Evolution of CLL treatment — from chemoimmunotherapy to targeted and individualized therapy

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Abstract | During the past 5 years, a number of highly active novel agents, including kinase inhibitors targeting BTK or PI3Kδ, an antagonist of the antiapoptotic protein BCL-2, and new anti-CD20 monoclonal antibodies, have been added to the therapeutic armamentarium for patients with chronic lymphocytic leukaemia (CLL). In these exciting times, care is needed to optimally integrate these novel agents into the traditional treatment algorithm without overlooking or compromising the benefits of established treatments, especially chemoimmunotherapy. A more personalized approach to CLL therapy that takes into account individual risk factors, patient characteristics, and their treatment preferences is now possible. Herein, we discuss the biological basis for the novel therapeutic agents and outline not only the major advantages of these agents over traditional therapies but also their adverse effects and the rationale for continued use of older versus newer types of therapy for selected patients with CLL. We conclude by providing recommendations for an individualized therapy approach for different populations of patients with CLL.

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adults in Western countries, with an incidence of approximately 4.7 cases per 100,000 people in the USA, equating to ~20,100 new diagnoses per year. The disease has a male predominance (approximately 2:1), and the median age at diagnosis ranges from 70 to 72 years[1,2]. CLL is caused by the monoclonal expansion of mature-appearing neoplastic B lymphocytes with a distinct immune phenotype characterized by expression of B cell markers, such as CD19 and CD20, together with CD5 and CD23, which are not usually expressed on non-malignant B cells, and the progressive accumulation of these cells in the blood, secondary lymphatic tissues, and bone marrow[3,4]. Small lymphocytic lymphoma (SLL) is a less frequent manifestation of the same disease, sharing tissue morphology and immune phenotype characteristics with CLL but lacking a leukaemic phase (with <5,000 clonal B cells per μl of blood). CLL cell proliferation occurs in distinct areas of secondary lymphoid organs (lymph nodes and spleen)[5], in so-called proliferation centres or pseudo-follicles, where the leukaemia cells receive growth and survival signals delivered by components of the tissue microenvironment; activation of the B cell receptor (BCR) signalling pathway in the leukaemia cells is particularly important[6] (FIGS. 1,2).

CLL has a highly variable presentation and clinical course. The diagnosis of CLL is based on the detection of lymphocytosis (lymphocyte count >5,000 per μl of peripheral blood) by flow cytometry, with lymphocytes having the typical CLL immunophenotype. Indeed, CLL is often an incidental diagnosis after work-up for persistent lymphocytosis. The majority of patients with CLL are asymptomatic, have indolent disease, and are managed with a watch-and-wait approach involving regular follow-up assessments with serial blood counts and physical examination; radiological examinations are not warranted in asymptomatic patients with early stage CLL[4]. A substantial proportion of patients do not experience disease progression throughout their lifetime and consequently never require therapy. The majority of patients, however, will eventually require treatment owing to active CLL. Manifestation of active disease can include constitutional symptoms, such as B symptoms (weight loss, fever, and night sweats) and fatigue, and/or clinical signs of disease activity, such as progressive lymphocytosis, cytopenias (anaemia and thrombocytopenia), lymphadenopathy and splenomegaly, and recurrent infections[4]. Treatment initiation is recommended when anaemia and/or thrombocytopenia, bulky disease, or constitutional symptoms develop[4]. Autoimmune complications, especially autoimmune cytopenias, and the development of symptomatic lymphadenopathy with bulky nodes, splenomegaly, or a short lymphocyte doubling

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Key points

- Novel drugs enable targeting of key pathogenic pathways of chronic lymphocytic leukaemia (CLL), including BTK, SYK, and PI3Kδ inhibitors that disrupt B cell receptor signalling and venetoclax, an antagonist of the anti-apoptotic protein BCL-2.
- The kinase inhibitors typically cause mobilization of tissue-resident CLL cells into the circulation, resulting in rapid resolution of lymphadenopathy and splenomegaly and transient redistribution lymphocytosis.
- Kinase inhibitor monotherapy mostly induces partial remissions, which are typically maintained with long-term therapy but can be compromised by toxicities and the emergence of resistance; hence, limited-duration therapy, if effective, would be desirable.
- Venetoclax has direct cytotoxic activity, sometimes resulting in tumour lysis; this drug has mostly been used after failure of kinase inhibitor therapy, but emerging data support its use in earlier treatment lines and/or in combination with other agents.
- Given the expanding therapeutic armamentarium for CLL, risk-based individualized therapy is now possible, ranging from chemoimmunotherapy for low-risk (*IGHV*-mutated) CLL to novel molecularly targeted therapy — primarily with BTK inhibitors — for high-risk (del(17p), *IGHV*-unmutated) disease.
- New anti-CD20 antibodies, immunomodulatory agents, and cellular therapies (such as chimeric antigen receptor T cells and allogeneic haematopoietic stem cell transplantation) are additional important components of CLL treatment.

time of <6 months are additional indications to initiate CLL therapy[4].

Clinical staging systems developed by Rai[7] and Binet[8] remain a cornerstone for the clinical assessment and staging of patients with CLL, enabling separation of those with early stage disease (Rai stage 0–II or Binet stage A) from those with advanced-stage disease (Rai III–IV or Binet B–C), primarily on the basis of the development of anaemia and/or thrombocytopenia at advanced disease stages. These staging systems were developed before the discovery of prognostic genetic and molecular features of CLL and therefore cannot be used to estimate the risk of disease progression in individual patients with early stage disease or to predict responses to therapy. By contrast, the subsequently identified prognostic molecular markers are helpful in estimating the individual risk of CLL progression, which can in turn be useful in determining appropriate treatment options. These risk factors include cytogenetic abnormalities detected using fluorescence in situ hybridization (FISH), such as del(13q), del(17p), trisomy 12, and del(11q)[9], and the mutational status of the BCR *IGHV* genes detected through PCR amplification and sequence analysis. The latter distinguishes patients with *IGHV*-mutated CLL (M-CLL), who generally have indolent disease, from patients with *IGHV*-unmutated CLL (U-CLL), who typically present with more active disease; the threshold for M-CLL is a ≥2% deviation of the *IGHV* sequence in CLL cells from the germline *IGHV* sequence[10–13]. To enable more accurate prognostication and thus patient stratification for therapy than is possible with the Rai and Binet classifications, some of these genetic features have been integrated into more comprehensive prognostic systems, such as the CLL international prognostic index (CLL-IPI)[14]. The CLL-IPI can be used to distinguish patients with low-risk, intermediate-risk, high-risk, and very-high-risk CLL through weighted grading according to *TP53* status (no aberration versus del(17p) or *TP53* mutation, or both), *IGHV* status (mutated versus unmutated), serum β_2-microglobulin concentration (≤3.5 mg/l versus >3.5 mg/l), clinical stage (Binet A or Rai 0 versus Binet B–C or Rai I–IV), and age (≤65 years versus >65 years).

Patients with CLL harbouring high-risk molecular and/or cytogenetic features — that is, those with U-CLL, del(17p), or del(11q) — characteristically have a shorter time to first treatment and inferior responses to chemotherapy-based regimens compared with patients who do not have these characteristics[9,12]. Consequently, patients with these high-risk features had shorter survival durations with traditional CLL therapies[9,12,15,16]; however, novel, highly efficacious molecularly targeted agents have been added to the CLL therapeutic armamentarium over the past 5 years, and the substantially improved outlook for these patients will likely be confirmed when long-term follow-up data from studies of these novel agents become available.

Before the introduction of the novel agents, younger patients with CLL that required therapy were offered a chemoimmunotherapy regimen provided they were in good health and had no major comorbidities. Combination therapy with fludarabine, cyclophosphamide, and the anti-CD20 antibody rituximab (FCR)[17,18] or bendamustine and rituximab (BR)[19,20], generally given for six cycles at monthly intervals, have been the most commonly used chemoimmunotherapy regimens for such patients. The goal of these higher-intensity treatments is to induce deep and durable remissions, requiring the achievement of minimal residual disease (MRD) negativity at the end of the treatment[21]. Considering that the median age at diagnosis is 70–72 years[1,2], however, many patients with CLL are elderly and/or have comorbidities that preclude the use of chemoimmunotherapy and instead have typically received low-intensity therapy with either an alkylating agent (such as chlorambucil[22]), an anti-CD20 monoclonal antibody (such as rituximab[23]), or combinations thereof[24]. With these treatments, the goal is to prevent or alleviate CLL-related symptoms and to ameliorate anaemia and/or thrombocytopenia. The advent and approval of novel molecularly targeted agents, particularly the BTK inhibitor ibrutinib[25,26], the PI3Kδ inhibitor idelalisib[27], and the apoptosis regulator BCL-2 antagonist venetoclax[28], have now provided additional treatment options for patients with CLL, which especially benefit those with high-risk disease who have unfavourable outcomes with chemotherapy-based regimens (TABLE 1). The rapid clinical development and approval of these agents were supported by their outstanding activity in patients with high-risk CLL, their generally favourable safety profiles (TABLE 2), and a typically low incidence of myelosuppression[29,30]. Additionally, obinutuzumab and ofatumumab are two novel anti-CD20 antibodies that, when combined with chlorambucil, provide substantial clinical benefit compared with chlorambucil alone or chlorambucil plus rituximab[24,31], establishing new low-intensity chemoimmunotherapy options for elderly and frail patients with CLL. With these new developments over the past decade, treatment algorithms for patients with CLL have become more complex and individualized. Herein, we discuss the changing landscape of

