Emerging Therapies in Chronic Lymphocytic Leukemia: Current Trials

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2017.8.7.17

Abstract

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in adults in the Western hemisphere, and in 2017, it is expected to be diagnosed in 20,110 people, with 4,660 dying of this disease. The median age at diagnosis of CLL is 72; 70% are aged 65 and older and 40% are aged 75 and older. Chronic lymphocytic leukemia is a heterogeneous disease, as some patients never require therapy and are kept under surveillance, whereas others progress through several lines of treatment, never achieving remission, and die within 2 to 3 years of diagnosis. Treatment for CLL has progressed from an era where traditional cytotoxic agents were the mainstay of treatment to an era where targeted therapies including monoclonal antibodies and small-molecule inhibitors play a key role in treatment, in addition to a new emerging role for immunotherapy. Although targeted therapies have demonstrated efficacy in CLL, some patients cannot tolerate treatment due to advanced age or significant comorbidities. Poor prognostic factors include high serum beta2-microglobulin level, 2% or less mutation in the immunoglobulin heavy-chain variable region, 30% or greater CD38 expression on flow cytometry, 20% or greater zeta-chain–associated protein 70 (ZAP-70) somatic mutation, deletion 11q, deletion 17p, lymphocyte doubling time of less than 6 months, and Rai stage III and IV disease. Despite the advances made in diagnosis and treatment, CLL still remains essentially an incurable malignancy (Masood et al., 2011). Patients with CLL also are at risk of developing Richter's transformation (about 2%–10%), which is a histologic transformation to a more aggressive type of lymphoma (diffuse large B-cell lymphoma or Hodgkin lymphoma. The risk of transformation increases with the more lines of therapy a patient receives. The development of agents with improved outcomes and the potential for cure are needed to minimize the amount of therapy a patient receives.

J Adv Pract Oncol 2017;8:71–86

The treatment landscape for chronic lymphocytic leukemia (CLL) has been evolving, especially over the past decade. Between 2008 and 2016, the US Food and Drug Administration (FDA) approved six new therapies for CLL: bendamustine, ofatumumab, ibrutinib, obinutuzumab, idelalisib, and venetoclax (CenterWatch, 2017). The agents approved thus far have made great improvements in outcomes for patients with CLL and are displaying efficacy as single agents and in combination with different regimens. Cutting-edge therapeutic research combined with a broadening basic science knowledge base is leading to a burgeoning era of expedited drug approval targeting new pathways and abrogating the progression of CLL, with many drugs still in the pipeline. This article will discuss some of the emerging therapies in the management of CLL. Several targets for exciting emerging therapies that will be reviewed are highlighted in Figure 1 (Zenz, Mertens, Kuppers, Dohner, & Stilgenbauer, 2010).

CHIMERIC ANTIGEN RECEPTOR T CELLS

The American Society of Clinical Oncology (ASCO) has named immunotherapy the clinical cancer advancement of the year for 2 years in a row (Burstein et al., 2017). It has taken more than a century of research to determine how to harness the immune system to fight cancer. A number of strategies have been tried with some success, and they continue to be refined. Chimeric antigen receptor (CAR) T-cell therapy is an exciting area of ongoing research in immunotherapies for hematologic malignancies, with 2 products approved by the FDA; 1 approved for advanced leukemia and the other for advanced large B-cell lymphomas (National Cancer Institute, 2017a). Improvements

