Chronic Lymphocytic Leukaemia: Current and Emerging Treatment Options

PEER REVIEWED

With the advent of new targeted and cellular therapies, the treatment landscape for patients with chronic lymphocytic leukaemia (CLL) has considerably changed in the last years.

Current CLL management is based on updated risk stratification strategies considering demography, fitness level, genetic aberrations, previous treatments, as well as disease relapse, in addition to the clinical stage. While the CLL treatment paradigm was changed in the last decade due to approval of novel targeted therapies, disease relapse rates are still high. Additional clinical trials are needed to answer outstanding questions or provide alternatives for further improvements of long-term efficacy and safety/tolerability in the overall CLL population and specifically in patients with high-risk CLL.

This article describes contemporary CLL management, with a focus on current and emerging therapies in first-line disease and subsequent settings.

Introduction

Chronic lymphocytic leukaemia (CLL), the most common form of leukaemia in the Western hemisphere[1,2], is a low-grade lymphoproliferative disease characterised by progressive accumulation of cluster of differentiation (CD)5+/CD19+ B lymphocytes in the peripheral circulation, bone marrow, and lymphoid tissues[3].

CLL has an annual age-adjusted incidence of 3-5 per 100,000 persons[4] and mostly arises in patients ≥65 years. Typically, CLL has an indolent disease progression and is preceded by monoclonal B-cell lymphocytosis (MBL)[5], present in 5% of healthy individuals older than 40 years[6,7]. While a relatively long survival is observed in the majority of patients with CLL, treatment-resistant disease is typically encountered in high-risk patient subsets[8]. For decades, treatment of patients with CLL, including high-risk subsets, was conservative and non-curative, focusing on purine analogues and alkylating agents. This became secondary with the emergence of novel targeted therapies, which led to significant changes in CLL therapy programmes.

Current Treatment Programs for CLL

Present-day CLL management programmes follow the International Workshop on CLL (IWCLL) criteria published in 2018[9]. These programmes are divided into three categories: for patients who do not meet criteria for therapy, for patients who meet criteria for therapy and have untreated CLL, and for patients who meet criteria for therapy and present with relapsed/refractory CLL.

For all patients, a risk stratification strategy is initially applied using the CLL-International Prognostic Index (CLL-IPI)[10], which classifies patients into four risk groups based on five factors (Table 1) that have been shown to be independently associated with overall survival (OS). Additionally, assessment of minimal residual disease following CLL therapy is recommended by the IWCLL guidelines, to help predict time to and individualise subsequent treatment phases (e.g. consolidation, maintenance)[9].

The majority of patients have MBL (B cell count <5 x 10^9/L) or early-stage CLL (B cell count ≥5 x 10^9/L) at diagnosis and do not meet criteria to initiate therapy[10]. The NCCN and IWCLL guidelines recommend a "wait-and-watch" approach, including close follow-up, for these patients[4,9]. For patients who meet criteria for therapy (e.g. advanced stage, progressive disease, significant disease-related symptoms), typical factors determining treatment approaches additional to those indicated by CLL-IPI are fitness level and untreated vs relapsed/refractory disease.

Currently, there are 509 clinical trials planned or ongoing that assess various therapies for CLL (GlobalData; Figure 1A), with the majority of trials in Phase II-II/III. This, together with the high number of drugs and drug combinations being evaluated in the preclinical and early clinical phases (Figure 1B), indicates that the field of CLL therapy remains to undergo significant developments. While historical CLL treatment was composed of chemotherapy agents, the development of new therapies led to the introduction of small molecules, cell therapies, immunotherapy, proteins, antibodies and other compounds in the treatment armamentarium of CLL. As opposed to chemotherapy agents, these new compounds rely on specific target inhibition or dysregulation of signalling pathways (Figure 1C). Based on recommendations from the IWCLL[9] and NCCN guidelines[4] and the aforementioned CLL treatment landscape, a summary of CLL management modalities can be found in Figure 2. The team at CATO SMS summarised the current treatment approaches and emerging CLL therapies, including their modes of action and targets, below.

First-line Treatment Options for CLL

Anti-CD20 Monoclonal Antibodies

A significant step forward in changing the CLL treatment paradigm was the development and subsequent approval of the anti-CD20 antibody rituximab (Table 2). Humanised chimeric monoclonal antibodies targeting CD20 induce killing of CD20+ cells by direct effects, such as complement-mediated and antibody-mediated cytotoxicity (ADCC), or indirect effects pertaining to structural changes, cell sensitisation to chemotherapy, and apoptosis.

According to NCCN guidelines[4], the chemoimmunotherapy regimen fludarabine-cyclophosphamide-rituximab (FCR) is part of the current first-line SoC for patients aged <65 years without del17p/*TP53* mutations and significant comorbidities (Figure 2). The approval of rituximab as part of this first-line SoC (Table 2) was based on the pivotal Phase III trial CLL8, in which FCR vs FC significantly improved the objective and complete response rates (ORR and CRR, Table 3), as well as the three-year median progression-free survival (PFS) and overall survival (OS) in 817 previously untreated, physically fit patients[11]. Updated analyses reported FC therapy, *TP53* mutations, del17p, and non-mutated *IGHV* as primary predictors of shorter OS/PFS[12] (Table 3). An alternative to FCR is bendamustine-rituximab (BR), recommended for treatment of genetically similar patient populations to those receiving FCR, but presenting with significant comorbidities[4].

