cyclophosphamide and rituximab should be omitted due to high toxicity. Currently, allo-HCT should be considered in patients refractory to chemoimmunotherapy with *TP53* mutation but who have responded to BCR and

BCL-2 inhibitors and demonstrate an acceptable risk of transplantation [1, 2, 107]. In addition, in patients who lack *TP53* dysfunction and demonstrate very long remission duration, as well those lacking targeted drugs or cellular therapy, chemoimmunotherapy with BR might still be an option. Allo-HCT should also be considered in patients refractory to chemoimmunotherapy and novel inhibitor therapy, even if the risk of transplantation is high.

However, currently available therapies are only partially effective in R/R CLL. Patients refractory to, or unsuitable for, approved drugs should be treated within clinical trials whenever possible. Several clinical trials with novel therapies are currently ongoing, and their findings should define the role of these drugs in the treatment of patients with R/R CLL. In particular, double or triple combinations of targeted drugs, bispecific antibodies, and CAR-T cells offer hope for these patients.

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Conflict of Interest Statement

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Author Contributions

P.S. and T.R. contributed equally to the conception/design, writing, and approval of the final version of the paper.

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