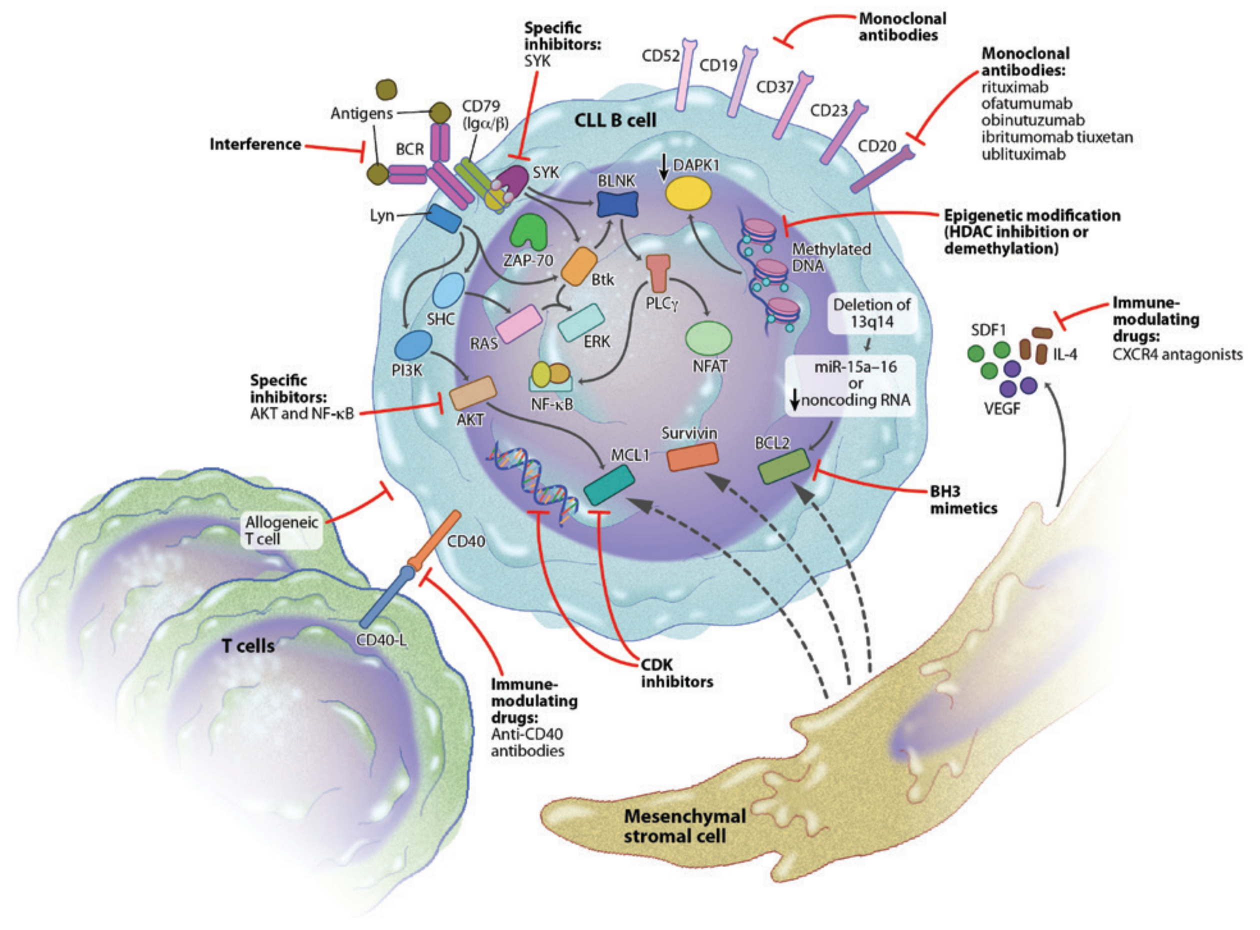

Figure 1. Treatment targets in CLL. Illustration by © Molecule Medical Arts. BLNK = B-cell linker protein; BTK = Bruton's tyrosine kinase; CDK = cyclin-dependent kinase; CXCR4 = C-X-C chemokine receptor 4; HDAC = histone deacetylase; IL-4 = interleukin 4; NF-κB = nuclear factor-κB; NFAT = nuclear factor of activated T cells; PLC-γ = phospholipase C-γ; SDF1 = stromal cell–derived factor 1; VEGF= vascular endothelial growth factor.

are needed in the area of treatment of patients with relapsed or refractory disease, and this is where CAR T cells play a key role. Chimeric antigen receptors are synthetic molecules engineered to redirect T-cell specificity to an antigen in a human leukocyte antigen (HLA)-independent manner and overcome obstacles related to T-cell tolerance (Kudchodkar & Maus, 2014).

In CLL, CD19 is the most-studied antigen, as it is expressed on normal B cells and most B-cell malignancies and non-Hodgkin lymphomas (NHLs) but not on normal hematopoietic stem cells (HSCs; Brentjens & Curran, 2012). By reprogramming a patient's T cells, it is possible to give the T cells a new specificity that is independent of HLA restriction, allowing CD19-directed CAR T cells to elicit an independent response (Davila, Brentjens, Wang, Riviere, & Sadelain, 2012). These engineered T cells have the ability to target CD19-expressing CLL cells and eliminate them and reactivate other immune cytokines that have been damped by the cancer's inhibitory signals. The development of CAR T cells requires several steps, which are highlighted in Figure 2 (Davila et al., 2012).

Chimeric antigen receptors are engineered to have two main components: an extracellular antigen-recognition domain and an intracellular signaling domain linked by a hinge/transmembrane domain to anchor the CAR into the T cell (Jackson, Rafiq, & Brentjens, 2016; Kudchodkar

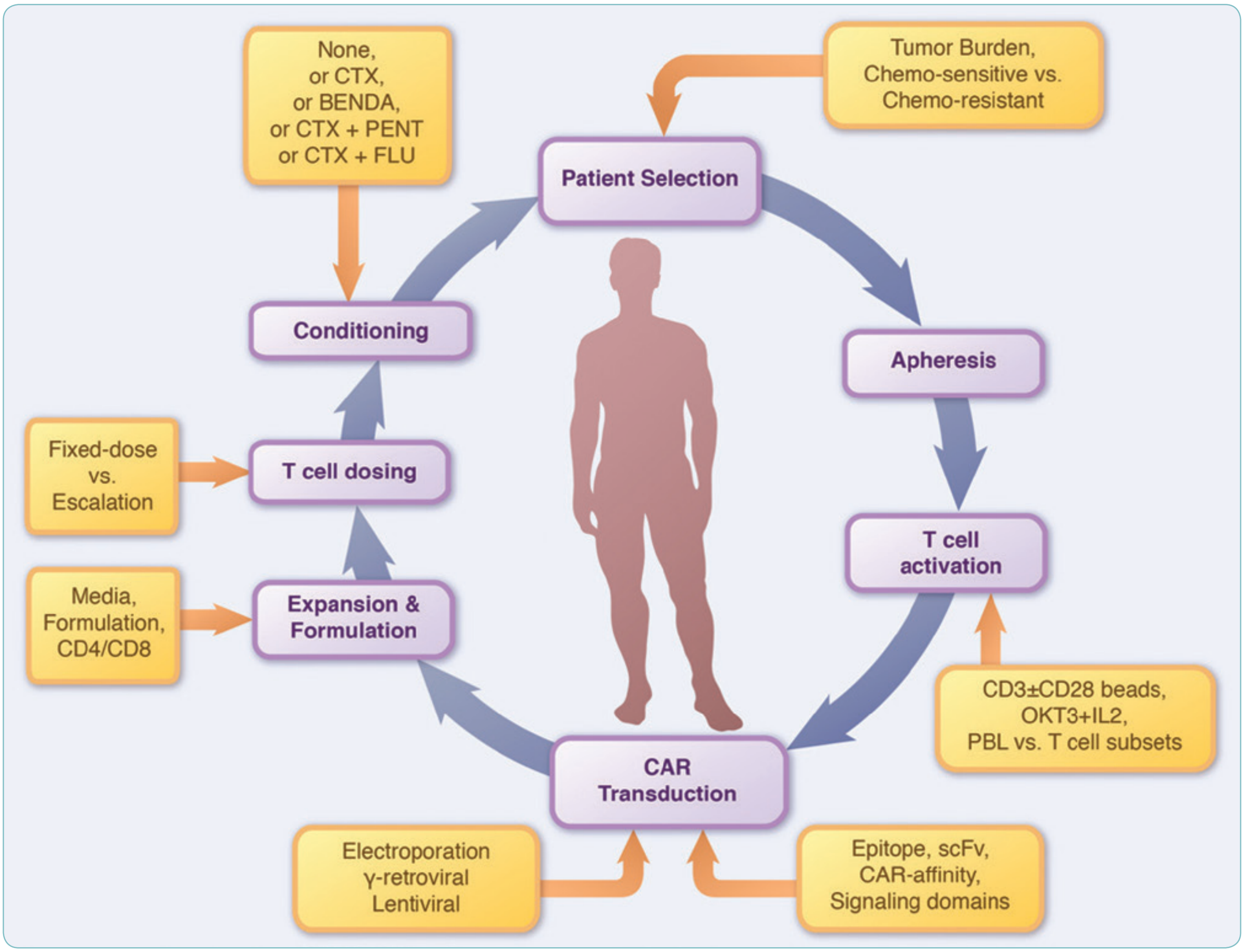

Figure 2. Overview of CAR T-cell therapy process. Several steps are required in the development of CAR T cells. The inner circle represents steps in patient preparation and T-cell manufacturing. The outer circle highlights differences in the process among clinical trials targeting CD19-positive malignancies. CAR = chimeric antigen receptor; CTX = cyclophosphamide; BENDA = bendamustine; PENT = pentostatin; FLU = fludarabine; PBL = peripheral blood lymphocytes. From Davila et al. (2012).