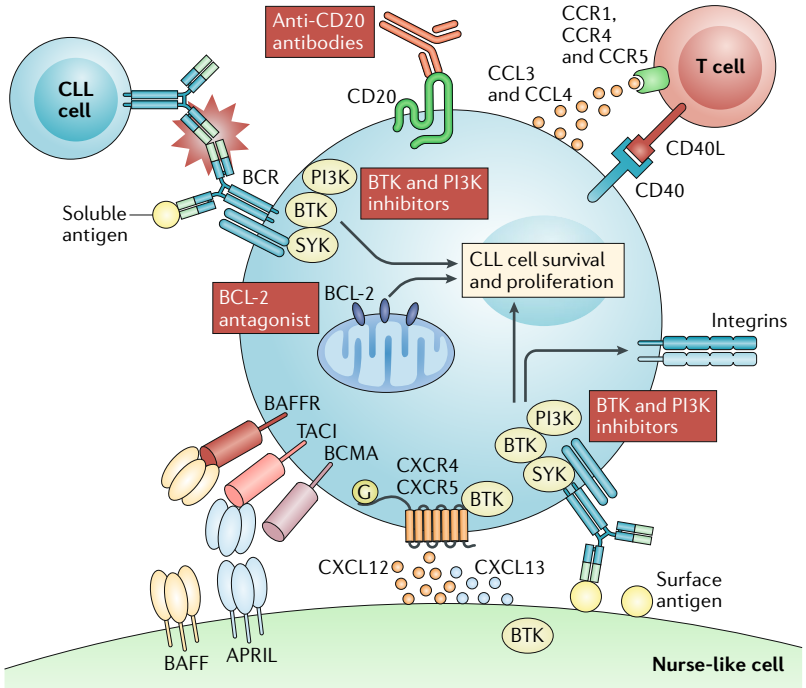

Fig. 1 | **Factors in the CLL microenvironment activate growth and survival pathways that can be targeted using novel therapeutic agents.** Chronic lymphocytic leukaemia (CLL) cells proliferate in secondary lymphatic organs, such as the lymph nodes and spleen[5], where they form characteristic proliferation centres termed 'pseudo-follicles'. Within these pseudo-follicles, CLL cells engage in a complex crosstalk with a range of non-malignant cells that constitute the CLL microenvironment[146]; monocyte-derived nurse-like cells (NLCs), often referred to as tumour-associated or lymphoma-associated macrophages in the context of other cancers, and T lymphocytes are important elements of this niche. As in non-malignant B cells, B cell receptor (BCR) activation and signalling have central roles in CLL cell proliferation and survival. BCR signalling is selectively activated in secondary lymphatic organs, but not in blood or bone marrow[6], after engagement of the BCR with soluble or surface-bound antigens, which can be microbial[147] or self-derived[148,149]. An alternative mechanism of BCR activation involves homotypic interactions between BCRs presented on the same CLL cell or on a neighbouring CLL cell (red star, upper left corner)[150–152]. Other microenvironmental factors that contribute to CLL survival and proliferation include B cell-activating factor (BAFF; also known as TNFSF13B) and a proliferation-inducing ligand (APRIL; also known as TNFSF13), which are produced by NLCs and activate corresponding receptors expressed by CLL cells, such as BAFF receptor (BAFFR), B cell maturation protein (BCMA; also known as TNFRSF17), and transmembrane activator and CAML interactor (TACI; also known as TNFRSF13B). Activated T helper cells express CD40 ligand, which can promote the growth of CLL cells via engagement of CD40 (also known as TNFRSF5). NLCs and other stromal cells also secrete chemokines, such as CXC-motif chemokine 13 (CXCL13) and stromal cell-derived factor 1 (SDF1; also known as CXCL12), which attract and retain CLL cells within secondary lymphatic organs through activation of CXC chemokine receptor 5 (CXCR5) and CXCR4, respectively, on the leukaemia cells. Similarly, upon BCR signalling, CLL cells can secrete chemokines (CC-motif chemokine 3 (CCL3) and CCL4)[153], which in turn attract T cells to the tumour microenvironment[154], thereby fostering a supportive niche. Apoptosis regulator BCL-2, which is an important anti-apoptotic protein, is overexpressed in CLL cells and promotes the survival of these cells by inhibiting pro-apoptotic proteins. The BCL-2 antagonist venetoclax can disrupt this survival mechanism. BTK and PI3Kδ are key kinases involved in signalling downstream of the BCR and are the respective targets of the novel approved CLL treatments ibrutinib and idelalisib, respectively. These kinases also have roles in signalling cascades, such as those induced via chemokine receptors (CXCR4) and adhesion molecules (integrins). Furthermore, these kinases are expressed not only by CLL cells but also by bystander cells in the microenvironment; for example, BTK is expressed by NLCs[155,156]. Thus, ibrutinib and idelalisib induce complex changes in the CLL microenvironment. Indeed, disrupted signalling and function of chemokine receptors and adhesion molecules explain the redistribution lymphocytosis that is characteristically observed in patients with CLL after treatment with BTK or PI3K inhibitors, as well as investigational inhibitors of SYK, which is also involved in BCR signalling. CD20 is the target of traditional (rituximab) and novel anti-CD20 antibodies (ofatumumab and obinutuzumab). CCR, CC chemokine receptor.

CLL therapy, review our current biological and clinical understanding of traditional and novel therapeutic agents, and provide recommendations for an individualized approach to treatment incorporating the available prognostic indicators and therapies.

Evolution of CLL therapy: the early days

In the 1940s, glucocorticoids were introduced as the first systemic therapy for patients with CLL (FIG. 3). Investigators noted an abrupt rise in blood lymphocyte counts up to >1,000,000 per μl after initiation of glucocorticoid therapy at doses ranging from 0.5 mg/kg to 1 mg/kg, together with rapid reductions in spleen and lymph node sizes[32]. After glucocorticoid therapy was withdrawn, lymphocyte counts declined and often stabilized at levels that were lower than pretreatment values[33–38]. Lymphocyte redistribution from the lymphatic tissues into the peripheral blood was proposed as the mechanism underlying this response pattern[37,39], which is reminiscent of the lymphocyte redistribution recognized as a class effect of kinase inhibitors targeting BTK, PI3Kδ, and SYK[39]. Glucocorticoids have not become part of standard CLL therapy because of the transient nature of responses and adverse effects of long-term administration, particularly infections; however, high-dose glucocorticoids, used alone or in combination with anti-CD20 antibodies, can effectively achieve remissions in treatment-refractory high-risk CLL[40–42].

In the 1950s, nitrogen mustard derivatives were introduced into the clinical management of patients with CLL. Given their mechanism of action (DNA damage by attachment of an alkyl group to guanine bases of DNA), agents in this class are termed 'alkylating agents'. Until recently, alkylating agents, especially chlorambucil, but also cyclophosphamide and bendamustine, remained standard therapy for patients with CLL and continue to be useful for certain patients, particularly in combination with anti-CD20 antibodies, as outlined above.

Chlorambucil and bendamustine

Chlorambucil can be given in continuous daily doses or intermittently, for example, in a biweekly fashion[43], and either alone or in combination with glucocorticoids, resulting in objective responses in 40–70% of patients, although mostly partial remissions (PRs)[44]. This agent has generally been used to improve symptoms in patients with advanced-stage CLL without a proven overall survival benefit. Accordingly, the use of chlorambucil in patients with early stage CLL has not been shown to improve long-term survival[45], corroborating the watch-and-wait approach for this group. The nucleoside analogue fludarabine has higher anti-leukaemia activity as a single agent than chlorambucil[46]; nonetheless, the results of two randomized comparisons of these agents failed to demonstrate any survival benefit of fludarabine[22,47] and, therefore, chlorambucil remained a standard CLL therapy for decades. Within the past 5 years, however, combinations of chlorambucil and anti-CD20 antibodies have been demonstrated to be superior to chlorambucil monotherapy in terms of progression-free survival (PFS) for combinations with rituximab[24] or ofatumumab[31] and in terms of both PFS and overall survival for

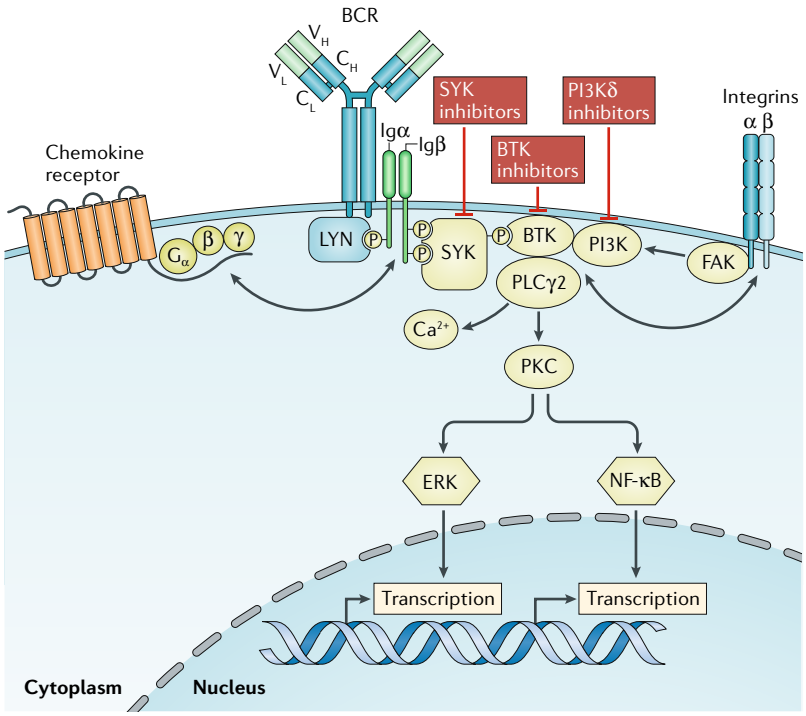

Fig. 2 | **Signalling by B cell receptors, chemokine receptors, and adhesion molecules.** Antigen binding by the B cell receptor (BCR) induces the formation of a signalling complex that is initiated by phosphorylation of immunoreceptor tyrosine-based activation motif (ITAM) residues within the cytoplasmic tails of BCR complex-associated protein-α (Igα) and protein-β (Igβ) chains. This event enables the recruitment of SYK, which is followed by the activation of BTK, PI3K, and phospholipase Cγ2 (PLCγ2). Further downstream responses include calcium (Ca^{2+}) mobilization and activation of PKC, as well as ERK and nuclear factor-κB (NF-κB) signalling. Activation of these pathways has multiple cellular effects, including downregulation of the transcriptional repressor B cell lymphoma 6 protein (BCL6) and upregulation of transcription[157,158]. These cascades can also be activated or enhanced by adhesion molecule (integrin) signalling via FAK and by chemokine receptor signalling. SYK, BTK, and PI3K inhibitors can disrupt oncogenic BCR signalling in CLL cells, resulting in abrogated CLL cell proliferation and accelerated CLL cell death[159]. Indeed, the BTK inhibitor ibrutinib and the PI3Kδ inhibitor idelalisib are currently approved for the treatment of CLL; different agents targeting BTK, PI3K, or SYK are also being investigated in clinical trials in patients with this disease.

combinations with obinutuzumab[24]. Moreover, results of a randomized comparison between chlorambucil and ibrutinib in patients with treatment-naive CLL demonstrated substantial PFS and overall survival benefits for patients receiving ibrutinib[26]. These findings discourage the use of single-agent chlorambucil in the treatment of CLL. Nevertheless, low-intensity chemoimmunotherapy comprising chlorambucil and an anti-CD20 antibody remains a treatment option for elderly and/or frail patients, at least while randomized comparisons with regimens in which chlorambucil is replaced with a novel agent are ongoing (ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab (NCT02264574) and obinutuzumab plus venetoclax versus obinutuzumab plus chlorambucil (NCT02242942)).

Bendamustine was originally synthesized in Eastern Germany in the 1960s for treatment of various malignancies and became more widely available after the German reunification. This alkylating agent has been compared with chlorambucil in patients with untreated CLL in a randomized fashion; bendamustine produced a higher objective response rate (ORR) and longer PFS durations[48]. Owing to greater efficacy when used in combination with rituximab (BR regimen)[49], single-agent bendamustine is now rarely used in the treatment of CLL.

Nucleoside analogues

The efficacy of purine nucleoside analogues fludarabine, cladribine, and pentostatin has been extensively explored in patients with CLL. Of these agents, fludarabine is the most widely used and induces high ORRs (up to ~80% in untreated patients), a considerable proportion of which are complete remissions (CRs; ~20%)[46]. Nucleoside analogues are incorporated into DNA and RNA, which interferes with DNA synthesis and repair and gene expression in both dividing and non-dividing cells. Lymphocytopenia, reflecting depletion of not only CLL cells but also non-malignant T cells, is commonly detected in patients treated with fludarabine and results in immunosuppression[50]. Randomized comparisons of fludarabine with chlorambucil or with the cyclophosphamide, adriamycin, and prednisone (CAP) regimen revealed higher ORRs in patients treated with fludarabine but without survival benefits[22,47,51]. On the basis of synergy demonstrated in vitro, the combination of fludarabine and cyclophosphamide (FC) was subsequently tested in the clinic[52], resulting in higher ORRs and improved treatment-free survival durations when compared to fludarabine alone (ORRs and CR rates 94% and 24%, respectively, versus 83% and 7% in patients with previously untreated CLL)[53].