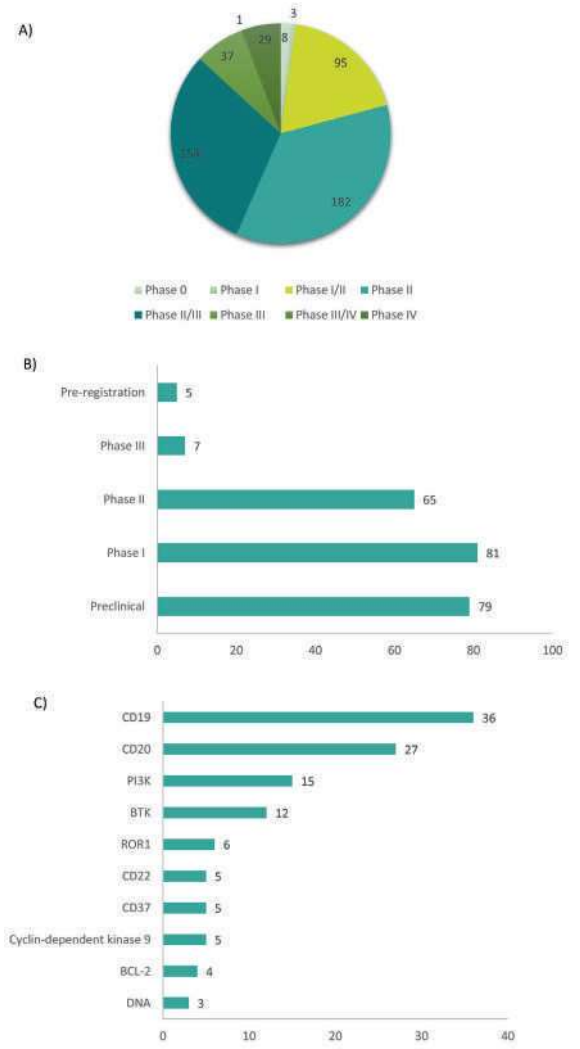

Figure 1. Summary of the current clinical trial landscape for CLL. Depicted are: A) Numbers of CLL clinical trials by phase, B) Numbers of therapies under evaluation for CLL by stage of development, and C) Top ten targets by drugs.
Abbreviations: BCL-2: B-cell lymphoma 2; BTK: Bruton's tyrosine kinase; CD: cluster of differentiation; CLL: chronic lymphocytic leukaemia; DNA: deoxyribonucleic acid; ROR1: neurotrophic tyrosine kinase, receptor-related 1; PI3K: phosphoinositide 3-kinase.

Prognostic factor	Points	Additional information
TP53 mutation or del17p* presence	4	Patients with *TP53* mutation experienced shorter time to first therapy, PFS, and OS[53,54,55,56,57,58] Increasing OS per patient group[59]: • Del17p13: OS~3 years • Del11q23: OS~6.5 years • Trisomy 12: OS~9.2 years • Negative FISH: OS~9.5 years • Del13q14: OS~14 years
No *IGHV* mutation	2	Higher OS in patients with mutated vs non-mutated IGHV (NR vs 10 years [60]; 24.4 vs 7.9 years[61]; >20 vs 8 years[62])
Serum β2 microglobulin >3.5 mg/L	2	Independent predictor of PFS and OS[63,64]
Clinical stage (Binet B-C or Rai stage I-IV)	1	Used for >4 decades as backbone for prognostication in clinical practice/trials, as well as for the decision on treatment initiation[65,66]
Age ≥65 years	1	Prognostic factor for OS, independent of cytogenetic or molecular genetic factors[67,68,69,70,71]

*As determined by FISH.
Abbreviations: CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukaemia; del: deletion; FISH: fluorescence in situ hybridisation; IGHV: immunoglobulin heavy chain variable region gene; IPI: International Prognostic Index; NR: not reached; OS: overall survival; PFS: progression-free survival; TP53: tumour protein 53.

Table 1. The CLL-International Prognostic Index: independent prognostic factors, cumulative score, and limitations[10].

This recommendation could potentially be explained by the better patient tolerance of BR versus FCR[13], while response and survival rates remained similar (Table 3). Other anti-CD20 monoclonal antibodies used as monotherapy for CLL are obinutuzumab and ofatumumab. In pivotal Phase III trials, both compounds showed significant improvements in ORR and PFS versus chlorambucil plus rituximab (Table 3), while maintaining a tolerable safety profile[14,15,16].

Combination therapy recommended for patients with del17p/*TP53* mutations includes obinutuzumab administered together with the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax, the BTK inhibitor acalabrutinib or chlorambucil[4,14,15,16] (Table 2 and Figure 2).

