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Chronic Lymphocytic Leukemia: Exploiting Vulnerabilities with Targeted Agents

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Abstract

The field of oncology has been transformed over the course of the last 20 years in large part due to the enhanced understanding of cellular biology and cellular signaling. The indolent natural history of chronic lymphocytic leukemia (CLL) has permitted extensive study of cancer biology and can in some ways be thought of a model for understanding and translating concepts to other diseases. By systematically probing the biology of CLL cells and working out in stepwise fashion the transduction of signals from the surface immunoglobulin to nuclear transcription factors, investigators have paved the way for rational targeting of therapies at natural vulnerabilities that mimic oncogene addiction. These key targets include Bruton's tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K), Src, Bcl2, and cyclin-dependent kinases (CDKs). In this review, we will consider these proteins and describe the current and future molecules designed to target them in CLL.

Keywords

Chronic lymphocytic leukemia; Targeted therapy; Novel therapy; Ibrutinib; ACP-196; Idelalisib

Introduction

Chronic lymphocytic leukemia (CLL) is a usually indolent lymphoid malignancy and is the most prevalent leukemia in the western world [1]. There are estimates that >14,000 cases are likely to be diagnosed in the year 2015, and close to a 1/3 of that number will perish from their disease in the same year [1]. The incidence of CLL has not changed significantly over

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the last 10 years, although the 5-year survival has climbed from ~60 % in the 1980s to ~80 % in the present day [1]. Nevertheless, there is an aging population worldwide and, given a median age of diagnosis of 71 [1], continued investigation into how to manage this disease as it progresses remains an important goal. In concert with these emerging management strategies, the goal of minimizing the untoward effects of new interventions relative to standard cytotoxic chemotherapy should be paramount.

Although chemotherapy with alkylating agents and purine analogs remains the most common intervention for most cases of CLL in the frontline setting, the prolonged T cell dysfunction and potentially high-grade neutropenia caused by these agents in a population who on average have a median of two comorbidities [2] at diagnosis are not normally acceptable. Augmenting chemotherapy with antibody therapy has offered dramatic improvements to survival with less long-term toxicity. The mechanisms of these antibody therapies continue to be further understood and refined. Parallel to this, understanding of intracellular signaling has ushered in an era of novel targeted small molecule therapeutics.

Among all cancers, CLL has enjoyed some of the most durable responses yet seen in this era of novel small molecule treatments. This is likely a result of its often-indolent course that permits multiple opportunities for innovative management approaches in the same patient. Knowledge gained from management of CLL has been applied to other lymphoid malignancies and to the general oncology arena as well.

In the present article, we will describe some mechanisms of CLL cell survival by way of the molecularly targeted therapeutic agents being used to exploit them. We will discuss emerging strategies currently under investigation. Finally, we will speculate about future potential targets (Table 1).

Monoclonal Antibodies

Monoclonal antibodies (MoAbs) directed against CD20, with or without chemotherapy, are a mainstay of currently approved treatment for CLL. CD20 is a defining surface molecule of pre-, naïve, and mature B cells (disappearing at the plasma cell transition) and is required for mediating cellular activation [3]. Although the CD20 concentration on CLL cells is “dim” compared to other B cell neoplasms, the improved outcomes seen with CD20 MoAbs in these diseases have been enjoyed in CLL as well. Agents approved in CLL include rituximab, ofatumumab, and obinutuzumab, with rituximab dominating routine clinical practice through 2015—albeit obinutuzumab is the agent of choice in most new trials including a CD20 MoAb. The actual anti-tumor effects are multifactorial but include primarily antibody-dependent cell cytotoxicity (ADCC) among others [4]. Other MoAbs including alternative targets (e.g., CD37) and constructions (e.g., bispecific T cell engagers and immunotoxin conjugates) are currently in development. Immunotherapy options including anti-CD20 MoAbs are reviewed extensively elsewhere in this issue.

The B Cell Receptor

The B cell receptor (BCR) molecular complex is a defining characteristic of the mature B cell and as such is present on CLL cells. The complex itself is composed of membrane

bound IgM linked to other transmembrane proteins including CD79 [5]. Activation of this complex promotes multiple signaling pathways within the cell, many of which have been found to be clinically relevant in CLL. This cascade has been well described in the context of CLL in a recent review article by Woyach et al. [6].