Cladribine as a single agent induces ORRs that are similar to those achieved with fludarabine alone[54]. When compared with chlorambucil in patients with previously untreated CLL, cladribine (both in combination with prednisone) induced substantially higher ORR and CR rates (87% and 47%, respectively, versus 57% and 12% with chlorambucil), but overall survival was not improved[55]. Pentostatin was developed for the treatment of CLL in combination with cyclophosphamide and rituximab as part of the PCR regimen, which induces high ORRs and CR rates (ORR 91%, CR rate 41%)[56], primarily in patients with favourable risk features[57]. Pentostatin might have advantages over fludarabine in terms of toxicity[58]; however, the lack of a demonstrated survival benefit of pentostatin-based or cladribine-based therapy when compared with other established CLL treatment regimens in randomized trials has limited the use of these agents — even more so now, given the current decline in the use of chemotherapy-based regimens owing to the effectiveness of novel therapeutic agents.

FCR and BR chemoimmunotherapy

The addition of rituximab to FC to form the FCR chemoimmunotherapy regimen transformed CLL therapy[17,59] (FIG. 3); for the first time, a major fraction of patients with newly diagnosed disease achieved CRs after finishing six cycles of therapy (40–70%; TABLE 1). When compared with first-line FC therapy in a randomized fashion, FCR provided a significant improvement in PFS (HR 0.56, 95% CI 0.46–0.69; $P<0.0001$) and, for the first time in CLL therapy, an overall survival benefit (HR 0.67, 95% CI 0.48–0.92; $P=0.01$)[18]. Subset analyses revealed that

Table 1 | **Key clinical trial data for CLL chemoimmunotherapy**

Regimen	Disease state (*n*)	ORR; CR rate	PFS	OS	Adverse effects[a] (frequency)	Refs
Fludarabine and cyclophosphamide plus rituximab (FCR)	Treatment-naive (*n* = 300)	95%; 70%	After 12.8 years: • M-CLL: 54% • U-CLL: 9%	Median: • All patients: 12.7 years • M-CLL: NR • U-CLL: 9.4 years	Grade 3–4 neutropenia (52%), major infections (2.6% per course), minor infections (10% per course), RT (9%), and t-AML (5%)	15,1762
	Treatment-naive (*n* = 408)	90%; 44%	After 3 years: • All patients: 65% • M-CLL: 80% • U-CLL: 55% • Del(17p): 18%	After 3 years: • All patients: 87% • M-CLL: 91% • U-CLL: 86% • Del(17p): 38%	Grade 3–4 neutropenia (34%) and grade 3–4 infections (25%)	18
	Treatment-naive (*n* = 282)	95%; 40%	Median: • All patients: 55.2 months • M-CLL: NR • U-CLL: 42.7 months	After 3 years: 91%	Grade 3–4 neutropenia (85%) and grade 3–4 infections (38%)	20
	Relapsed and/or refractory (*n* = 177)	74%; 30%	Median: • All patients: 21 months • Responding patients: 37 months • M-CLL: 84 months • U-CLL: 28 months	Median: 47 months	Grade 3–4 neutropenia (81%), myelosuppression (46%), thrombocytopenia (34%), anaemia (24%), and major infections (16%)	59,168
Bendamustine plus rituximab (BR)	Treatment-naive (*n* = 117)	88%; 23%	Median (EFS): 33.9 months	After 27 months: 91%	Thrombocytopenia (22%), grade 3–4 neutropenia (20%), anaemia (20%), and grade 3–4 infections (8%)	49
	Treatment-naive (*n* = 279)	96%; 31%	Median: • All patients: 38.5 months • M-CLL: 55.4 months • U-CLL: 33.6 months	After 3 years: 92%	Grade 3–4 neutropenia (59%) and grade 3–4 infections (24%)	20,49
	Relapsed and/or refractory (*n* = 78)	59%; 9%	Median: 15 months	Median: • All patients: 33.9 months • M-CLL: NR • U-CLL: 25.6 months	Myelosuppression (50%), thrombocytopenia (28%), severe neutropenia (23%), anaemia (17%), and severe infections (9%)	19

CLL, chronic lymphocytic leukaemia; CR, complete remission; EFS, event-free survival; M-CLL, *IGHV*-mutated CLL (≥2% deviation from the *IGHV* germline sequence); NR, not reached; ORR, overall remission rate; OS, overall survival; PFS, progression-free survival; RT, Richter transformation; t-AML, therapy-related acute myeloid leukaemia; U-CLL, *IGHV*-unmutated CLL (<2% deviation from the *IGHV* germline sequence). [a]Of any grade, unless specified.

patients with high-risk disease harbouring 17p or 11q deletions and patients with U-CLL had shorter durations of remission after FCR therapy[60], whereas patients with M-CLL or other low-risk features had durable remissions often exceeding 10 years[15] (TABLE 1). Besides these cytogenetic and molecular risk factors, achievement of MRD negativity, commonly assessed by flow cytometry analysis of blood or bone marrow cells, also predicted durable remissions. Indeed, MRD negativity can be a useful criterion to guide treatment discontinuation before completing six cycles of FCR[61] in an individualized therapy approach, with the aim of reducing exposure to chemotherapy and thereby reducing the risk of secondary cancers. Treatment-related acute myeloid leukaemia or myelodysplastic syndrome (t-AML/MDS) and Richter transformation have been reported to occur at rates of 5% and 9%, respectively, after FCR chemoimmunotherapy[60,62], portend a poor prognosis, and remain an important drawback of chemotherapy-based regimens in patients with CLL. Whether t-AML/MDS can also occur with the use of novel molecularly targeted agents is currently unknown but seems unlikely given the different mechanism of action — that is, DNA damage with alkylating agents and nucleoside analogues versus more targeted interference with kinase signalling or BCL-2-mediated apoptosis. Owing to the inferior responses in patients with high-risk CLL when compared with those achieved with the novel agents, the use of chemoimmunotherapy is increasingly focused on patients with low-risk disease, with efforts to reduce the number of chemotherapy cycles in patients who achieve MRD negativity and thus decrease the risk of t-AML/MDS. Additionally, the incorporation of novel agents into chemoimmunotherapy regimens for patients with low-risk CLL is being tested in ongoing trials (for example, ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab (iFCG); NCT02629809), in which only three cycles of the FC chemotherapy backbone are administered.

When compared with FCR in patients with previously untreated CLL, the alternative widely used chemoimmunotherapy regimen BR was associated with less frequent infections and neutropenia and with shorter PFS durations, whereas no difference in overall survival was observed[20] (TABLE 1). On the basis of these data, BR remains useful in selected patients for whom chemoimmunotherapy with less myelosuppression is considered the preferred treatment. Nonetheless, bendamustine is associated with a substantially greater frequency of

Table 2 | **Key clinical trial data for kinase inhibitors in patients with CLL**

Treatment	Disease state (*n*)	ORR	PFS	OS	Adverse effects[a] (frequency)	Refs
BTK inhibitors						
Ibrutinib	Relapsed and/or refractory (*n* = 85)	71% after 20.9 months; 94% after 44 months	• All patients: 88% after 6 months; 69% at 30 months[169] • Del(17p): 48% at 30 months[169] • Del(11q): 74% at 30 months[169]	• All patients: 79% at 30 months[169] • Del(17p): 65% at 30 months[169] • Del(11q): 85% at 30 months[169]	Diarrhoea (48–55%), bleeding events (44%), hypertension (22%), pneumonia (19%), neutropenia (16%), grade 3–4 infections (11%), atrial fibrillation (3%), and major haemorrhage (1%)	25,74,79,169,170
	Treatment-naive (*n* = 136)	86% (4% CR rate) at 18.4 months; 85% (26% CR rate) after 44 months	90% after 18 months; 96% after 30 months	98% at 24 months; 96% at 30 months	Diarrhoea (68%), grade 3– 4 infections (48%), hypertension (22%), atrial fibrillation (6%), pneumonia (4%), neutropenia (4%), and major haemorrhage (4%)	26,170
Acalabrutinib	Relapsed and/or refractory (*n* = 61)	95% after 14 months	90% at 16 months	>90% at 16 months	Headache (46%), diarrhoea (43%), upper respiratory tract infection (28%), fatigue (27%), nausea (27%), arthralgia and pyrexia (each 23%), contusion (22%), petechiae and weight increased (each 21%), hypertension (11%), grade 3–4 neutropenia (11%), grade 3–4 pneumonia (10%), and atrial fibrillation (3%)	97,171
Tirabrutinib (GS-4059 or ONO-4059)	Relapsed and/or refractory (*n* = 28)	96% (lymph node responses)	Median 38.5 months	Median 44.9 months	Bruising (36%), neutropenia (36%), and anaemia (32%); one grade 3 bleeding event (3.6%; haematoma)	172
PI3Kδ inhibitors						
Idelalisib	Relapsed and/or refractory (*n* = 54)	72%	Median 15.8 months	Not reported	Grade 3–4: pneumonia (20%), neutropenic fever (11%), and diarrhoea (6%)	89
Idelalisib plus rituximab	Relapsed (*n* = 110)	81% (all PR)	93% at 24 weeks	92% at 12 months	Pyrexia (29%), fatigue (24%), nausea (24%), chills (22%), and diarrhoea (19%)	27
	Treatment-naive (*n* = 64)	97% (19% CR rate)	83% at 36 months	90% at 36 months	Elevated serum levels of liver enzymes (67%), diarrhoea (64%), rash (58%), and pyrexia (42%)	92
Idelalisib plus ofatumumab	Relapsed and/or refractory (*n* = 174)	75% (<1% CR rate)	Median 16.3 months	Median NR	Neutropenia (34%), diarrhoea (20%), pneumonia (14%), serious infections (13%), sepsis (6%), and *Pneumocystis jiroveci* pneumonia (5%)	95
Idelalisib as single agent for 2 months, then combined with ofatumumab for 6 months	Treatment-naive (*n* = 24)	Not reported	Not reported	Not reported	Immune-mediated hepatotoxicity (79% after a median of 28 days) and grade 3–4 hepatotoxicity (54%)	91
Idelalisib plus bendamustine and rituximab	Relapsed and/or refractory (*n* = 207)	70% (1% CR rate)	Median 20.8 months	Median NR	Neutropenia (60%), grade 3–4 infections (39%), and febrile neutropenia (23%)	93
Umbralisib (TGR-1202)	Relapsed and/or refractory (n = 24; 20 evaluable for response)	50% (per iwCLL criteria) plus 25% PR with lymphocytosis	Not reported	Not reported	Grade 3–4 (for all 90 patients with different B cell malignancies): neutropenia (13%), anaemia (9%), thrombocytopenia (7%), pneumonia (3%), and colitis (2%)	105
PI3Kδ and PI3Kγ inhibitor						
Duvelisib	Treatment-naive (*n* = 18) or relapsed and/or refractory (*n* = 55)	• Treatment-naive: 83% • Relapsed and/or refractory: 56%	• Treatment-naive: not estimable • Relapsed and/or refractory: median 15.7 months	Not reported	Grade 3–4: neutropenia (32%), elevated serum ALT (20%) and/or AST (15%) levels, anaemia (14%) and thrombocytopenia (14%), diarrhoea (11%), and pneumonia (10%)	102
SYK inhibitors						
Fostamatinib (R406)	Relapsed and/or refractory (*n* = 11)	55%	Median 6.4 months	Not reported	Not reported	63
Entospletinib (GS-9973)	Relapsed and/or refractory (*n* = 41)	61% (0% CR rate)	Median 13.8 months	Not reported	Pneumonia, neutropenia, anaemia, pyrexia, and elevated liver enzymes (frequencies in patients with CLL, specifically, not reported)	109

ALT, alanine aminotransferase; AST, aspartate transaminase; CLL, chronic lymphocytic leukaemia; CR, complete remission; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; NR, not reached; ORR, overall remission rate; OS, overall survival; PFS, progression-free survival; PR, partial remission. [a]Of any grade, unless specified.