Bruton's Tyrosine Kinase (BTK) Inhibitors

Ibrutinib and acalabrutinb are currently the only small-molecule BTK targeted therapies approved by the Food and Drug Administration (FDA) for first-line treatment of CLL (Table 2). Similar to other BTK inhibitors, ibrutinib covalently binds to and ultimately inhibits the BTK enzyme, thus impairing the rate of abnormal B-cell multiplication and subsequent CLL development. Initially, ibrutinib was approved for relapsed/refractory patients and subsequently for treatment-naïve patients with and without del17p/*TP53* mutations.

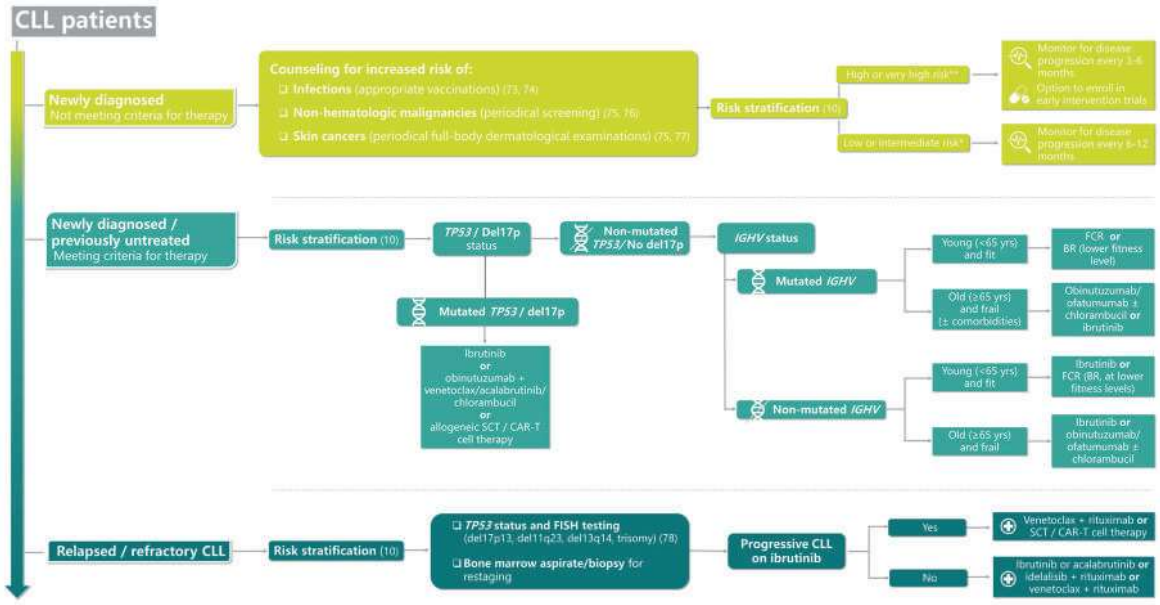

*Figure 2. Summary of current CLL management and treatment programmes[4,9]. *Approximately 75% of patients, with a median time to first therapy of approx. seven years. **Approximately 25% of patients, with a median time to first therapy of approx. two years[10]. Abbreviations: BR: bendamustine rituximab; CAR-T: chimeric antigen receptor T cell; CLL: chronic lymphocytic leukaemia; del: deletion; FCR: fludarabine cyclophosphamide rituximab; FISH: fluorescence in situ hybridisation; IGHV: immunoglobulin heavy chain variable region gene; IPI: International Prognostic Index; SCT: stem cell transplant; TP53: tumour protein 53; yrs: years.*

Drug	Mechanism of action	Initial approval	Current approval indications
Rituximab	Anti-CD20 mAbs	FDA: Feb 2010 EMA: Feb 2009	FDA: • In combination with fludarabine and cyclophosphamide (as FCR), for treatment of patients with previously untreated and previously treated CD20+ CLL EMA: • In combination with chemotherapy, for treatment of patients with previously untreated and relapsed/refractory CLL
Ofatumumab		FDA: Oct 2009 EMA: Apr 2010	FDA and EMA: • In combination with chlorambucil, for treatment of previously untreated patients with CLL and contraindications to fludarabine-based therapy • For treatment of patients with CLL refractory to fludarabine and alemtuzumab • In combination with FC, for treatment of patients with relapsed CLL.
Obinutuzumab		FDA: Nov 2013 EMA: July 2014	FDA: • In combination with chlorambucil, for treatment of patients with previously untreated CLL EMA: • In combination with chlorambucil, for treatment of adult patients with previously untreated CLL and comorbidities contraindicating fludarabine-based therapy
Alemtuzumab*	Anti-CD52 mAb	FDA: May 2001 EMA: July 2001	FDA: • For treatment of patients with B-cell CLL, as a single agent EMA: • For treatment of patients with B-cell CLL for whom treatment combinations including fludarabine are not appropriate
Ibrutinib	BTK inhibitors	FDA: Feb 2014 EMA: Oct 2014	FDA and EMA: • As monotherapy, for treatment of patients with previously untreated CLL (±del17p) or relapsed/refractory CLL to at least one prior therapy
Acalabrutinib		FDA: Nov 2019 EMA: -	FDA: • For treatment of adults with CLL or small lymphocytic lymphoma
Idelalisib	PI3K inhibitors	FDA: Jul 2014 EMA: Sep 2014	FDA and EMA: • In combination with an anti-CD20 monoclonal antibody (rituximab/ofatumumab), for treatment of adult patients with previously untreated CLL and del17p/*TP53* mutations or patients with relapsed/refractory CLL to at least one prior therapy, and ineligible for other therapies
Duvelisib		FDA: Sep 2018 EMA: -	FDA: • Relapsed/refractory CLL after at least two prior therapies
Venetoclax	Bcl-2 inhibitor	FDA: Apr 2016 EMA: Dec 2016	FDA: • For treatment of adult patients with relapsed/refractory CLL to at least one prior therapy, with/without del17p EMA: • As monotherapy, for treatment of patients with CLL, but no genetic changes, who failed on chemoimmunotherapy and ibrutinib/idelalisib or with CLL and genetic changes (del17p, TP53 mutation) who failed on ibrutinib/idelalisib • In combination with rituximab, for treatment of adult patients with relapsed/refractory CLL to at least one prior therapy