& Maus, 2014). First-generation CARs most commonly utilize a CD3 zeta-signaling chain, resulting in an activation signal called signal 1 (Jackson et al., 2016). In clinical trials, first-generation CARs experienced limited success, likely due to activation-induced cell death of the transplanted T cells, or deficiency in long-term T-cell expansion. Disappointing results remained despite the use of lymphodepleting therapy to reduce T-regulatory cell–mediated inhibition and favor homeostatic expansion of the infused cells (Dotti, Gottschalk, Savoldo, & Brenner, 2014).

Second-generation CARs improved on first-generation technology and added an additional costimulatory signaling domain called signal 2. This additional domain allowed the same receptor to deliver signal 1 and signal 2 to optimally activate the T cell, resulting in T-cell persistence. The improvement of an additional costimulatory signaling domain (CD28) was confirmed in six patients with relapsed or refractory NHL who were infused with a first- and second- generation CAR T-cell therapy against CD19 (Savoldo et al., 2011). The second-generation therapy produced enhanced expansion and persistence of T cells. Second-generation CAR T cells specific for CD19 have included a CD3 zeta domain with a CD28 or 4-1BB (CD137) costimulatory signaling domain.

In attempts to further improve CARs, third-generation CARs have been developed with a CD3 zeta domain and two costimulatory domains (CD28, and 4-1BB, or OX40 [CD134]). There are no published data in humans comparing third-generation CARs with second-generation CARs.

To introduce the CAR transgene to the T cell, genetic manipulation must occur typically through the use of a retrovirus or lentivirus vector. Higher gene-transfer efficiency is seen with the gamma-retroviral vectors (4%–71%) than with lentiviral vectors (4.7%–23%; Davila et al., 2012). The variation in gene-transfer efficiency does not appear to influence CAR-modified T-cell function. This variation in transduction efficiency highlights the large variability seen in individual patient products. The variability in T-cell dose can be minimized by infusion of the same amount of CAR-positive T cells within a study. The long-term impact of using different gene-transfer methods has yet to be elucidated (Hosing et al., 2013). Controlled studies comparing manufacturing processes are needed to determine their impact on clinical outcomes.

CLINICAL TRIALS WITH CAR T CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA

The initial studies utilizing CAR T cells directed at CD19 have had mixed results in CLL. Outcomes have ranged from no objective response to a complete response (CR). A study conducted at the National Cancer Institute (NCI) by Kochenderfer et al. (2012) included eight adult patients with advanced B-cell malignancies, four of whom had CLL. Patients were given a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine, followed by reinfusion of anti–CD19-CAR-transduced T cells engineered with a retroviral vector and CD28 costimulatory domain (Kochenderfer et al., 2012). The number of infused CAR-positive cells/kg ranged from 0.3 to 3.0×10^7.

Of the patients with CLL included, one patient experienced a CR (15+ months), two patients had a partial response (PR; each 7+ months), and one patient had stable disease (SD; 6 months; Kochenderfer et al., 2012). Grade 3 and 4 toxicities seen in at least 25% of patients include hypotension (50%), capillary leak syndrome (50%), acute renal failure (37.5%), fatigue (37.5%), hypoxemia (25%), elevated liver enzymes (25%), hyperbilirubinemia (25%), and electrolyte abnormalities (25%; Kochenderfer et al., 2012).

A study by Brentjens et al. (2011) conducted at Memorial Sloan Kettering Cancer Center included patients with relapsed purine-analog refractory CLL. In this phase I dose-escalation study, eight patients with CLL were included and received second-generation retroviral vector, CD3/CD28 anti-CD19 CAR T cells. Patients in step 1 received CAR-positive T-cell doses between 1.2 and 3.0×10^7 T cells/kg without cyclophosphamide pretreatment. All three patients treated in step 1 did not have a response and required additional salvage treatment. In step 2, patients received dose-escalating cyclophosphamide followed by infusion of 0.4 to 10.0×10^7 CAR-positive T cells/kg. In step 2, only four out of five patients were evaluable for response. Two patients experienced SD (lasting 4 months and longer than 8 weeks), one patient had a marked reduction in lymphadenopathy at 3 months with SD for 6 months, and one patient experienced progressive disease. Adverse events of any grade seen in at least two patients included fever (75%), rigors (62.5%), chills (62.5%), febrile neutropenia (37.5%), and hypotension (25%).

A clinical trial from the University of Pennsylvania evaluated CAR T cells in three patients with CLL (Kalos et al., 2011; Porter, Levine, Kalos, Bagg, & June, 2011). This study utilized a self-inactivating lentiviral vector and included the CD137 (4-1BB) signaling domain. Patients were given pentostatin and cyclophosphamide as lymphodepleting pretreatment followed by CAR T-cell infusions in doses from 1.0 to 1.6 × 10^7 cells/kg. Two patients experienced a CR (10+ months, 11+ months), and one patient experienced a PR for 7 months. One patient experienced grade 3 tumor lysis syndrome. Grade 1 and 2 adverse events seen include fevers, chills, diaphoresis, myalgias, headache, and fatigue.

The NCI published results on an additional study that included four patients with CLL who received CD19-targeted T cells after allogeneic hematopoietic stem cell transplantation and at least one standard donor lymphocyte infusion (Kochenderfer et al., 2013). No lymphodepleting chemotherapy was used prior to CAR T-cell therapy. The CD28 costimulatory molecule was used to engineer these anti-CD19 CAR T cells with a gamma-retroviral vector. Patients received CAR-positive T-cell doses of 0.4 to 2.4 × 10^6 cells/kg. One patient achieved a CR (9+ months), one patient experienced SD (3 months), and two patients experienced progressive disease. Treatment-related grade 3 or 4 toxicities seen in patients with CLL include fever (50%), tumor lysis syndrome (25%), fatigue (25%), cardiac ventricular function (25%), tachycardia (25%), troponin increase (25%), anemia (25%), neutropenia (25%), pneumonitis (25%), hypoxia (25%), dyspnea (25%), hypophosphatemia (25%), and hypotension (25%).