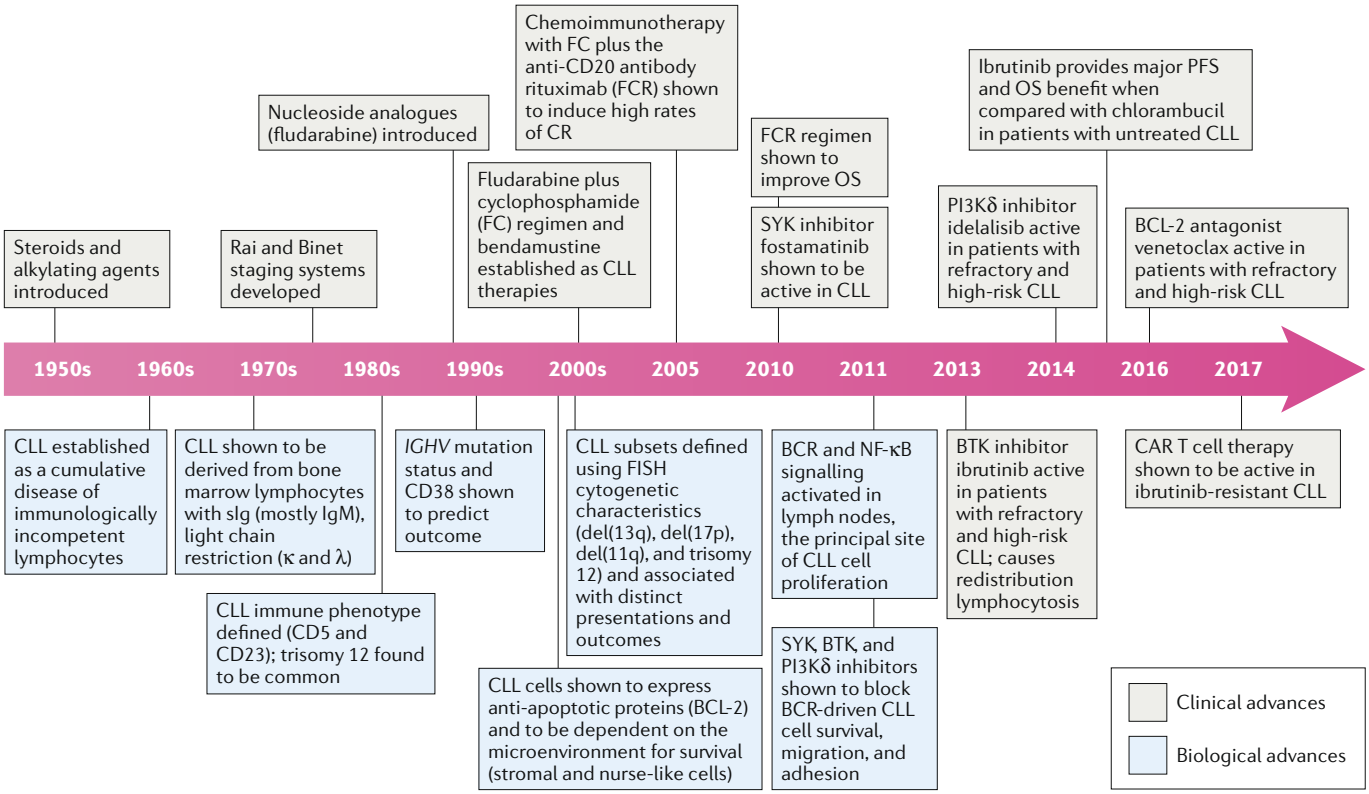

Fig. 3 | **Milestones in biological and clinical CLL research that have paved the way for new targeted therapies.** Clinical landmarks include the introduction of steroids[34,37] and alkylating agents[36] as the first systemic treatments of chronic lymphocytic leukaemia (CLL). This advance was followed 2 decades later by the introduction of the Rai[7] and Binet[8] classification systems, which enable clinical staging of CLL based on physical examination and peripheral blood counts. The introduction of nucleoside analogues, especially fludarabine[46], was the next step forward in CLL therapy, followed by combination approaches with fludarabine plus cyclophosphamide (FC)[53] and, subsequently, addition of the anti-CD20 antibody rituximab to this combination to form the FCR chemoimmunotherapy regimen[17]. FCR was the first regimen to induce high complete remission (CR) rates[17] and to provide an overall survival (OS) benefit when compared with the FC regimen[18]. SYK, BTK, and PI3Kδ inhibitors (fostamatinib[63], ibrutinib[25,26], and idelalisib[27], respectively) enabled the next breakthroughs in CLL therapy, followed by the apoptosis regulator BCL-2 antagonist venetoclax[28,30]. On the basis of promising data from early stage trials[134,135], chimeric antigen receptor (CAR) T cell therapy has the potential to become a more widely used therapy option in the near future. Preclinical milestones include the initial definition of CLL as a cumulative disease of lymphocytes that are immunologically incompetent[160], followed by the characterization of these cells as monoclonal B lymphocytes[161,162] and definition of their characteristic immunophenotype (expression of conventional B cell markers, such as CD20 and CD19, with co-expression of CD5 and CD23)[163,164]. Subsequently, prognostic molecular (*IGHV* mutational status and CD38 expression[12,13]) and cytogenetic markers[9] (del(11q), del(13q), and del(17p) and trisomy 12) were identified, and the importance of anti-apoptotic proteins, especially BCL-2[165], and the dependency of CLL cells on the microenvironment[146] were established. In the past decade, the importance of B cell receptor (BCR) signalling in CLL pathogenesis has been underscored by in vivo demonstration of selective activation of BCR signalling in lymph nodes[6], the principal site of CLL cell proliferation, and the inhibition of BCR signalling and, thus, CLL cell function and survival by the novel kinase inhibitors[87,166,167]. FISH, fluorescence in situ hybridization; NF-κB, nuclear factor-κB; PFS, progression-free survival; sIg, secreted immunoglobulin.

myelosuppression than that observed with chlorambucil in patients with untreated CLL (neutropenia in 27% versus 14%, thrombocytopenia in 25% versus 21%, and anaemia in 22% versus 14%)[48]; thus, the aforementioned combination of chlorambucil and an anti-CD20 antibody remains a reasonable treatment option for selected patients.

The novel molecularly targeted agents

Approved kinase inhibitors

Kinase inhibitors targeting the BCR-related kinases SYK, BTK, and PI3Kδ were initially tested in cohorts of patients with various B cell malignancies[27,63–65]. During these early trials, three major themes emerged. First, patients with CLL have high response rates and durable remissions with these agents, whereas patients with other B cell malignancies often have lower response rates and/or shorter remissions. Second, patients with CLL have a distinctive response pattern characterized by rapid shrinkage of enlarged lymph nodes and other involved tissue sites, such as the spleen, generally within the first few days on treatment, with redistribution of CLL cells into the circulation leading to a parallel increase in peripheral blood lymphocyte counts — termed 'redistribution lymphocytosis' (FIG. 4). This redistribution phenomenon has also been noted, to a lesser extent, in patients with other disease entities, such as mantle-cell lymphoma (MCL)[66], and might at least partially account for the therapeutic efficacy of these agents. Third, the differences in response rates across CLL subsets and the adverse effects typically observed with chemoimmunotherapy are not, or only rarely, seen with the kinase inhibitors. Specifically, patients with high-risk and/or chemotherapy-refractory CLL respond very well to these agents, and myelosuppression is uncommon.

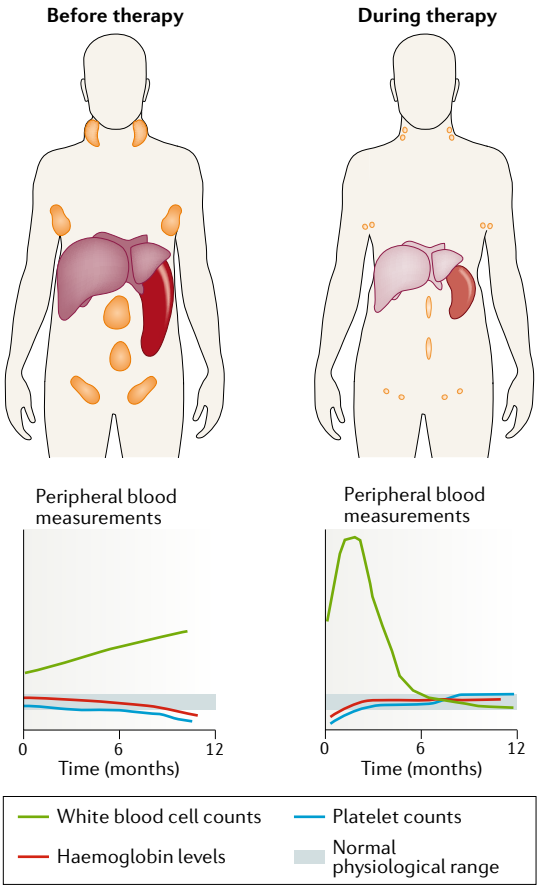

Fig. 4 | **Characteristic response of patients with CLL to treatment with BTK or PI3Kδ inhibitors.** Before kinase inhibitor therapy, patients with active chronic lymphocytic leukaemia (CLL) have a gradual increase in white blood cell counts (leukocytosis) owing to the presence of increasing numbers of leukaemia cells in the peripheral blood, together with development of anaemia (indicated by declining haemoglobin levels) and thrombocytopenia (declining platelet counts). Concurrently, patients can have lymph node enlargement, splenomegaly, and hepatomegaly. After treatment is initiated, the leukocytosis transiently increases as a result of CLL cell redistribution from tissue sites into the circulation. Subsequently, peripheral blood, absolute lymphocyte and platelet counts, and haemoglobin levels all typically normalize as patients achieve remissions. More immediately (often within the first few weeks on therapy), the involved organs (liver, lymph nodes, and spleen) shrink and return to their physiologically normal sizes.