*In August/September 2012, alemtuzumab was withdrawn from the markets in the United States and Europe, to prevent off-label use for treatment of multiple sclerosis and to prepare for a relaunch with a different dosage and trade name, aimed for treatment of multiple sclerosis.

Abbreviations: BTK: Bruton's tyrosine kinase; CD: cluster of differentiation; CLL: chronic lymphocytic leukaemia; CR: complete response; del: deletion; EMA: European Medicines Agency; FC: fludarabine cyclophosphamide; FCR: fludarabine cyclophosphamide rituximab; FDA: Food and Drug Administration; IV: intravenous; PI3K: phosphoinositide 3-kinase; PR: progressive response; TP53: tumour protein 53.

Table 2. Overview of approved targeted agents for treatment of CLL.

These approvals were based on the demonstrated efficacy of single-agent ibrutinib in treatment-naïve[17,18] and relapsed/refractory CLL patients[19] (Table 3). Subsequent trials demonstrated a five-year sustained efficacy in these patient populations, with response rates and tolerability improving over time[20] (Table 3).

Acalabrutinib is a second-generation BTK inhibitor with superior selectivity as compared to ibrutinib[21]. This, and its efficacy similar to that of ibrutinib (Table 3) make acalabrutinib a suitable treatment alternative for previously untreated and relapsed/refractory CLL. On the basis of the Phase III clinical trial ELEVATE TN[22], which reported higher OS rates in treatment-naïve patients receiving acalabrutinib alone or combined with obinutuzumab versus obinutuzumab plus chlorambucil (85% and 94% vs 79%, Table 3), while maintaining a tolerable safety, acalabrutinib monotherapy received FDA approval for treatment of adult patients with CLL in November 2019 (Table 2). As a result, NCCN guidelines included acalabrutinib, alone or in combination therapies, as a preferred regimen for CLL treatment[4].

Treatment Options for Relapsed/Refractory CLL

According to the CLL-IPI[10], patients with relapsed/refractory CLL should undergo restaging/restratification prior to assignment to any new therapies (Figure 2). The specific therapies to be used will be based on fitness level, presence of comorbidities, and intolerance to previous treatments.

Anti-CD20 Monoclonal Antibodies

In addition to their use in the first-line setting, anti-CD20 monoclonal antibodies are among the recommended options for treatment of relapsed/refractory CLL[4] (Table 2) in elderly (≥65 years) patients without del17p/*TP53* mutations, but presenting with coexisting comorbidities that make these patients ineligible for purine analogs-based therapies[4,14,15,16] (Figure 2).

BTK Inhibitors

The pivotal Phase III trial RESONATE demonstrated significant benefits of ibrutinib versus ofatumumab in patients with relapsed/refractory CLL, including clinically relevant improvements in haematologic function and patient-reported outcomes[19,23]. Improved efficacy and similar safety profiles were observed in the Phase III HELIOS trial comparing ibrutinib versus placebo, upon combination with bendamustine-rituximab[24]. Lastly, results of a recent cross-trial