An abstract presented at the 2016 American Society of Hematology Annual Meeting & Exposition presented data on 18 patients with CLL previously treated with ibrutinib therapy and infused with 3 dose levels of CD19 CAR T cells after lymphodepleting chemotherapy: cyclophosphamide alone, fludarabine alone, or cyclophosphamide and fludarabine (Turtle et al., 2016). The overall response rate (ORR) was 78%, with eight PRs and five CRs. In the patients with ibrutinib-refractory (10) or -intolerant disease (3), the ORR was 77% (seven PRs and three CRs). Only two of the four venetoclax-refractory patients responded with PRs. Cytokine release syndrome (CRS) of any grade was seen in all 17 evaluable patients (eight grade 0–1, five grade 2, three grade 3, one grade 4). Three patients received tocilizumab and dexamethasone to treat CRS and/or neurotoxicity.

There are currently areas of ongoing debate and research to design the optimal CAR T-cell agent. The best method for T-cell manufacturing, gene transfer, and T-cell infusion are yet to be determined. It is also unknown what the optimal T-cell dose, lymphodepleting chemotherapy regimen, or place in therapy is for CAR T cells. Studies are also bringing to light new challenges to overcome. Antigen escape, or loss of CD19 expression on the tumor cells, renders CAR T-cell therapy ineffective (Jackson & Brentjens, 2015). This challenge has emerged in clinical trials with CD19 agents in CLL (Wang, Wu, Liu, & Han, 2017)

This exciting immunotherapy continues to be evaluated in CLL with the hopes of answering some of these questions; Table 1 lists select clinical trials in the United States.

MONOCLONAL ANTIBODIES

History of Monoclonal Antibodies in Chronic Lymphocytic Leukemia

In addition to the aforementioned therapies, monoclonal antibodies (mAbs) have also shown efficacy in treating CLL, and new mAbs are being developed. Monoclonal antibodies utilize antibody-dependent cell-mediated cytotoxicity leading to an effector immune cell lysing a target malignant cell whose surface antigen binds the mAb (Weiner, 2015). Monoclonal antibodies utilizing the immune system to attack malignant cells are being evaluated for their potential role in CLL management.

Rituximab is a chimeric monoclonal anti-CD20 antibody that consists of murine variable regions of the parent 2B8 murine that have been grafted to a human immunoglobulin G1 (IgG1)-constant region (Reff et al., 1994). CD20 is an

Table 1. **CAR T-Cell Clinical Trials for Chronic Lymphocytic Leukemia in the United States**

ClinicalTrials.gov identifier	Center	Patient population	Age	Lymphodepleting chemotherapy	Intervention	Gene-transfer method
NCT01853631	BCM	Advanced B-cell NHL, ALL, and CLL	≤ 75 years	± Flu/Cy	CD19.CAR/28 and CD19.CAR/28.137 T cells	Retrovirus
NCT01865617	FHCRC	R/R CLL, NHL, or ALL	≥ 18 years	± Flu/Cy	Autologous anti-CD19.CAR-4-1BB-CD3zeta-EGFRt-expressing T lymphocytes	Lentivirus
NCT02050347	BCM	Relapsed CD19+ malignancies post-alloHSCT	No restriction	± Flu/Cy	CD19.CAR-CD28Z T cells	Retrovirus
NCT00881920	BCM	CLL, B-cell lymphoma, or MM	≥ 18 years	± Flu/Cy	Kappa CD28 T cells	Retrovirus
NCT00466531[a]	MSKCC	R/R CLL or indolent B cell lymphoma	≥ 18 years	± Cy	CD28 (19-28z) and 4-1BB (CART-19:CD3z-4-1BB)	Retrovirus vs. lentivirus

Note. CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukemia; BCM = Baylor College of Medicine; NHL = non-Hodgkin lymphoma; ALL = acute lymphoblastic leukemia; Flu = fludarabine; Cy = cyclophosphamide; FHCRC = Fred Hutchinson Cancer Research Center; R/R = relapsed or refractory; alloHSCT = allogeneic hematopoietic stem cell transplant; MM = multiple myeloma; MSKCC = Memorial Sloan Kettering Cancer Center. Information from ClinicalTrials.gov.

[a] Active trial, but not recruiting.

excellent target in CLL, as it is expressed in malignant mature B cells and not in other B-cell precursors, nor is this antigen internalized, shed, or modulated after attaching to an antibody (Anderson et al., 1984). This characteristic served as a pretext for studying this drug not only in B-cell lymphomas, but also in CLL.

A landmark phase II study conducted at MD Anderson Cancer Center that evaluated the combination of fludarabine, cyclophosphamide, and rituximab (FCR) indicated excellent results and tolerability to the combination (Wierda et al., 2005). This phase II trial enrolled 177 patients with refractory CLL who were treated with rituximab at 375 mg/m^2 on day 1 of course 1 and subsequently at 500 mg/m^2 on day 1 of courses 2 to 6; fludarabine at 25 mg/m^2 on days 2 to 4 of course 1 and subsequently days 1 to 3 of courses 2 to 6; and cyclophosphamide at 250 mg/m^2 on days 2 to 4 of course 1 and subsequently days 1 to 3 of courses 2 to 6 (Wierda et al., 2005). Interim results revealed 25% of the 177 patients achieved a CR and 48% of patients achieved a PR, for an ORR of 73%. When published, this regimen showed the highest rate of CR compared with previous trials in patients with refractory or relapsed CLL. The final results after completion of the study and accruing 284 patients (280 patients were evaluable for response) revealed an ORR of 74% (Badoux et al., 2011).