Ibrutinib. BTK, a member of the TEC family of kinases, is primarily expressed in haematopoietic cells, particularly in B cells but not in T cells or plasma cells. Upon BCR activation, SRC-family kinases, including LYN, phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmatic tails of BCR complex-associated protein-α (Igα) and protein-β (Igβ) chains, which are the signal transduction moieties of the BCR (FIG. 2). SYK is then recruited to the phosphorylated ITAMs and activated. In turn, SYK recruits an adaptor protein complex containing Cbl-interacting protein of 85 kDa (CIN85; also known as SH3KBP1) and B cell linker protein (BLNK), which coordinate the activation of BTK. At the same time, activated PI3K produces phosphatidylinositol-3,4,5-trisphosphate (PIP_3), which recruits BTK to the plasma membrane. Downstream of BTK, phospholipase Cγ2 (PLCγ2) is activated, which results in calcium and PKC signalling and, in turn, transcriptional activation via nuclear factor-κB (NF-κB) and ERK, thereby promoting B cell survival and proliferation. In addition to its involvement in BCR signalling, BTK also regulates the signalling and function of other cell-surface receptors, especially adhesion molecules (integrins)[67] and chemokine receptors (such as CXC-chemokine receptor 4 (CXCR4) and CXCR5)[68], thus affecting B cell migration and tissue homing. Ibrutinib, formerly called PCI-32765, is an irreversible BTK inhibitor that forms a covalent bond with a conserved cysteine residue (Cys481) in the active site of BTK[69]. Ibrutinib is currently the only BTK inhibitor approved for the treatment of CLL, in both the first-line and relapsed and/or refractory disease settings. In clinical trials, ibrutinib had activity in patients with CLL[25,26], MCL[70], Waldenström macroglobulinaemia[71], marginal zone lymphoma[72], or activated B cell diffuse large B cell lymphoma[73]. The vast majority of patients with CLL (>85%) respond to ibrutinib, irrespective of clinical and genomic risk factors or line of therapy (TABLE 2). Patients with CLL characteristically demonstrate the aforementioned pattern of response after ibrutinib treatment, with early, transient redistribution lymphocytosis and concurrent rapid normalization of the size of involved organs; over time, once the blood counts normalize, patients achieve remissions (FIG. 4). Owing to the longevity of circulating CLL cells, the lymphocytosis can persist for an extended period of time, especially in patients with relapsed and/or refractory disease; therefore, the rates of objective responses — which require ≥50% reductions in peripheral blood lymphocyte counts — are lower at earlier time points of analysis (for example, 71% ORR at ~21 months in a cohort of patients with relapsed and/or refractory disease[25]) and increase over time as lymphocytosis resolves (89% ORR after 5 years in a related cohort)[74] (TABLE 2). Persistence of redistribution lymphocytosis does not affect survival outcomes[75] and seems to be more frequent in patients with M-CLL[75], and the lymphocytosis eventually resolves in the vast majority of patients. Nevertheless, most responses to single-agent ibrutinib in patients with CLL are PRs, owing to low-level persistent disease. Hence, combination therapies are being pursued in clinical trials, with the aim of increasing the rates of CRs and MRD negativity[76,77]. Combining ibrutinib with anti-CD20 monoclonal antibodies[76], chemoimmunotherapy[77], or venetoclax[78] seems to increase CR rates, but signals indicating beneficial effects on PFS or overall survival are currently lacking because randomized trials to address the efficacy of these combination therapies are ongoing (for example, NCT02264574, NCT01886872, NCT03462719, and NCT02950051). As such, ibrutinib monotherapy remains the standard-of-care approach for patients with CLL in the frontline and the relapsed and/or refractory disease settings. Clinical trial protocols stipulating treatment discontinuation versus maintenance therapy with ibrutinib in MRD-negative patients (NCT02910583 and

NCT03226301) will address the question of whether a limited-duration therapy will become an alternative to the current practice of continuous long-term kinase inhibitor therapy — reminiscent of current efforts with tyrosine kinase inhibitor therapy for chronic myeloid leukaemia (CML; for example, NCT01850004 and NCT01627132).

The common adverse effects of ibrutinib therapy are generally mild and transient, typically diarrhoea or musculoskeletal pains and cramps (TABLE 2). Effects on platelet aggregation result in minor bleeding events, such as superficial bruising, in a considerable proportion of patients; however, severe bleeding events are rare and were not substantially increased in frequency with ibrutinib compared with ofatumumab (1% versus 2%)[79] or chlorambucil (4% versus 2%)[26] in randomized trials, which might be attributable, in part, to the exclusion of patients at a high-risk of bleeding events and those taking vitamin K antagonists. In clinical practice, such patients should be monitored closely for any signs of bleeding, and ibrutinib therapy interruption is recommended for all patients undergoing surgical intervention for 3 days before and after minor surgery and for 7 days before and after major surgery. Atrial fibrillation is an uncommon but clearly ibrutinib-related adverse effect, on the basis of the higher prevalence of this condition among ibrutinib-treated patients in randomized clinical trials, while arterial hypertension is a more common drug-related event associated with long-term ibrutinib use. Despite the generally very favourable and manageable safety profile, toxicities are commonly associated with long-term use of ibrutinib and are the main reason for treatment discontinuation. In a retrospective analysis with a median follow-up duration of 17 months, 42% of patients treated outside of clinical trials discontinued ibrutinib therapy owing to adverse effects; the median time to discontinuation was 7 months[80]. Similar high rates of ibrutinib discontinuation due to long-term toxicities were reported in patients treated in clinical trials[81]. Disease relapses owing to development of ibrutinib resistance is a less common cause for therapy discontinuation and mainly occurs in subgroups of patients with high-risk CLL, often characterized by receipt of multiple prior lines of therapy and high-risk cytogenetic features (17p or 11q deletion). Disease with a complex metaphase karyotype (CKT), defined as the presence of ≥3 distinct chromosomal abnormalities, is an additional strong predictor of an unfavourable outcome and development of resistance in ibrutinib-treated patients[82]. Ibrutinib resistance is associated with clonal evolution[83] and with *BTK* mutations at the ibrutinib binding site (C481S) or mutations affecting PLCγ2 (R665W, L845F, and S707Y)[84–86].

Idelalisib. Idelalisib (previously known as GS-1101 and CAL-101) is an oral, reversible inhibitor of the PI3K catalytic subunit-δ isoform and blocks signalling downstream of the BCR (FIG. 2), resulting in decreased AKT phosphorylation and disrupted interactions between CLL cells and their microenvironment[87–89]. Thus, similar to ibrutinib, idelalisib commonly causes redistribution lymphocytosis in patients with CLL[89] and less frequently in patients with follicular lymphoma or marginal zone lymphoma[90]. This redistribution lymphocytosis persists in many patients with CLL[89] rather than resolving over time; therefore, combination therapy with rituximab to target CLL cells in the blood has subsequently been pursued in clinical trials[27]. In a phase I trial involving patients with relapsed and/or refractory CLL[89], single-agent idelalisib induced an ORR of 72% after a median treatment duration of 15 months, and the median PFS was 15.8 months across all of the different dose levels tested (TABLE 2) but was increased to 32 months in patients who received 150 mg twice daily or higher doses; the 150 mg twice daily dose has been moved forward in subsequent trials. Data from a phase III clinical trial of idelalisib plus rituximab versus placebo and rituximab in patients with heavily pre-treated CLL demonstrated a markedly higher ORR with idelalisib (81% versus 13%; $P<0.001$) and significantly improved overall survival at 12 months (92% versus 80%; $P=0.02$), resulting in an early termination of the study owing to the clear superiority of the idelalisib combination[27]. These data supported the FDA approval of idelalisib plus rituximab for the treatment of patients with relapsed and/or refractory CLL.

In the pivotal phase III trial[27], neutropenia (37% grade ≥3), transaminitis (8% grade ≥3), and diarrhoea and/or colitis (5% grade ≥3) occurred more frequently in the patients on idelalisib therapy. Results with idelalisib therapy in treatment-naive patients with CLL, either as a single agent during the first 2 months of treatment — followed by idelalisib plus ofatumumab for a further 6 months — in younger patients (median age of 67 years, range 58–85 years)[91] or in combination with rituximab in older patients (median age of 71 years, range 65–90 years) have been reported[92]. The trial in younger patients was complicated by frequent immune-mediated hepatotoxicity, which was less common in the trial involving older patients (TABLE 2). Moreover, data from a series of idelalisib combination trials demonstrate increased toxicity in patients receiving idelalisib as part of their treatment, including hepatotoxicity, infections, and rashes[93,94]. Indeed, infections, including opportunistic infections (with cytomegalovirus or *Pneumocystis jiroveci* pneumonia) were found to be more frequent with idelalisib plus ofatumumab than with ofatumumab alone in patients with relapsed CLL[95]. The toxicities of hepatitis, colitis, and pneumonitis are considered to be autoimmune-mediated, a hypothesis supported by the responsiveness of these adverse effects to glucocorticoids and demonstration of T cell infiltration into the inflamed organs[91], as well as the preclinical demonstration that inactivation of PI3Kδ in regulatory T cells unleashes $CD8^+$ cytotoxic T cell responses[96]. Owing to an unfavourable safety profile compared with that of ibrutinib, idelalisib is generally reserved for patients with CLL who have contraindications to or are intolerant of ibrutinib, or have progressed on treatment with a BTK inhibitor.

Other BTK inhibitors

Several second-generation BTK inhibitors are in clinical development. Similar to ibrutinib, most of these agents form a covalent bond with the C481 residue in BTK, but exhibit higher target selectivity and, thus, might have fewer toxicities and/or different efficacy profiles.

Acalabrutinib. Acalabrutinib (ACP-196) is a potent, irreversible inhibitor of BTK, targeting the C481 active-site residue, and is administered at a dose of 100 mg twice daily. Acalabrutinib has a higher selectivity than ibrutinib for BTK and might therefore cause fewer off-target adverse events. For example, acalabrutinib does not inhibit EGFR, ITK, or TEC kinases[97], whereas ibrutinib does[98]. Whether these pharmacological properties translate into clinically relevant differences in terms of toxicity and/or efficacy will be determined in a randomized trial in which ibrutinib and acalabrutinib are being compared (NCT02477696). Results of a phase I–II multicentre study of acalabrutinib demonstrate a high ORR of 85%, increasing to 95% when including PRs with lymphocytosis, in patients with relapsed and/or refractory CLL[97], which is comparable to the rates achieved with ibrutinib (TABLE 2). Common adverse effects of acalabrutinib in patients with CLL, many of which overlap with ibrutinib, are headache, diarrhoea, upper respiratory tract infections, fatigue, nausea, arthralgia, pyrexia, contusion, petechiae, weight gain, hypertension, and atrial fibrillation (TABLE 2). In 2017, acalabrutinib was approved for the treatment of patients with MCL who have received at least one prior therapy. Approval of this agent for patients with CLL will depend on the outcome of three pivotal randomized trials: a three-arm study of acalabrutinib monotherapy versus acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in mostly older patients (aged >65 years) with treatment-naive CLL (NCT02475681); a study to compare ibrutinib with acalabrutinib in patients with relapsed and/or refractory high-risk CLL (NCT02477696); and a trial of acalabrutinib versus either idelalisib plus rituximab or BR in patients with relapsed and/or refractory CLL (NCT02970318).

Tirabrutinib. Also known as ONO-4059 or GS-4059, tirabrutinib is another potent irreversible inhibitor of BTK, which covalently binds to the C481 residue. Similar to acalabrutinib, tirabrutinib is a more selective BTK inhibitor than ibrutinib[99]. Findings of a phase I study demonstrate the potent activity of tirabrutinib in patients with CLL or SLL: among 25 evaluable patients, the ORR was 96%, with typical BTK inhibitor-induced rapid reductions in lymphadenopathy, redistribution lymphocytosis, and improvements in haematological parameters[99] (TABLE 2). In ongoing trials involving patients with CLL, tirabrutinib is being combined with either the SYK inhibitor entospletinib (GS-9973) or idelalisib, in both cases, with or without obinutuzumab (NCT02983617 and NCT02968563).