Drug	CLL type	Treatment arms	Trial name/ phase	ORR	CRR	Median OS/ OS rate	Median PFS/ PFS rate
Anti-CD20 mAbs							
Rituximab	Previously untreated (young and fit pts)	FCR vs FC (6 courses)	CLL8 (Phase III)[11,12]	90% vs 80% (p<0.0001)	44% vs 22% (p<0.0001)	At 3 yrs: 87% vs 83% (HR, 0.67; 95% CI, 0.48–0.92; p=0.012)	At 3 yrs: 65% vs 45% (HR, 0.56; 95% CI, 0.46-0.69; <0.0001)
	Previously untreated (young pts with lower fitness level or old pts)	FCR vs BR	CLL10 (Phase III)[13]	96% vs 95% (p=1.0) In pts <65 yrs: 95% vs 98% (p=0.096) In pts ≥65 yrs: 97% vs 92% (p=0.164)	40% vs 31% (p=0.034) In pts <65 yrs: 41% vs 30% (p=0.022) In pts ≥65 yrs: 36% vs 32% (p=0.648)	At 3 yrs: 91% vs 92% (HR, 1.034; 95% CI, 0.620–1.724; p=0.897)	55.2 vs 41.7 mths (HR, 1.643; 90.4% CI, 1.308–2.064; p=0.0003) In pts <65 yrs: 53.6 vs 38.5 mths (95% CI, 33.1–44.8; p=0.0004) In pts ≥65 yrs: NR vs 48.5 mths (95% CI, 34.6–52.0; p=0.172)
Ofatumumab	Previously untreated pts not eligible for fludarabine-based therapy due to older age/ comorbidities	OC vs C	COMPLEMENT (Phase III)[15]	82% vs 69% (OR, 2.16; 95% CI, 1.36–3.42, p=0.001)	14% vs 1% (p value not mentioned)	At 3 yrs: 85% vs 83% (HR, 0.91; 95% CI, 0.57–1.43; p=0.666)	22.4 vs 13.1 mths (HR, 0.57; 95% CI, 0.45–0.72; p<0.0001)
	Maintenance in R/R CLL	Ofatumumab maintenance or observation	PROLONG (Phase III)[16]	–	–	–	29.4 vs 15.2 mths (HR 0.50; 95% CI, 0.38–0.66; p<0·0001)
Obinutuzumab	Treatment-naïve pts ≥65 years with coexisting comorbidities	OC vs RC vs C	CLL11 (Phase III)[14]	At 3 mths after EOT: 77.3% vs 65.7% vs 31.4% (p<0.001)	At 3 mths after EOT: 22.3% vs 7.3% vs 0% (p<0.001)	• OC vs C: 91% vs 80% (HR, 0.41; 95% CI, 0.23-0.74; p=0.002) • RC vs C: 85% vs 80% (HR, 0.66; 95% 0.39–1.11; p=0.11)	• OC vs C: 26.7 vs 11.1 mths (HR 0.18; 95% CI, 0.13–0.24; p<0.001) • RC vs C: 16.3 vs 11.1 mths (HR 0.44; 95% CI, 0.34–0.57; p<0.001)
Ublituximab	R/R CLL with prior exposure to rituximab	Ublituximab (single arm)	Phase I[38]	67%	0%	–	NR
	R/R CLL	Ublituximab + ibrutinib (single arm)	Phase II[39]	88%	5%	–	–
BTK inhibitors							
Ibrutinib	Previously untreated or R/R CLL with del17p and TP53 mutations	Ibrutinib (single arm)	Phase II[17]	At 24 months: • Treatment-naïve pts: 97% • R/R CLL: 80%	No CRs observed	At 24 months: • All pts: 80% (95% CI, 68–94) • Treatment-naïve pts: 84% (95% CI, 72–100) • R/R CLL: 74% (95% CI, 57–100)	At 24 months: • All pts: 82% (95% CI, 71–94)
	Treatment-naïve and R/R CLL	Ibrutinib (single arm)	PCXYC-1102 and PCYC-1103 (Phase II)[20]	At the 5-yr follow-up: • Treatment-naïve pts: 87% • R/R CLL: 89%	At the 5-yr follow-up: • Treatment-naïve pts: 29% • R/R CLL: 10%	Median OS: • Treatment-naïve pts: NR • R/R CLL: NR At the 5-yr follow-up: • Treatment-naïve pts: 92% • R/R CLL: 60%	Median PFS: • Treatment-naïve pts: NR • R/R CLL: 51 mths At the 5-yr follow-up: • Treatment-naïve pts: 92% • R/R CLL: 44%
	R/R CLL	Ibrutinib vs ofatumumab	RESONATE (Phase III)[19]	63% vs 4.1% (OR, 2.16; 95% CI, 8.1–37.3; p<0.001)	No CRs observed in either group	42.6% vs 4.1% (p<0.001)	Median follow-up of 9.4 mths: NR vs 8.1 mths (p<0.001)
	Previously untreated pts ≥65 years	Ibrutinib vs chlorambucil	RESONATE-2 (Phase III)[18]	86% vs 35% (HR, 0.09; 95% CI, 0.04–0.17; p<0.001)	4% vs 2%	At 24 mths : 98% vs 85% (HR, 0.16; p<0.001)	Median follow-up of 18.4 mths: NR vs 18.9 mths (HR, 0.28; 95% CI, 0.09-0.28; p<0.001)
	R/R CLL	Ibrutinib + BR vs placebo + BR	HELIOS (Phase III)[24]	82.7% vs 67.8%	10.4% vs 2.8%	Median OS: NR (HR, 0.628; 95% CI, 0.385–1.024; p=0.0598)	At the 18-month follow-up: 79% vs 24% (HR 0.203, 95% CI 0.150–0.276; p<0·0001)
Acalabrutinib	Relapsed CLL	Acalabrutinib (single arm)	Phase I/II[21]	At the 14.3-month follow-up: 95%	No CRs observed	NR	NR
	Pts with R/R CLL and intolerant to ibrutinib	Acalabrutinib (added cohort of the open-label Phase II dose-expansion)	Phase I/II[72]	75.8%	3%	–	Median PFS: NR • 1-year PFS: 83.4% (95% CI, 64.5–92.7) • 2-year PFS: 75.0% (95% CI, 54.2–87.4)
	Treatment-naïve CLL	Acalabrutinib alone (A) vs A + obinutuzumab (A + O) vs OC	ELEVATE TN (Phase III)[22]	• A: 85% • A + O: 94% • OC: 79%	A: One patient had CR A + O and OC: No CRs	Median OS: • A + O vs OC: NR vs NR (HR, 0.47, 95% CI, 0.21–1.06, p=0.0577) • A vs OC: NR vs NR (HR 0.60, 95% CI 0.28–1.27, p=0.1556)	Median PFS: • A + O vs OC: NR vs 22.6 mths (HR, 0.10, 95% CI, 0.06–0.18, p<0.0001) • A vs OC: NR vs 22.6 mths (HR 0.20, 95% CI 0.13–0.31, p<0.0001)
	Relapsed/refractory CLL	A vs rituximab + idelalisib (IDR)/BR	ASCEND (Phase III)[26]	81% vs 75% (p=0.22)	–	At 12 mths: 94% vs 91%	At 12 mths: 88% vs 68% Median follow-up of 16.1 mths: NR vs 16.5 mths (HR, 0.31, 95% CI, 0.20–0.49, p<0.0001)