However, more impressive was a single-arm study as first-line therapy with FCR, with results showing an ORR of 95% (95% confidence interval [CI] = 92%–98%), with 70% of patients achieving a CR (Keating et al., 2005). A phase III randomized trial subsequently established efficacy with FCR, as 65% of patients in the FCR arm were in remission after 3 years of treatment compared with 45% in the fludarabine and cyclophosphamide arm (Hallek et al., 2010; Keating et al., 2005). This result has established a role for rituximab not only in relapsed disease but also in front-line therapy.

Ofatumumab is another mAb that binds a distinct epitope of small and large loops of the CD20 molecule (Teeling et al., 2006). Like rituximab, ofatumumab kills malignant B cells by antibody-dependent complement activation culminating to cell-mediated cytotoxicity. This drug has been studied in multiple combinations that included chemotherapy and targeted drugs; however, a single-arm study that enrolled 138 patients with refractory disease showed an ORR of 58% in patients with alemtuzumab-refractory disease and an ORR of 47% in patients with fludarabine-refractory disease (Wierda et al., 2010). This trial was among the first studies that led to larger trials with the drug and eventual approval.

Alemtuzumab is a humanized IgG1 mAb that targets the CD52 antigen, which is overexpressed in a variety of lymphoid neoplasms and hence CLL (Alinari et al., 2007). Early trials of alemtuzumab showed an ORR of 35% in heavily pretreated patients and an ORR of 80% in previously untreated patients (Alinari et al., 2007).

Obinutuzumab is a humanized glycoengineered type 2 antibody also targeted against CD20, which in preclinical studies showed superiority compared with rituximab by inducing direct cell death and enhanced antibody-dependent cellular cytotoxicity (Mössner et al., 2010). A randomized trial that compared chlorambucil, obinutuzumab and chlorambucil (OC), and rituximab and chlorambucil (RC) revealed a higher progression-free survival, CR, and molecular response favoring OC over RC in patients with untreated CLL (Goede et al., 2014).

New Monoclonal Antibodies

Several mAbs are under development for the management of refractory or relapsed CLL, most of which are administered intravenously (Table 2). Two active studies are evaluating anti-CD37 mAbs (NCT02759016 and NCT01644253). CD37 is a tetraspanin antigen expressed on mature B cells and minimally on T cells, monocytes, and macrophages (Schwartz-Albiez, Dörken, Hofmann, & Moldenhauer, 1988). It is highly expressed among all subtypes of B-cell NHL, including CLL.

Based on in vitro studies with TRU-16 (otlertuzumab), one of the anti-CD37 mAbs, important differences in the mechanisms of action were seen compared with anti-CD20 mAbs (Robak, Robak, & Smolewski, 2009). This includes CD37 signaling–induced apoptosis, which was found to be caspase independent, and involved tyrosine phosphorylation (Finn, 2011; Gopal et al., 2014). It also appears to have a greater binding affinity, resulting in improved antibody-dependent cellular cytotoxicity. A phase IB trial that evaluated TRU-16 in combination with rituximab in patients with relapsed indolent lymphoma—including patients with small lymphocytic lymphoma—revealed an ORR of 83% (Gopal et al., 2014).

Another target is the receptor tyrosine kinase–like orphan receptor 1 (ROR1)—an exciting new target being pursued in CLL (Cui et al., 2016). ROR1 is an oncoembryonic antigen that is expressed on the cell surface of CLL cells but not normal B cells or other postpartum tissue (Borcherding, Kusner, Liu, & Zhang, 2014). ROR1 downstream effects include the activation of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway, and it may also be a substrate for other signaling molecules such as Met proto-oncogene (also called hepatocyte growth factor). UC-961 (cirmtuzumab) is a first-in-class mAb targeting ROR1 currently being evaluated in patients with relapsed or refractory disease (NCT02222688; Choi et al., 2015; Yu et al., 2017).

Lirilumab is an anti–killer-cell immunoglobulin-like receptor (KIR) mAb being investigated for its activity in CLL when utilized in combination with rituximab (NCT02481297). By administering the KIR mAb in combination with rituximab, natural killer (NK) cell–mediated, rituximab-dependent cytotoxicity is boosted to enhance lymphoma cell kill in vitro and in vivo in murine models (Kohrt et al., 2014; Sola et al., 2014).

Another approach to harnessing the immune system is through targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway. Targeting this pathway has been effective in solid tumors as well as Hodgkin lymphoma (HL) and NHL and is being explored in CLL, as these cells have been shown to express PD-1 and PD-L1 (Freeman & Gribben, 2016). Drugs targeting PD-1/PD-L1 stimulate an antitumor effect by utilizing cytotoxic T cells from the host's immune system to attack cancer cells (Chen & Han, 2015). In CLL, this therapy may also affect the B-cell receptor (BCR) signaling pathway, directly influencing cancer growth and proliferation (Kater & van der Windt, 2015).

Durvalumab is an anti–PD-L1 mAb being studied as monotherapy and in combination with various FDA-approved agents for the management of CLL (NCT02733042). Also utilizing the immune system is monalizumab (IPH2201), a novel mAb targeting the immune checkpoint receptor natu-