Zanubrutinib. Zanubrutinib (BGB-3111) is a highly bioavailable covalent inhibitor that binds to C481 of BTK and is more selective than ibrutinib for this kinase. In an ongoing phase I–II study[100], 45 patients with CLL or SLL have been treated with zanubrutinib, predominantly at a dose of 160 mg twice daily or 320 mg daily. Therapy seems to be well tolerated, although the follow-up duration is limited. Grade 2 atrial fibrillation occurred in one patient, and one patient had grade 3 purpura. The ORR was 90% after a median follow-up duration of 7.5 months. A phase III trial to compare the efficacy of zanubrutinib monotherapy with that of BR is ongoing in patients with untreated CLL (NCT03336333).

SNS-062. Unlike the aforementioned drugs, SNS-062 is a potent reversible (noncovalent) BTK inhibitor. This agent is being developed to potentially overcome ibrutinib resistance related to the BTK C481S mutation; the results of in vitro studies have demonstrated that SNS-062 has activity against cancer cells that harbour this mutation[101]. This compound is in the early phases of clinical development in patients with different B cell malignancies (NCT03037645) and has not yet been advanced towards registration trials.

Other PI3K inhibitors

Duvelisib. The dual PI3K inhibitor duvelisib (IPI-145) has activity against both PI3Kδ and PI3Kγ and is in late-stage clinical development for the treatment of haematological malignancies (at an oral dose of 25 mg twice daily). A phase Ib study of duvelisib monotherapy revealed ORRs of 56% in patients with relapsed and/or refractory CLL ($n = 55$) and 83% in those with treatment-naive CLL ($n = 18$)[102]; the most common grade ≥3 adverse events included neutropenia (39%), febrile neutropenia (15%), and pneumonia (11%); hepatotoxicity was observed in about a third of patients, with elevated serum alanine transaminase (ALT) levels in 39% of patients (19.5% grade 3–4) and serum aspartate transaminase (AST) elevations in 38% (5% grade 3–4) (TABLE 2). Notably, more patients discontinued duvelisib therapy owing to adverse events (31%) than owing to disease progression (24%)[102]. In an ongoing phase III trial (NCT02004522), duvelisib is being compared with ofatumumab alone in patients with relapsed and/or refractory CLL.

Duvelisib has also been tested in combination with other CLL therapies. In a three-arm study[103], duvelisib was combined with either rituximab, bendamustine, or BR in the treatment of patients with relapsed and/or refractory indolent non-Hodgkin lymphoma or CLL. At a median follow-up duration of 16.3 months, the ORR in patients with CLL was 92%[103]. Therapy with duvelisib plus FCR has also been evaluated in approximately 30 younger patients (aged ≤65 years) with previously untreated CLL; results were encouraging with up to 89% of patients achieving MRD negativity in the bone marrow[104].

Umbralisib. Umbralisib (TGR-1202) is a next-generation PI3Kδ inhibitor with a chemical structure that is markedly different from those of idelalisib and duvelisib[105]. On the basis of the limited clinical experience with umbralisib, the safety profile of this agent also differs — with less frequent hepatic toxicity and colitis, in particular — from that of these other PI3Kδ inhibitors[105]. In a phase I dose-escalation study[105], 85% of patients with relapsed and/or refractory CLL achieved an objective response (TABLE 2). Umbralisib is currently in phase III of clinical development in combination with ublituximab (TG-1101), a novel anti-CD20 antibody: this combination is being compared with obinutuzumab plus chlorambucil in a randomized fashion in patients with treatment-naive or previously treated CLL (NCT02612311).

SYK inhibitors

Fostamatinib. The SYK inhibitor fostamatinib (also known as R406)[106] has been explored in a phase I–II trial for treatment of patients with relapsed and/or refractory B cell malignancies (NCT00446095), including CLL ($n = 11$); responses were most frequent in patients with CLL (ORR 55%)[63]. Common toxicities observed in this study included diarrhoea, fatigue, and cytopenias, which are similar to toxicities observed in rheumatoid arthritis studies[63,107]. The focus for clinical development of fostamatinib has shifted from haematological malignancies to autoimmune diseases, especially rheumatoid arthritis[107] and immune thrombocytopenia; this drug is not currently used in the treatment of CLL.

Entospletinib. Entospletinib (GS-9973) is a SYK inhibitor that displays greater target selectivity than fostamatinib[108]. Patients with relapsed and/or refractory CLL ($n = 41$) have been treated with this agent in a phase II study that enrolled patients with different B cell malignancies; the ORR was 61.0% and the median PFS duration was 14 months[109]. The most common treatment-emergent toxicities included dyspnoea, pneumonia, febrile neutropenia, dehydration, and pyrexia[109]. Common grade 3–4 laboratory abnormalities included neutropenia (14.5%) and reversible serum ALT and/or AST elevations (13.4%)[109].

Other kinase inhibitors

Dasatinib, originally developed as a pan-SRC kinase inhibitor, is mainly used in the treatment of patients with CML and *BCR–ABL1*-positive B cell acute lymphoblastic leukaemia (ALL) owing to the ability of this agent to potently inhibit the ABL1 kinase. Dasatinib also effectively inhibits LYN, which is constitutively activated in CLL cells and has been linked to BCR signalling-related resistance of leukaemic B cells to apoptosis[110]. A phase II trial of dasatinib in patients with relapsed and/or refractory CLL ($n = 15$) revealed that the primary toxicity was myelosuppression, with grade 3 or 4 thrombocytopenia and neutropenia observed in six and ten patients, respectively[111]. Partial responses were achieved in 20% of patients[111]. At this time, dasatinib is no longer under clinical development for the treatment of CLL.

The BCL-2 antagonist venetoclax

Venetoclax is an orally administered, highly selective, potent small-molecule inhibitor of the anti-apoptotic protein BCL-2, which is expressed at high levels in CLL cells. After cases of severe tumour lysis syndrome (TLS) were observed in patients with CLL during the early clinical development of this drug, a slower dose-escalation regimen, with weekly dose ramp-up to the recommended dose of 400 mg daily, was subsequently implemented in the expansion cohort of the pivotal phase I–II trial[28] and no further cases of severe TLS were seen. The results of this trial demonstrated an ORR of 79%; CRs occurred in 20% of patients, and 5% of patients had MRD-negative remissions[28]. The estimated 15-month PFS in patients receiving 400 mg venetoclax was 69%[28]. Notably, in a separate phase II study involving 107 patients with high-risk CLL[30], defined as relapsed and/or refractory disease with del(17p), an ORR of 85% was achieved with venetoclax. Common grade 3–4 adverse events in this population were neutropenia, infections, anaemia, and thrombocytopenia (TABLE 3).

Venetoclax is also well tolerated when combined with rituximab (VR regimen), a combination that results in improved CR rates (up to 41%) and high rates of MRD negativity in the bone marrow (up to 75% in patients with a CR and 53% overall) in patients with relapsed and/or refractory CLL[112]. Importantly, a major improvement in the PFS of patients with relapsed and/or refractory CLL has been demonstrated with the VR regimen in the phase III MURANO trial[113]: estimated 2-year PFS of 84.9% versus 36.3% with BR chemoimmunotherapy (HR 0.17, 95% CI 0.11–0.25; $P < 0.001$); the level of benefit was similar in patients with del(17p) CLL (2-year PFS 81.5% versus 27.8%) and across all other clinical and biological patient subgroups. Overall survival was also superior with the VR regimen[113] (TABLE 3).

Table 3 | **Key clinical trial data for the BCL-2 antagonist venetoclax in patients with CLL**

Treatment	Disease state (*n*)	ORR; CR rate	PFS	OS	Adverse effects[a] (frequency)	Refs
Venetoclax	Relapsed and/or refractory ($n = 116$)	79%; 20%	Median: 25 months (in dose-escalation cohort)	84% after 2 years	Grade 3–4 neutropenia (41%), RT (16%), major infections (13%), thrombocytopenia (12%), and anaemia (12%)	28
	Relapsed and/or refractory disease with del(17p) ($n = 107$)	85%; 8%	72% after 12 months	87% after 12 months	Grade 3–4 neutropenia (40%), grade 3–4 infections (20%), anaemia (18%), and thrombocytopenia (15%)	30
Venetoclax plus rituximab	Relapsed and/or refractory ($n = 49$)	86%; 51%	82% after 2 years	Not reported	Grade 3–4 neutropenia (53%), thrombocytopenia (16%), grade 3–4 infections (16%), and anaemia (14%)	173
Venetoclax plus rituximab versus BR	Relapsed and/or refractory ($n = 194$ plus 195 treated with BR)	93% versus 68%; 27% versus 8%	85% versus 36% at 2 years (estimated)	Venetoclax combination superior: 92% versus 87% (estimated) at 2 years (HR 0.48, 95% CI 0.25–0.90)	Grade 3–4 neutropenia (58% versus 39%) and grade ≥ 3 TLS (3% versus 1%)	113

BR, bendamustine plus rituximab regimen; CLL, chronic lymphocytic leukaemia; CR, complete remission; ORR, overall remission rate; OS, overall survival; PFS, progression-free survival; RT, Richter transformation; TLS, tumour lysis syndrome. [a]Of any grade, unless specified.

When venetoclax was tested in patients with relapsed and/or refractory CLL that had progressed on therapy with ibrutinib or idelalisib, 65% of patients responded, 56% with a PR, and 9% with a CR[114]. Median PFS in this setting was 24.7 months[114]. In the USA, venetoclax is currently approved for the treatment of patients with del(17p) CLL who have received at least one prior line of therapy and is often used in patients who progressed on therapy with ibrutinib or idelalisib. Given the positive results of the randomized MURANO trial, however, wider use of venetoclax in earlier lines of therapy and in patients with lower-risk disease is expected.

Immune-related therapies for CLL

Novel antibodies

Ofatumumab. Ofatumumab is a fully humanized anti-CD20 antibody that binds an epitope distinct from that recognized by rituximab[115] and results in more effective complement-dependent cytotoxicity in vitro, possibly owing to the close proximity of the small-loop CD20 binding site for this antibody to the cell surface, which might support more effective antibody-driven deposition of complement on the cell surface[116]. Ofatumamab has a toxicity profile similar to that of rituximab and has been shown to be active as a monotherapy in patients with CLL who were refractory to fludarabine and alemtuzumab, with ORRs ranging between 47% and 58% and a median PFS of approximately 6 months[117] (TABLE 4). Indeed, this agent is currently approved for the treatment of patients with fludarabine-refractory CLL and served as the control treatment in a randomized RESONATE trial of ibrutinib in patients with previously treated CLL[79]. The results of this trial demonstrated that ibrutinib was superior in terms of ORR (43% versus 4%), median PFS (not reached versus 8.1 months after a median follow-up duration of 9.4 months), and 12-month overall survival (90% versus 81%)[79]. Another randomized trial explored the added benefit of ofatumumab when combined with chlorambucil in patients with previously untreated CLL who are not candidates for fludarabine-based treatment[31]. The median PFS duration was significantly increased in patients treated with this combination compared with patients receiving chlorambucil alone (22.4 months versus 13.1 months; $P<0.0001$)[31].