After antigen binding of the extracellular IgM component, the cytoplasmic portion of the co-stimulating CD79 molecule is phosphorylated by Src family tyrosine kinases Lyn and spleen tyrosine kinase (Syk) [7] which subsequently recruit adaptor proteins for further amplification of the signal. It is worth noting here that some CLL patients' clonal cell population have immunoglobulin molecules that have not undergone somatic hypermutation ("*IGHV* mutated"), a maturation step which normally takes place within the germinal center [8]. The prognostic significance of *IGHV* mutation status in a CLL patient is relevant at this stage of BCR signaling as unmutated patients have higher baseline levels of BCR signaling, due to one or both of (1) a more reactive surface immunoglobulin and (2) overexpression of a tyrosine kinase called ZAP-70 [9], a protein which has been shown to enhance downstream phosphorylation and improve viability in comparison to *IGHV* mutated CLL cells [10]. Thus, measurement of ZAP-70 overexpression has been used as surrogate for *IGHV* unmutated status in CLL patients and is associated with poor survival [11].

As noted, the Src family kinases are adaptor proteins which are responsible for further downstream signaling. Specifically, Syk is responsible for dual phosphorylation of CD79a/CD79b [12] and Lyn provides continued amplification of the BCR through recruitment of other tyrosine kinases to assist formation of the BCR/CD19 molecular complex [13]. Lyn and Syk have been shown to be upregulated in CLL cells with higher levels of Lyn being associated with shorter treatment-free survival [14].

At this stage, there are intertwined and diverging pathways that function to complete the activation of the BCR and stimulate cell growth and survival. One of these is the phosphatidylinositol 3-kinase (PI3K) pathway; PI3K is a family of ubiquitous effector proteins with relevance in a wide variety of cancers, and the PI3K-δ form is especially relevant in lymphoid malignancies including CLL [15]. In B cells, PI3K-δ signals through a variety of pathways, including AKT/mTOR, and is responsible for activation of the costimulatory molecule CD19. This activation is one step preceding the critical activation of Bruton's tyrosine kinase (BTK) [16], a branch-point in signaling and another key pathway in CLL cells. BTK itself is critical to influx of calcium [17, 18], a necessary cofactor for the downstream effector protein kinase C, one phosphorylation step removed from NF-κB nuclear transcription factor activation [19]. NF-κB target genes, including anti-apoptotic genes [20, 21], are overexpressed in CLL and associated with disease progression [22]. BTK signaling is also effected through the MAP kinase pathway and activation of these target genes. Thus, although at the initial stages of BCR engagement and activation PI3K and BTK act as partners, they each have distinct downstream transcription factor pathways and thus each represents a unique targetable opportunity in CLL.

BTK Inhibition

Ibrutinib (PCI-32765)—Ibrutinib is a first in class irreversible inhibitor of BTK [23] that acts by covalent binding to the cysteine 481 residue of this protein [24] and subsequently

inhibiting phosphorylation. Pre-clinical work in John Byrd's laboratory at Ohio State identified caspase-dependent apoptosis as a result of this BTK inhibition [25]. Jan Burger's group at MD Anderson further showed ibrutinib could abrogate CLL migration through blocking secretion of CLL cell-derived chemokines and slow disease progression in an animal model [26]. Pivotal phase Ib/ II data with this agent in relapsed/refractory CLL patients demonstrated an overall response rate (ORR) of 71 % and 26-month progression-free survival (PFS) of 75 % that was independent of clinical and genomic risk factors (such as 17p deletion) present before treatment [27•]. This study included a subgroup of elderly treatment-naïve CLL patients who achieved an ORR of 71 % leading to consideration of this agent being used in the first-line setting [27•]. Subsequent phase III monotherapy data of single agent ibrutinib vs. chlorambucil confirmed this agent had a well-tolerated side effect profile and established that 420 mg daily provided >90 % occupancy of the BTK protein (similar to the 840 dose); 420 mg daily was thus established as the FDA-approved dose.