Table 3. Efficacy overview of approved and emerging targeted agents for CLL – Part 1

Drug	CLL type	Treatment arms	Trial name/ phase	ORR	CRR	Median OS/ OS rate	Median PFS/ PFS rate
PI3K inhibitors							
Idelalisib	R/R CLL	Idelalisib + rituximab vs rituximab	Phase III[27]	81% vs 13% (OR, 29.92; p<0.001)	–	At 12 mths: 92% vs 80% (HR, 0.28; 95% CI, 0.09–0.86; p=0.02)	NR vs 5.5 mths (HR, 0.15; 95% CI, 0.08–0.28; p<0.001)
	R/R CLL	Idelalisib + ofatumumab vs placebo-ofatumumab	Phase III[28]	75.3% vs 18.4%	<1% (1 pt) vs 0%	NR (HR, 0.75; 95% CI, 0.48–1.18; p=0.27)	16.3 vs 8.0 mths (0.27, 95% CI 0.19–0.39, p<0·0001)
Duvelisib	R/R CLL	Duvelisib (single arm)	Phase I[42]	55%	2%	–	–
	R/R CLL	Duvelisib vs ofatumumab	DUO (Phase III)[43]	73.8% vs 45.3% (p<0.0001)	PR: 72.5% vs 44.7% CR: 0.6% vs 0.6%	NR in either treatment arm	13.3 vs 9.9 mths (HR, 0.52; p < 0.0001)
	R/R CLL	Duvelisib + BR vs duvelisib + R	Phase I[44]	75.0% vs 88.9%	0% vs 0%	NR	NR vs 22.1 mths (95% CI 13.7-NA)
Umbralisib	R/R CLL	Umbralisib (single arm)	Phase I[45]	94%	0%	–	–
Bcl-2 inhibitors							
Venetoclax	Relapsed CLL	Venetoclax (single arm)	Phase I[30]	92%	20%	–	At 15 mths: 66% (95% CI, 51–77)
	R/R CLL and del17p	Venetoclax (single arm)	Phase II[31]	79.4% (95% CI, 70.5–86.6)	10%	At 12 mths: 86.7% (95% CI, 78.6-91.9)	At 12 mths: 72% (95% CI, 61.8–79.8)
	R/R CLL	Venetoclax + rituximab vs bendamustine + rituximab	MURANO Phase III[32]	93.3% vs 67.7%	26.8% vs 8.2%	At 2 yrs: 91.9% vs 86.6% (HR, 0.48; 95% CI, 0.25-0.90)	At 2 yrs: 84.9% vs 36.3% (HR, 0.17; 95% CI, 0.11–0.25, p<0.x001)
Anti-CD37 mAbs							
Otlertuzumab	Untreated pts ineligible for standard chemotherapy due to age and comorbidities	Otlertuzumab + rituximab	Phase Ib[35]	54%	8%	–	16 months
	Relapsed CLL	Otlertuzumab + bendamustine vs bendamustine	Phase II[36]	69% vs 39% (p=0.025)	9% vs 3%	NR	15.9 vs 10.2 months (p=0.0192)
Anti-PD1 mAbs							
Pembrolizumab	Relapsed and transformed (Richter) CLL	Pembrolizumab (single arm)	Phase II[46]	• Relapsed CLL: 16% (95% CI, 0.05-0.36) • Richter's transformation (RT): 44% (95% CI, 0.14-0.79)	Relapsed CLL: 0% RT: 11%	• All pts: 10.7 mths (95% CI, 4.4-NR) • Relapsed CLL: 11.2 months (95% CI, 2.8-NR) • RT: 10.7 mths (95% CI, 4.4-NR)	• All pts: 3.0 mths (95% CI, 2.1-5.6) • Relapsed CLL: 2.4 months (95% CI, 1.2-3.3) • RT: 5.4 mths (95% CI, 2.8-12.2)
Cellular therapies							
CAR-T	Multiple R/R CLL	CD19-directed CAR-T alone	Pilot Phase I[48]	57%	29%	• Median OS: 29 mths • Estimated 18-mth OS rate: 71% (95% CI, 40.6-88.2)	• Median PFS: 6 mths • Estimated 18-mth PFS rate: 28.6% (95% CI, 8.8-52.4)
	R/R high-risk CLL	Liso-cel CD19-directed CAR-T alone	TRANSCEND (Phase I/II)[49]	75%	50%	–	–
	R/R CLL	CD19-directed CAR-T + ibrutinib vs CAR-T alone	Phase I/II[50]	88% vs 56%, p=0.06)	Not reported	Not reported	Not reported
SCT	High-risk CLL	Autologous vs allogeneic SCT	Long-term follow-up trial[51]	Not reported	Not reported	At 6 years: 58% vs 55% (HR, 0.98; 95% CI, 0.53-1.83; p=0.96)	At 6 years: 30% vs 24% (HR, 0.62; 95% CI, 0.39-0.98; p=0.04)
	Purine analog refractory pts	RIC vs myeloablative allogeneic SCT	Long-term follow-up trial[52]	Not reported	Not reported	At 5 years: 83% vs 47%, p=0.003	At 5 years: 64% vs 47%, p=0.15