Obinutuzumab. The glycoengineered type II anti-CD20 antibody obinutuzumab (GA101) induces higher rates of direct death of non-malignant and malignant B cells as well as antibody-dependent cellular cytotoxicity (ADCC) than non-glycoengineered antibodies, such as rituximab, when tested in a series of in vitro and in vivo models[118]. Single-agent obinutuzumab has been shown to be active in a phase I–II study in patients with relapsed and/or refractory CLL ($n=33$), with ORRs ranging from 62% (phase I portion) to 30% (phase II portion) and a median duration of response of 8.9 months (phase II portion only)[119]. In a randomized three-arm study[24], obinutuzumab plus chlorambucil was compared with chlorambucil alone or to rituximab plus chlorambucil for frontline therapy of elderly patients (median age of 73 years) with CLL and coexisting comorbidities. The obinutuzumab–chlorambucil combination prolonged median PFS (26.7 months versus 11.1 months with chlorambucil and 16.3 months with rituximab–chlorambucil; $P<0.001$ for both comparisons) as well as overall survival when compared with that observed with chlorambucil (HR 0.41, 95% CI 0.23–0.74; $P=0.002$)[24]. Infusion-related reactions and neutropenia were more common with obinutuzumab than with rituximab, but the risk of infection was not increased[24] (TABLE 4). Obinutuzumab is currently being explored in ongoing clinical trials as a combination partner with novel molecularly targeted agents, such as BTK inhibitors (NCT02264574, NCT02629809, NCT02475681, NCT02983617, and NCT02968563) and venetoclax (NCT02242942).

Other antibodies. The glycoengineered chimeric anti-CD20 antibody ublituximab has a high affinity for FcγRIIIa (CD16) receptors and greater ADCC activity against CLL cells than rituximab in vitro[120]. Ublituximab monotherapy induced responses in 50% of patients with relapsed and/or refractory CLL after rituximab therapy ($n=6$)[121]. This agent is currently being developed in combination approaches with the PI3Kδ inhibitor umbralisib (NCT02612311 and NCT02656303), the BTK inhibitor ibrutinib (NCT02013128 and NCT02006485), and the BCL-2 antagonist venetoclax (NCT03379051).

MOR208 (XmAb5574) is an Fc-engineered humanized anti-CD19 monoclonal antibody. Results of a phase I trial have demonstrated the safety and preliminary efficacy of MOR208 in patients with CLL[122], although at present, this agent is no longer being developed for the treatment of CLL. Otlertuzumab (TRU-16) is a humanized anti-CD37 single-chain variable fragment (scFv)-based immunoglobulin G1 (IgG1) antibody construct that has been shown in a phase I trial to induce single-agent objective responses in 23% of patients with CLL[123]. Moreover, adding otlertuzumab to bendamustine therapy for relapsed CLL significantly increased the ORR (69% versus 39% with bendamustine alone; $P=0.025$) and prolonged the median PFS (15.9 months versus 10.2 months; $P=0.0192$) in a phase II trial[124]. This agent continues to be developed for the treatment of CLL in combination therapy approaches (NCT01644253).

Immunomodulatory drugs

Lenalidomide is a thalidomide analogue that belongs to the imide class of immunomodulatory drugs (IMiDs), which have proven therapeutic activity in MDS and multiple myeloma — lenalidomide is approved for the treatment of these diseases. The mechanism of action of lenalidomide is not entirely clear, although this agent enhances immune recognition of CLL cells[125] and inhibits the proliferation of CLL cells via a cereblon-dependent and p21-dependent mechanism[126]. Targeted sequencing of CLL samples from patients treated with lenalidomide revealed that risk factors established in the context of chemotherapy-based treatment — that is, del(17p), del(11q), the CKT, and *TP53* and *SF3B1* mutations — are also predictive of inferior responses to lenalidomide[127]. When tested in patients aged >65 years with previously untreated CLL ($n=60$), lenalidamide was associated with an ORR of 65%, a CR rate of 10%, and an estimated 2-year PFS of 60%[128]. In patients with relapsed and/or

Table 4 | **Key clinical trial data for immunomodulatory or immunological therapies for CLL**

Treatment	Disease state (*n*)	ORR; CR rate	PFS	OS	Adverse effects[a] (frequency)	Refs
Lenalidomide	Relapsed and/or refractory (*n* = 44)	32%; 7%	Not reported	73% after 14 months	Grade 3–4 neutropenia (41%), thrombocytopenia (15%), diarrhoea (15%), and anaemia (3%)	129
	Treatment-naive (*n* = 60)	58%; 41%	Not reported	82% at 4 years	Grade 3–4 neutropenia (34%)	174
Lenalidomide plus rituximab	Relapsed and/or refractory (*n* = 59)	66%; 12%	Median TTF: 17.4 months	71% after 36 months	Grade 3–4 neutropenia (40%), grade 3–4 infections (24%), anaemia (18%), and thrombocytopenia (15%)	130
Rituximab	Relapsed and/or refractory (*n* = 40)	45% (up to 75% with high rituximab doses in the dose-escalation cohort); 3%	Median: 6 months	Not reported	Infusion-related toxicities (12%)	23,175
Ofatumumab	Fludarabine-refractory (*n* = 59), including bulky disease group (*n* = 79)	• Fludarabine-refractory group: 58%; not reported • Bulky disease group: 47%; not reported	• Fludarabine-refractory group: median of 5.7 months • Bulky disease group: median of 5.9 months	• Fludarabine-refractory group: median of 13.7 months • Bulky disease group: median of 15.4 months	Infusion-related toxicity (64%) and infections (67%)	117
Ofatumumab plus chlorambucil	Treatment-naive (*n* = 221)	82%; 14%	Median 22.4 months	89% after 24 months	Neutropenia (26%) and grade ≥ 3 infusion-related adverse events (10%)	31
Obinutuzumab	Relapsed and/or refractory (*n* = 33)	62%; 0%	Median: 8.9 months for responders	Not reported	Infusion-related reactions (> 60%) and grade 3–4 neutropenia (~50%)	119
Obinutuzumab plus chlorambucil	Treatment-naive (*n* = 238)	75.5%; 22.2%	Median: 23 months	NR	Neutropenia (34%), grade 3–5 infusion-related reactions (21%), and infections (6%)	24
Anti-CD19 CAR T cell therapy	Relapsed and/or refractory (*n* = 24)	74% (at 4 weeks after CAR T cell infusion); 21%	Median: 8.5 months	NR	Cytokine-release syndrome (83%) and neurotoxicity (33%)	135

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CR, complete remission; NR, not reached; ORR, overall remission rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure. [a]Of any grade, unless specified.

refractory CLL, single-agent lenalidomide induced ORRs of 32% in the overall population (CR rate 7%), 31% in those with 11q or 17p deletion, 24% in those with U-CLL, and 25% in those with fludarabine-refractory disease[129]. The most common toxicities of lenalidomide stem from myelosuppression (TABLE 4), with a median tolerated dose of 10 mg daily[129]. Notably, when this agent was combined with rituximab, the ORR in patients with relapse and/or refractory CLL was increased to 66%, including 12% CRs and 12% nodular PRs; the median time to treatment failure was 17.4 months[130]. Although clearly an active agent against CLL, the use of lenalidomide in this disease has been limited given the higher efficacy and better tolerability of other novel agents, such as ibrutinib.

CAR T cell therapy

CD19-specific chimeric antigen receptor (CAR) T cell therapy after lymphodepleting chemotherapy induces high ORRs in patients with B cell ALL or B cell non-Hodgkin lymphoma[131,132]. In proof-of-principle studies[133,134], anti-CD19 CAR T cell therapy induced remissions in patients with relapsed and/or refractory CLL (ORR of 57% among 14 patients in one study, including 4 CRs and 4 PRs[133,134]). In 2017, results of a trial in a larger cohort of patients with ibrutinib-refractory CLL (*n* = 24) demonstrated high response rates with the use of a defined 1:1 ratio of $CD4^+$:$CD8^+$ CAR T cells[135]. The ORR was 74%, with a CR rate of 21%; with a limited follow-up duration (median 6.6 months), none of the patients who achieved MRD negativity (*n* = 7) had disease progression, while those that remained MRD positive (*n* = 7) had a median PFS of 8.5 months[135]. With regard to toxicities, 83% of patients developed cytokine-release syndrome (CRS) and 33% had neurotoxicity, which was reversible in all but one patient who died with CRS and neurotoxicity[135]. Considering the substantial toxicity and treatment-related morbidity and mortality associated with CAR T cell therapy (TABLE 4), at present, this approach is suitable for only a minority of patients with high-risk CLL, given that most patients with this disease are elderly and have comorbidities. In particular, use of CAR T cell therapy is generally restricted to younger patients with CLL who have relapsed, or are at high risk of relapse, on treatment with the novel molecularly targeted agents. Hence, cellular therapy remains an important option because, at this time, the novel

agents that have been added to the CLL armamentarium are not curative, and disease control with the new approved therapies is generally shorter in high-risk groups of patients, especially in patients with relapsed and/or refractory, del(17p) and *TP53*-mutated, and CKT disease[74,82,136]. In such patients, the durations of response after failure of ibrutinib therapy are generally short[137]; the most durable responses in this setting are achieved with venetoclax (median PFS 24.7 months)[114]. Thus, continued exploration of novel cellular therapies in younger patients with high-risk CLL, for example, in all patients with del(17p) in the relapsed setting, those with CKT, those with early relapses after chemoimmunotherapy, and in those who develop resistance to one of the novel agents, remains critical[138].

Stem cell transplantation

Autologous haematopoietic stem cell transplantation (HSCT) has no proven benefit in patients with CLL[139], and allogeneic HSCT (allo-HSCT) — like CAR T cell therapy — is feasible in only a minority of younger patients with high-risk CLL, given the substantial treatment-related morbidity and mortality[140]. On the other hand, about 50% of patients treated with allo-HSCT for high-risk CLL can achieve MRD negativity and have long-term survival, independent of the underlying genomic risk factors[140]. Thus, allo-HSCT remains an important treatment option in the management of selected patients with high-risk CLL. The timing of allo-HSCT has changed considerably with the introduction of the novel CLL therapies. Currently, given the very high ORRs with molecularly targeted agents, patients with high-risk CLL generally receive BTK inhibitor and/or BCL-2 antagonist treatment before allo-HSCT. Patients who either have disease progression on treatment or are at high risk of therapeutic failure during treatment with these drugs should undergo work-up for allo-HSCT, ideally before developing resistant disease. Given the risks associated with HSCT and the durability of responses of other disease subsets to alternative therapies, we generally reserve allo-HSCT for patients who are younger and have high-risk features — that is, those with del(17p) and/or *TP53*-mutated, and/or CKT, and multiply relapsed and/or refractory disease[74,82,136,138].

Richter transformation

The transformation of CLL into large cell lymphoma or Hodgkin lymphoma (Richter transformation) is a rare event, but continues to have a poor prognosis, with limited-durability responses to chemoimmunotherapy resulting in median PFS and overall survival durations of <1 year[141]. Immune-checkpoint inhibitors targeting PD-1 (such as pembrolizumab) can sometimes have activity in patients with Richter transformation[142] — an observation that needs to be further explored. In this study[142], responses to pembrolizumab were noted in 4 of 9 patients with Richter transformation of CLL (44%) but in none of 16 patients without transformation of CLL. After a median follow-up duration of 11 months, the median overall survival in the Richter transformation cohort was 10.7 months[142]. The reason for the observed difference in responses to immune-checkpoint inhibitor therapy between patients with or without CLL transformation is unknown; a potential explanation is that the transformed cells, in contrast to ordinary CLL cells, carry antigens that can be recognized by T cells and thus can trigger a cytotoxic response.