Table 2. **Selected Clinical Trials in CLL With Monoclonal Antibodies**

ClinicalTrials.gov identifier	Study phase	Age	Patient population	Intervention	Mechanism of experimental agent(s)	Primary outcome(s)
NCT02005289[a]	II	18–80 years	R/R or older untreated patients with CLL, SLL, or PLL	MOR00208 + lenalidomide	MOR00208: anti-CD19 mAb	Response
NCT02759016	I	18–99 years	Patients with R/R CLL who have received at least one prior systemic therapy and are eligible for treatment with ibrutinib	Ibrutinib + BI 836826	BI 836826: anti-CD37 mAb	MTD; DLTs
NCT01644253	I	≥ 18 years	CLL	TRU-016 and rituximab, obinutuzumab, idelalisib, or ibrutinib	TRU-016: anti-CD37 mAb	OR
NCT02222688	I	18–70 years	R/R CLL	UC-961	UC-961 (cirmtuzumab): ROR1 mAb	MTD; DLTs
NCT02481297[b]	II	≥ 18 years	R/R or high-risk untreated CLL	Rituximab + lirilumab	Lirilumab: anti-KIR mAb	OR
NCT02733042	I/II	≥ 18 years	Lymphoma or CLL	Durvalumab monotherapy or combination with lenalidomide + rituximab, ibrutinib, or bendamustine + rituximab	Durvalumab: anti–PD-L1 antibody	AEs; DLT; NTD; MTD; OR
NCT02557516	I/II	≥ 18 years	R/R or previously untreated CLL	IPH2201 + ibrutinib	IPH2201 (monalizumab): NKG2A checkpoint inhibitor	DLTs
NCT02924402	I	≥ 18 years	CD20-expressing hematologic malignancies	XmAb13676	XmAb13676: anti-CD20 and CD3-bispecific mAb	MTD; DLTs
NCT02500407	I	≥ 18 years	NHL, CLL	BTCT4465A	BTCT4465A: anti-CD20 and CD3-bispecific mAb	DLTs; AEs
NCT02290951	I	≥ 18 years	CD20+ B-cell malignancies	REGN1979	REGN1979: anti-CD20 and CD3-bispecific mAb	AEs
NCT02454270	I	≥ 18 years	R/R B-cell malignancies	Duvortuxizumab	Duvortuxizumab: CD19 × CD3 dual-affinity retargeting protein	RP2D; OR
NCT02669017	I	≥ 18 years	R/R B-cell lineage NHL	ADCT-402	ADCT-402: anti-CD19 ADC; PBD dimer cytotoxin	DLTs; MTD
NCT02175433[a]	I	≥ 18 years	R/R lymphoid malignancies	AGS67E	AGS67E: anti-CD37 ADC; MMAE	AEs
NCT02361346	I	≥ 18 years	Relapsed NHL and CLL	MT-3724	MT-3724: CD20-internalizing immunotoxin	AEs; DLTs

Note. CLL = chronic lymphocytic leukemia; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; PLL = prolymphocytic leukemia; mAb = monoclonal antibody; MTD = maximum tolerated dose; DLTs = dose-limiting toxicities; CR = complete response; OR = overall response; ROR1 = receptor tyrosine kinase–like orphan receptor 1; KIR = killer-cell immunoglobulin-like receptor; PD-L1 = programmed cell death ligand 1; AEs = adverse events; NTD = not tolerated dose; NKG2A = natural killer group 2A; NHL = non-Hodgkin lymphoma; RP2D = recommended phase II dose; ADC = antibody-drug conjugate; PBD = pyrrolobenzodiazepine; MMAE = monomethyl auristatin E. Information from ClinicalTrials.gov.

[a] Suspended recruitment.

[b] Active trial, but not recruiting.

ral killer group 2A (NKG2A), which is expressed as a heterodimer with CD94 on some cytotoxic lymphocytes (McWilliams et al., 2016). When a ligand binds to this complex, inhibitory signaling results in mitigated NK and CD8-positive T-cell responses. By blocking the binding of the CD94-NKG2A complex, NK and cytotoxic T-cell responses are boosted to attack malignant cells (Sola et al., 2016). This pathway is being evaluated as a potential target with the use of monalizumab in combination with ibrutinib in patients with CLL (NCT02557516).

Strategies to treat CLL with mAbs also include the use of bispecific antibodies (Peters & Brown, 2015). Bispecific antibodies being evaluated include anti-CD3/CD19 or CD20 agents (NCT02924402, NCT02500407, NCT02290951, and NCT02454270). Blinatumomab (CD3/CD19) is the only FDA-approved agent of this kind, and it is approved only for use in B-cell acute lymphoblastic leukemia at this time (Broderick, 2016). Bispecific antibodies presenting both CD3 and CD19 or CD20 can bring T cells in close proximity to the CD19- or CD20-expressing B cells to induce killing of the cancerous B cells (Hoffman & Gore, 2014; Naddafi & Davami, 2015). In fact, the advantage of blinatumomab includes its ability to draw malignant B cells in close proximity to CD3-positive T cells without regard to the specificity and the reliance on major histocompatibility complex (MHC)-I molecules on the surface of antigen-presenting cells for activation (Hoffman & Gore, 2014). This, therefore, allows the recruitment of polyclonal T cells, which circumvents resistance to T-cell–based therapy through the downregulation of MHC molecules.

Finally, another class of molecules with promise includes antibody-drug conjugates (ADCs), which exhibit their effect by a different mechanism. They contain an antibody linked to a cytotoxic agent and, when attached to a specific antigen expressed on cancer cells, lead to internalization of the cytotoxic agent, culminating in malignant cell death (Sassoon & Blanc, 2013). This unique mechanism leads to improved efficacy and minimizes off-target and systemic toxicities when the ADC is internalized after binding (Naddafi & Davami, 2015). The antibody targets being evaluated in CLL include CD19, CD20, and CD37 linked to monomethyl auristatin E (brentuximab vedotin) or pyrrolobenzodiazepine dimer cytotoxin (such as vadastuximab talirine; NCT02669017, NCT02175433, and NCT02361346).

Targeted Therapies

Many molecules targeting the BCR pathway in CLL are currently being developed, some of which have established exceptional efficacy in mature randomized clinical trials in first- and second-line therapies such as ibrutinib (Burger et al., 2015; O'Brien et al., 2014a; Zhang, Sanchez, Liu, Chang, & Goldberg, 2016). The BCR pathway has been a target of many of the recently FDA-approved agents for the management of CLL (Stevenson, Krysov, Davies, Steele, & Packham, 2011). This pathway is important to CLL biology, as it is associated with many downstream signaling pathways needed for cell growth. Signaling in this pathway is mediated by phosphorylation of the Src family kinases Lyn and spleen tyrosine kinase (Syk) resulting in recruitment of the signalosome (Contri et al., 2005). This process involves several kinases (Syk, Bruton's tyrosine kinase [BTK], and Lyn) and adaptor proteins (Grb2 and B-cell linker). Three main downstream pathways are activated by the signalosome: BTK, phospholipase C-γ (PLC-γ2), and phosphatidylinositol 3-kinase (PI3K; Woyach, Johnson, & Byrd, 2012). Table 3 shows several agents being investigated that target components (PI3K, BTK, and Syk) of the BCR pathway. Therefore, the most advanced BCR-signaling targets include Syk, BTK, PI3K, and PLC-γ2.

Considering the SYK pathway, the only targeting molecule in clinical use/study includes R788 (fostamatinib disodium [FosD]). FosD is a prodrug that is converted in vivo to R406, a bioactive form (Weinblatt et al., 2008). This drug has shown efficacy and tolerability in B-cell CLL in a phase I/II trial (Friedberg et al., 2010). However, this molecule has been developed in rheumatoid arthritis, and no SYK inhibitors are currently being used in the treatment of patients with B-cell CLL.