Abbreviations: A: acalabrutinib; BTK: Bruton's tyrosine kinase; C: chlorambucil; CAR-T: chimeric antigen receptor T cell; CD: cluster of differentiation; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CR: complete response; CRR: complete response rate; EOT: end of treatment; FC: fludarabine cyclophosphamide; FCR: fludarabine cyclophosphamide rituximab; HR: hazard ratio; IGHV: immunoglobulin heavy chain variable region gene; mAb: monoclonal antibody; MRD: minimal residual disease; NR: not reached; O: obinutuzumab; OC: obinutuzumab chlorambucil; OR: odds ratio; ORR: objective response rate; OS: overall survival; PD1: programmed cell death protein 1; PI3K: phosphoinositide 3-kinase; PFS: progression-free survival; PR: partial response; pts: patients; R/R: relapsed/refractory; RC: rituximab chlorambucil; RIC: reduced intensity conditioning; SCT: stem cell transplant.

Table 3. Efficacy overview of approved and emerging targeted agents for CLL – Part 2

comparison of pivotal Phase III CLL trials (CLL8, CLL10, CLL11, COMPLEMENT, RESONATE-2) demonstrated that ibrutinib versus chemoimmunotherapy led to longer PFS in the overall analysed population and in high-risk (e.g. advanced/bulky disease, del11q, unmutated IGHV) patients[25]. Similarly, in older patients with comorbidities, ibrutinib reached an OS longer than chemoimmunotherapy, but comparable to that reached with FCR/BR in younger patient populations[25]. Based on these data, ibrutinib is currently one of the preferred and guideline-recommended treatment options for relapsed/refractory patients with CLL[4] (Figure 2).

In the recent Phase III ASCEND trial, the median PFS rate at 16.1 months follow-up was not reached with acalabrutinib versus 16.5 months with the investigator's choice (rituximab-idelalisib or rituximab-bendamustine) (Table 3), representing a 69% reduction in the risk of progression or death[26]. Based on the positive results from this trial, acalabrutinib has become an alternative for treatment of relapsed/refractory CLL in patients intolerant to ibrutinib[4].

PI3K Inhibitors

Due to their capacity to modulate the PI3K/AKT/mTOR signalling

pathway involved in cellular growth control, metabolism, and translation initiation, PI3K inhibitors are investigated for treatment of various cancers. In alignment with the rising trend of combination therapies for CLL to improve outcomes, combined therapy of the PI3K inhibitor idelalisib and rituximab substantially improved efficacy (ORR: 81% vs 13%, p<0.001; Table 3) and safety of relapsed/refractory CLL patients versus rituximab monotherapy[27]. Similar results were observed upon combination of idelalisib with ofatumumab versus ofatumumab alone[28] (Table 3).

BCL-2 Inhibitors

The selective BCL-2 inhibitor venetoclax, a guideline-recommended treatment option for relapsed/refractory CLL[4], was shown to promote rapid apoptosis in CLL cells by selectively mimicking the action of antitumoural BH3-only proteins and antagonising the activity of BCL-2 pro-survival proteins[29]. In patients with relapsed/refractory CLL, single-agent venetoclax achieved ORR rates >75%[30,31] (Table 3). However, despite the demonstrated efficacy, venetoclax was reported to lead to grade 3–4 neutropenia and tumour lysis syndrome (TLS), if dose adjustments are not performed[30]. Adjusting the venetoclax dose when combined with rituximab was shown to account for potential TLS[32], while simultaneously improving outcomes and eradicating minimal residual disease[33] as compared to other therapies[32] (Table 3). Based on this data, venetoclax received FDA approval for treatment of patients with relapsed/refractory CLL (Table 2).