The activity of novel molecularly targeted agents approved for the treatment of CLL, especially ibrutinib and venetoclax, in patients with Richter transformation has not been tested systematically; however, the fact that a number of Richter transformations have been detected as progression events in the pivotal trials of both agents[28,81], although typically in heavily pre-treated patients, makes it unlikely that these drugs will have broader activity in this setting.

Individualized CLL therapy

With the increasing availability of novel agents for the treatments of patients with CLL in the frontline and salvage therapy settings, implementation of an individualized therapy approach, based on individual risk factors, is now possible (FIG. 5). Chemoimmunotherapy with FCR, which was the predominant treatment regimen a decade ago, is currently preferentially used in younger patients with low-risk disease characteristics: long-term follow-up data from FCR-treated patients demonstrate very durable responses that persist beyond 10 years in ~60% of those with M-CLL[15] and the possibility of a cure fraction. The risk of secondary MDS or AML, which occur in ~5% of FCR-treated patients (TABLE 1), remains a major concern related to this approach and might be reduced by decreasing the number of chemotherapy (FC) cycles, as is being pursued with the iFCG regimen. Notably, iFCG treatment has been reported to produce high rates of MRD negativity, despite a reduction of the FC backbone (three cycles, instead of six cycles in the original FCR regimen)[17,143]. For patients who are not candidates for FCR or BR chemoimmunotherapy, such as elderly patients with comorbidities, combination therapy with chlorambucil plus an anti-CD20 antibody[24,31] remains an option while randomized trials comparing these combinations to novel agents are ongoing. Preferably, however, ibrutinib can be used in this population of patients, with dramatic efficacy and a good safety profile[26]. Patients with low-risk CLL who relapse after chemoimmunotherapy are generally treated with a kinase inhibitor (ibrutinib or idelalisib; FIG. 5).

For patients with high-risk disease, regardless of their age and comorbidities, we recommend the use of novel agents, primarily a BTK inhibitor at present, especially for patients with del(17p) CLL, who should not be treated with chemotherapy-containing regimens, which are of limited effectiveness in this population[18]. Patients with 11q deletion and those with U-CLL also have unfavourable outcomes with chemoimmunotherapy and, consequently, are best suited for BTK inhibitor therapy in the frontline or relapsed disease settings. A key problem with this approach is the necessity for continuous long-term treatment, owing to the fact that the vast majority of patients do not achieve MRD-negative remissions. Long-term therapy with ibrutinib can result in issues with compliance, toxicities emerging as a result of long-term use[81], high costs, and the risk of acquired drug resistance[83,84,144].

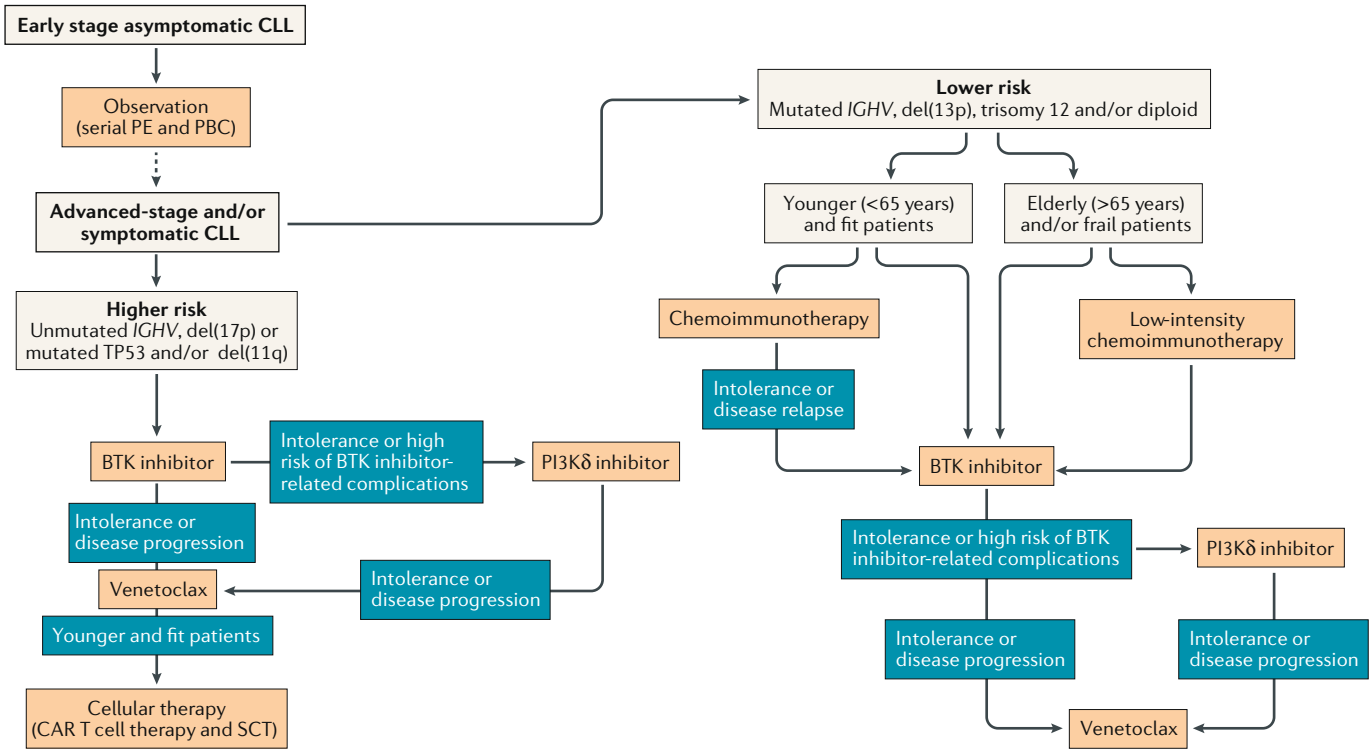

Fig. 5 | **Algorithm for management of patients with CLL.** Patients with asymptomatic early stage chronic lymphocytic leukaemia (CLL) are managed with observation, with serial physical examination (PE) and peripheral blood counts (PBC). Those who have CLL progression to advanced disease stages or have CLL-related symptoms require therapy. Choices of therapy are influenced by the disease risk profile. Patients with higher-risk disease according to cytogenetic characteristics and *IGHV* mutational status generally have an inferior outcome with chemotherapy-based treatments and, therefore, should be treated with a BTK inhibitor or, if intolerant of such agents or at high risk of BTK inhibitor-associated complications (such as bleeding or atrial fibrillation), with a PI3K inhibitor. Patients who are intolerant of or develop disease progression on treatment with a kinase inhibitor can be treated with the apoptosis regulator BCL-2 antagonist venetoclax. Such patients also should be evaluated for eligibility for cellular therapy approaches and, if eligible, proceed to such therapy, ideally before developing resistant disease. Younger and fit patients with lower-risk CLL can have long-term benefit from chemoimmunotherapy, and pros and cons of chemoimmunotherapy versus kinase inhibitors should be discussed with such individuals. For elderly and/or frail patients with low-risk disease, reduced-intensity chemoimmunotherapy is an option, as well as BTK inhibitor therapy. For those who receive chemoimmunotherapy and subsequently have disease relapse, novel agents — a BTK inhibitor or a PI3Kδ inhibitor for those intolerant of or at high risk of complications with a BTK inhibitor — are generally the first-choice second-line therapy. Those who are intolerant of or develop progressive disease on second-line kinase inhibitor therapy are likely to respond well to treatment with venetoclax. CAR, chimeric antigen receptor; SCT, stem cell transplantation.

Patients with del(17p) and/or *TP53*-mutated disease are at particularly high risk of developing resistance to ibrutinib (and presumably other BTK inhibitors), and although these patients do sometimes respond to venetoclax[114], they should undergo a work-up for cellular therapy (FIG. 5), predominantly allo-HSCT at present; although, CAR T cell therapy will probably become a more commonly used alternative to allo-HSCT in the near future. Patients who are intolerant of ibrutinib (or other BTK inhibitors) can respond well to idelalisib[145], whereas venetoclax is currently the most established salvage therapy in the setting of ibrutinib resistance[114]. The very positive data for venetoclax combined with rituximab, when compared with BR chemoimmunotherapy[113], support the wider use of venetoclax-based therapy in earlier lines of therapy, beyond the setting of ibrutinib resistance.

The substantial risk of long-term toxicities and the eventual development of acquired resistance are two of the most immediate challenges with the novel molecularly targeted agents. These complications could potentially be addressed by limiting the duration of therapy, which would be a desirable step forward. This notion might soon become a reality, given the promising early results of combination therapy approaches, for example, with ibrutinib plus venetoclax[78], which seems to induce deep remissions and a high rate of MRD negativity.

Conclusions

The approval of a range of new targeted therapies within the past 5 years has revolutionized CLL treatment. While chemoimmunotherapy became standard CLL therapy between 2000 (REF.[17]) and 2010 (REF.[18]), the use of this approach has since steadily declined as novel molecularly targeted agents with higher efficacy in patients with high-risk disease features and better tolerability in elderly and frail patients were successfully translated into the clinic (FIG. 3). In particular, BTK, PI3Kδ, and potentially also SYK inhibitors that block signalling downstream of the BCR (FIGS. 1,2), which is critical for the survival and proliferation of non-malignant and malignant B cells, can greatly improve the outcomes of patients with CLL. The approved BTK and PI3Kδ inhibitors — ibrutinib

and idelalisib, respectively — generally lack myelotoxicity and induce durable remissions in the majority of patients, although mostly PRs (TABLE 2). Hence, long-term treatment is warranted, which can be complicated by the emergence of toxicities with longer-term use and, eventually, therapy resistance. The ongoing development of novel second-generation kinase inhibitors and/or new combination therapy approaches will address these issues and might open the door to limited-duration therapy. The BCL-2 antagonist venetoclax has more recently been added to the therapeutic armamentarium. Similar to the kinase inhibitors, venetoclax is also very active in patients with CLL harbouring high-risk features (TABLE 3) and more rapidly induces remissions than observed with the slower-acting kinase inhibitors, to which true objective responses are preceded by prolonged increases in peripheral blood lymphocyte counts owing to redistribution lymphocytosis.

We are fortunate to be entering an era of individualized CLL therapy, wherein disease risk features guide treatment decisions (FIG. 5). For example, patients with high-risk CLL harbouring del(17p) and/or *TP53* mutations and those with U-CLL have short remission duration with chemoimmunotherapy and should be treated with the novel agents. By contrast, younger and fit patients with low-risk M-CLL can have very long-term benefit from chemoimmunotherapy and should therefore continue to be offered this treatment option, at least while randomized trials comparing chemoimmunotherapy with the novel agents are ongoing. Clearly, the novel agents have already changed the lives and outlook of many patients with CLL, especially those with high-risk disease, for whom the prior treatment options were particularly unsatisfactory. The challenge in the coming years will be to transition this early success into practical and tolerable regimens that reduce the duration of drug exposure and the associated risk of toxicity while also producing deep and durable responses that limit the emergence of resistance.

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