Moreover, BTK is a nonreceptor kinase of the TEC family and plays a key role in the differentiation and proliferation of B cells (Wang et al., 2012; Zhang et al., 2016). Bruton's tyrosine kinase signaling is downstream to CXCR4 and CXCR5 chemokine receptors and integrins, which are central to

Table 3. Selected Clinical Trials in CLL With Targeted Agents

ClinicalTrials.gov identifier	Study phase	Age	Patient population	Intervention	Mechanism of experimental agent(s)	Primary outcome(s)
NCT02914938	I	≥ 18 years	R/R CLL/SLL or FL	ME-401	ME-401: PI3Kδ inhibitor	mBED; MTD; DLTs
NCT02742090	II	≥ 18 years	CLL who are intolerant to prior therapy	TGR-1202	TGR-1202 (RP5264): PI3Kδ inhibitor	PFS
NCT02656303	II	≥ 18 years	Patients previously enrolled on protocol UTX-TGR-304	Ublituximab + TGR-1202	TGR-1202 (RP5264): PI3Kδ inhibitor TG-1101 (ublituximab): anti-CD20 mAb	OR
NCT02268851	I	≥ 18 years	CLL, MCL	TGR-1202 + ibrutinib	TGR-1202 (RP5264): PI3Kδ inhibitor	MTD
NCT02535286	I/II	≥ 18 years	R/R CLL	Pembrolizumab + TGR-1202 + TG-1101	TGR-1202 (RP5264): PI3Kδ inhibitor TG-1101 (ublituximab): anti-CD20 mAb	AEs
NCT02006485	I	≥ 18 years	B-cell malignancies	Ublituximab + TGR-1202 ± ibrutinib or bendamustine	TGR-1202 (RP5264): PI3Kδ inhibitor TG-1101 (ublituximab): anti-CD20 mAb	MTD
NCT02717611[a]	II	≥ 18 years	R/R CLL and intolerant of ibrutinib therapy	Acalabrutinib	Acalabrutinib (ACP-196): BTK inhibitor	OR
NCT02362035[a]	I/II	≥ 18 years	Hematologic malignancies	Acalabrutinib + pembrolizumab	Acalabrutinib (ACP-196): BTK inhibitor	AEs
NCT02337829	II	≥ 18 years	R/R and treatment-naive deletion 17p CLL/SLL	Acalabrutinib	Acalabrutinib (ACP-196): BTK inhibitor	OR
NCT02328014	I/II	≥ 18 years	B-cell malignancies	Acalabrutinib + ACP-319	Acalabrutinib (ACP-196): BTK inhibitor ACP-319: PI3K inhibitor	AEs
NCT02900716	I	≥ 18 years	CLL and B-cell lymphomas	DTRMWXHS-12 + everolimus or everolimus + pomalidomide	DTRMWXHS-12: BTK inhibitor	AEs
NCT02457598	I	≥ 18 years	B-cell malignancies	ONO/GS-4059 monotherapy, or + idelalisib, entospletinib, idelalisib + obinutuzumab, or entospletinib + obinutuzumab	ONO/GS-4059: BTK inhibitor	DLTs; OR
NCT02000934	I	≥ 18 years	Advanced solid tumor and lymphoma malignancies	TAK-659	TAK-659: SYK inhibitor	DLTs
NCT01799889[a]	II	≥ 18 years	R/R hematologic malignancies	Entospletinib	Entospletinib (GS-9973): SYK inhibitor	PFS
NCT01994382	I/II	≥ 18 years	CLL, SLL, or NHL	PRT062070 ± rituximab	PRT062070 (cerdulatinib): dual SYK-JAK inhibitor	MTD
NCT02684617	I	≥ 18 years	Hematologic malignancies	Dinaciclib + pembrolizumab	Dinaciclib (MK-7965): CDK inhibitor	DLTs; AEs; OR
NCT01003769	I/II	≥ 18 years	Relapsed B-cell CLL	Lenalidomide + AT-101	AT-101 (gossypol): BCL2 inhibitor	MTD; OR

Table 3. Selected Clinical Trials in CLL With Targeted Agents (cont.)

ClinicalTrials.gov identifier	Study phase	Age	Patient population	Intervention	Mechanism of experimental agent(s)	Primary outcome(s)
NCT02787369[a]	I	≥ 18 years	Relapsed CLL	ACY-1215 + ibrutinib or idelalisib	ACY-1215 (ricolinostat): HDAC inhibitor	MTD
NCT01943851	I	≥ 18 years	R/R hematologic malignancies	GSK525762	GSK525762: BET inhibitor	AEs; DLTs; OR
NCT02303392	I	≥ 18 years	R/R CLL or aggressive NHL	Ibrutinib + selinexor	Selinexor (KPT-330): selective inhibitor of nuclear export	DLTs

Note. CLL = chronic lymphocytic leukemia; R/R = relapsed or refractory; SLL = small lymphocytic lymphoma; FL = follicular lymphoma; PI3K = phosphatidylinositol 3-kinase; mBED = minimum biologically effective dose; MTD = maximum tolerated dose; DLTs = dose-limiting toxicities; PFS = progression-free survival; mAb = monoclonal antibody; OR = overall response; MCL = mantle cell lymphoma; AEs = adverse events; BTK = Bruton's tyrosine kinase; SYK = spleen tyrosine kinase; NHL = non-Hodgkin lymphoma; JAK = Janus kinase; CDK = cyclin-dependent kinase; HDAC = histone deacetylase; BET = bromodomain and extra-terminal. Information from ClinicalTrials.gov.

[a] Active trial, but not recruiting.

B-cell trafficking (Spaargaren et al., 2003). It is specifically inhibited by PCI32765 (ibrutinib) through BTK phosphorylation, leading to abrogation of its enzymatic activity. It also inhibits chemokine receptor–mediated signaling pathways and secretion of CCL3 and CCL4 chemokines (Ponader et al., 2012). This molecule has shown efficacy in both first- and second-line treatments of CLL, including for high-risk patients with 17p deletions as indicated previously (Burger et al., 2015; O'Brien et al., 2014b).