Emerging Treatment Programmes for CLL

Despite the gradual introduction of the aforementioned targeted therapies, new treatment strategies efficacious for patients ineligible for/unresponsive to these therapies are still required. These new strategies should ideally overcome disease relapse and circumvent compound-specific safety challenges. Emerging treatment options include new compounds aimed for both untreated and relapsed/refractory CLL and combination therapies of existing compounds that extend single-agent efficacy in specific high-risk patient populations.

A member of the tetraspanin superfamily of cell surface antigens, CD37 has been suggested to offer advantages over CD20 as a treatment target because it is selectively expressed by most B-cell malignancies[34]. The humanised anti-CD37 antibody otlertuzumab triggers caspase-independent apoptosis of malignant cells and induces ADCC. In treatment-naïve CLL patients with comorbidities, combination of otlertuzumab with rituximab led to a 54% ORR (Table 3), lower than that typically observed with the SoC FCR or BR, but almost no grade 3–4 AEs[35]. Addition of otlertuzumab to bendamustine was shown to improve efficacy (Table 3), while maintaining a safety profile similar to that of bendamustine alone[36].

Another novel therapy is the next-generation anti-CD20 monoclonal antibody ublituximab, which binds to an epitope on the CD20 antigen distinct from rituximab, ofatumumab, and obinutuzumab, and that has been glycoengineered to achieve ADCC superior to that of rituximab[37]. Initial Phase I and II trials have shown that ublituximab is able to achieve high ORR, either as single-agent in patients previously exposed to rituximab (67%)[38] or in combination with the SoC ibrutinib (88%)[39]. Other promising combination regimens with ublituximab are currently being evaluated (Table 3).

A novel inhibitor of the delta and gamma PI3K isoforms active in the presence of BTK mutations[40,41], duvelisib alone achieved a 55% ORR in a heavily pretreated patient population[42] (Table 3). In the pivotal Phase III DUO trial, duvelisib vs ofatumumab significantly improved PFS and ORR[43] (Table 3). Furthermore, combined therapy of duvelisib with SoC bendamustine-rituximab led to similar results in patients with relapsed/refractory CLL[44]. While duvelisib has recently been approved by the FDA for treatment of relapsed/refractory CLL after at least two prior therapies (Table 2), EMA approval is still pending.

Another PI3K gamma inhibitor currently under investigation for treatment of patients with relapsed/refractory CLL is umbralisib, which led to a 94% ORR in a Phase I dose-escalation trial[45] (Table 3). While preliminary data indicates a low incidence of grade 3–4 AEs[45], the tolerability profile of umbralisib still needs to be completely defined.

Other treatment modalities currently under development in Phase I–II clinical trials include checkpoint inhibitors and cellular therapies. The most commonly employed checkpoint inhibitor is the anti-PD-1 antibody pembrolizumab, already approved for clinical use in various solid tumours. In the first Phase II trial to demonstrate the efficacy of single-agent pembrolizumab in patients with transformed CLL who relapsed after ibrutinib treatment, the observed ORR was 44%[46] (Table 3). Considering that most common (>20%) AEs observed with pembrolizumab were drug-related[46], improving its safety profile in this patient population by potential use of lower doses in combination therapies is an approach currently under investigation (Table 3).

While experience with chimeric antigen receptor (CAR)-T cell therapy for CLL treatment is limited[47], preliminary results reported a 57% ORR in heavily pretreated patients[48] (Table 3). In the ongoing Phase I/II TRANSCEND trial in relapsed/refractory CLL patients previously treated with ibrutinib and venetoclax and presenting with *TP53* alterations, treatment with the liso-cel CD19-directed CAR-T cell product led to a 75% ORR[49] (Table 3). Cytokine release syndrome (CRS), a common AE typical for CAR-T cell therapy, was encountered in 80% of patients, but was categorised as grade 1–2 and managed with the interleukin-6 receptor antibody tocilimumab[49]. Combination of CAR-T cell therapy with an established treatment might help diminish CRS severity, as reported in a recent Phase I/II trial[50].

Another emerging option for patients with high-risk CLL is stem cell transplantation (SCT). Initial results demonstrated long-term efficacy of both autologous and allogeneic SCT, with autologous SCT leading to a significantly longer PFS[51] (Table 3). Subsequent approaches focused on reduced intensity conditioning SCT (RIC SCT), due to lower incidences of non-relapse mortality than with myeloablative SCT (9.5% vs 46%)[52].

Conclusions

Despite the recent progress made by targeted therapies, approaches that consistently address CLL relapse, aim to improve safety/tolerability, and enhance efficacy in high-risk patient populations are still required. Emerging findings with combination therapies allowing for more patient-tailored approaches indicate a promising therapeutic outlook for CLL.

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