Idelalisib (CAL-101) is a potent and highly selective inhibitor of the delta isoform of PI3K, which plays a critical role in B-cell function medicated through BCR signaling. This drug also inhibits many other signaling pathways including CXCR4 and CXCR5, which are involved in the trafficking and homing of B cells to lymph nodes and the bone marrow. Inhibition of this isoform induces apoptosis and prevents proliferation of B-cell malignant cell lines (Brown et al., 2014). This drug demonstrated efficacy in mature randomized trials, including a phase III randomized trial that showed the efficacy of idelalisib when added to rituximab in the treatment of patients with relapsed CLL unable to undergo treatment with chemotherapy (Furman et al., 2014).

Moreover, numerous other targets, besides those involved in the BCR pathway, are being evaluated for their potential role in the management in CLL. Cyclin-dependent kinases (CDKs) regulate various steps in the cell cycle. Cyclin-dependent kinases are a family of protein kinases that regulate the cell-cycle through regulation of transcription, mRNA processing, and differentiation of cells (Crosby, 2007). Several different CDKs bind to various different cyclins to form cyclin-dependent kinases complexes (CDKCs), regulatory proteins that regulate progression through the cell cycle (Casimiro, Crosariol, Loro, Li, & Pestell, 2012). The inhibition of transcription by CDK7 and CDK9 is one potential target in CLL (Larochelle et al., 2012).

Dinaciclib is a CDK1, 2, 5, and 9 inhibitor currently being evaluated (NCT02684617; Danilov, 2013). A phase III study that compared dinaciclib with ofatumumab demonstrated the antitumor activity and tolerability of dinaciclib in refractory or relapsed CLL, with median survivals of 21.2 and 16.7 months, respectively (Ghia et al., 2015).

Targeting Bcl-2 is another option in the management of CLL, as it is associated with increased Bcl-2 expression (Rogalinska & Kilianska, 2012). Bcl-2 is localized in the outer membrane of the mitochondria and plays an important role in cell survival and inhibition of the action of proapoptotic proteins (Tsujimoto, 1998). The Bcl-2 family is made up of antiapoptotic proteins (Bcl-2, Bcl-x1) and proapoptotic proteins (Bax, Bak, and BH3), which are important for the regulation of apoptosis.

Venetoclax is a selective BCL2 inhibitor that has already been approved for the treatment of CLL (FDA, 2016). A phase I trial with venetoclax that enrolled patients with relapsed or refractory CLL and poor prognosis reached the maximum tolerated dose and revealed a response in 79% of patients (Roberts et al., 2016). Ongoing trials evaluating the optimal drug combination with venetoclax and treatment sequencing is being studied in CLL.

AT-101 is a BH3 mimetic with the ability to induce CLL cell apoptosis in vitro (Masood et al., 2011) and is currently being studied in combination with lenalidomide in patients with relapsed disease (NCT01003769). The BH3 mimetics are small-molecule antagonists of the antiapoptotic Bcl-2 members that function as competitive inhibitors by binding to the hydrophobic cleft and therefore abrogating cancer cell survival (Chonghaile & Letai, 2009).

Histone deacetylase (HDAC) inhibitors continue to be evaluated for their potential role as a therapy in cancer. Elevated levels of HDAC enzymes are linked with the development of cancer, including CLL (Wang et al., 2011). Inhibiting HDAC can hinder the heat shock protein 90 (Hsp90) protein chaperone system through hyperacetylation of Hsp90. This prevents protein degradation, which may eventually induce apoptosis of the CLL cell (NCI, 2017b). Ricolinostat (ACY-1215) is a HDAC inhibitor that is being studied in combination with ibrutinib or idelalisib in patients with relapsed CLL (NCT02787369).

The bromodomain and extraterminal (BET) family proteins are a new therapeutic target being evaluated in CLL that also impacts histones. The BET proteins are responsible for recognizing acetylated chromatin on the tails of histones and regulating gene expression (Larsson et al., 2013). By inhibiting BET, protein expression can be regulated and potentially halt cancer cell growth (Padmanabhan, Mathur, Manjula, & Tripathi, 2016). GSK525762 is a bromodomain-containing protein-4 (BRD4) inhibitor currently being evaluated in clinical trials (NCT01943851; Maxmen, 2012). Bromodomain-containing protein 3 (BRD3) and BRD4 are associated with the regulation of the proto-oncogene Myc, which plays a role in the development of CLL (Padmanabhan et al., 2016), and inhibiting this protein may lead to CLL cell death.

Selective inhibition of nuclear export (SINE) is another unique target for CLL therapy. Cancer cells are capable of exporting key nuclear proteins that impact survival and proliferation signaling. Chromosome region maintenance 1/exportin-1 (CRM1, XPO1) is an exporter of cargo-proteins such as p53, p73, CDKN1A, Rb, BRCA1, and IκBα, which are involved in cancer cell growth and apoptosis (Parikh, Cang, Sekhri, & Liu, 2014). High levels of CRM1 can increase the removal of tumor-suppressor genes from the nucleus and support cancer cell survival (Sun et al., 2014). Selinexor (KPT-330) is a SINE inhibitor, specifically CRM1, which is being evaluated in patients with relapsed or refractory CLL (NCT02303392).

CONCLUSION

We are certainly witnessing a burgeoning era in drug development with the rapid approval of many drugs targeting hematologic malignancies and specifically CLL. The treatment of CLL is a continually evolving area, with much excitement regarding the emerging therapies under investigation highlighted in this article. The improved understanding of disease biology and rigorous basic science research have allowed for continued progress and the development of novel targets in CLL.

The use of CAR T cells has shown promise in early clinical trials in CLL, but many questions remain regarding the optimal strategy for cell preparation and the ideal patient and time to implement this therapy, in addition to safety. Monoclonal antibodies with alterations to the binding structure and new antigen targets are being explored, as well as the use of bispecific mAbs and ADCs in CLL, which are very interesting modalities. The BCR pathway continues to be an area of growth for targeted therapies, with improvements being made to currently FDA-approved agents targeting this pathway. There is also progress in the area of targeted therapies to include other pathways such as the use of CDK, PI3K, and BCL2 inhibitors. Novel therapies continue to emerge from the pipeline, altering the treatment landscape and improving patient outcomes in the management of this disease. ●

Disclosure

The authors have no potential conflicts of interest to disclose.

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