Since its approval in 2014, ibrutinib, more than any other single therapy, has transformed the current management and treatment of CLL. Follow-up studies in other populations and in direct head-to-head comparisons confirm this remarkable activity. In the phase III RESONATE trial, ibrutinib monotherapy had an 18-month OS rate of 85 % compared to single agent ofatumumab at 78 %, as well as an ORR of 90 % in the ibrutinib group vs. 25 % in the ofatumumab group [28•]. Further, phase II data of only high-risk CLL/SLL patients with 17p deletion cytogenetics revealed a ORR of 82.6 % and a 12-month PFS rate of 79 % [29]. In response to unprecedented efficacy in a group with poor outcomes after conventional immunochemotherapy, ibrutinib is now FDA approved in the front-line setting for patients with 17p deletion.

Ibrutinib is also being tested in combined therapy approaches. Phase II data with ibrutinib in combination with rituximab demonstrated an 87 % PR, 8 % CR, and an ORR of 95 %. The ORR in the 20 patients with del17p or *TP53* mutation was 90 % [30]. This study interestingly also demonstrated a shortened duration of redistribution lymphocytosis often seen in high-risk patients when given ibrutinib monotherapy [30].

The response rates and PFS noted above, specifically in this high-risk population, were not seen prior to the molecularly targeted era. In CLL, ibrutinib leads the way with regard to understanding molecular targeted therapy intervention, limitations, and improvements. Unfortunately, some patients become resistant while on ibrutinib due to acquisition of mutations in the *BTK* gene or *PLCG2*, its immediate downstream effector. The *BTK* mutation is invariably at C481; this mutation results in ibrutinib binding reversibly as opposed to its normal irreversible binding [31•], with the expected diminution of its inhibitor effects. Molecules are being developed to overcome this barrier, akin to ponatinib and T315I mutation in chronic myelogenous leukemia. Additionally, Dubovsky et al. have shown that ibrutinib actually antagonizes rituximab-dependent NK cell-mediated cytotoxicity (ADCC) [32] through inhibition of interleukin-2 inducible T cell kinase (ITK). These considerations have not been fully assessed in the clinic but their implications for combination therapy and need for next-generation BTK inhibitors have been heard, and there are now second-generation BTK inhibitors available.

ACP-196—ACP-196 is to date the most clinically studied second-generation BTK inhibitor. It differs from ibrutinib chiefly in its selectivity of binding: whereas ibrutinib can bind to cysteine residues on related proteins like ITK but also to more distantly related proteins like epidermal growth factor receptor (EGFR), ACP-196 demonstrates marked selectivity for BTK when incubated in vitro with a panel of kinases. Increased selectivity for BTK is clinically relevant in the context of therapeutic combinations, as it has been demonstrated that ibrutinib's on-target ITK inhibition in T and NK cells may impair ADCC. As a result, we may see deeper and longer responses when a MoAb is combined with ACP-196 compared to ibrutinib. In terms of side effect profile, the diarrhea and rash of ibrutinib may be a result of EGFR inhibition; as predicted, this has not been a major toxicity with ACP-196. Finally, ACP-196 at 200 mg QD demonstrated 94 % BTK target occupancy after 7 days [27•], a slight improvement over ibrutinib with potential implications in the prevention of nodal relapses. Confirming expectations of ACP-196's clinical potential, a recently published phase I–II trial using this agent as monotherapy in heavily pre-treated CLL patients reported no dose-limiting toxicity during dose escalation nor any grade 3–4 toxicity rate >7 % during extended drug administration. Most notable was the response rate of 95 % for all comers and 100 % in patients with the adverse risk 17p deletion [33].

Other BTK Inhibitors—Apart from ibrutinib and ACP-196, other BTK inhibitors in preclinical or clinical development include BGB-3111, CC-292, and ONO-4059. Like ACP-196, BGB-3111 was developed as a highly selective inhibitor permitting strong on-target inhibition with less toxicity. A phase I study of BGB-3111 reported at the American Society of Hematology 2015 annual meeting [34] reached the recommended phase II dose endpoint pharmacodynamically with no dose-limiting toxicities reported. Building on the successes seen with ibrutinib, second-generation BTK inhibitors may provide deeper and even longer lasting responses, alone or in combination.

PI3K Inhibition

Idelalisib (GS-1101; Formerly CAL-101)—Idelalisib is an orally bioavailable selective competitive inhibitor of PI3K-δ [35]. Initial phase II data of idelalisib as monotherapy in patients with relapsed or refractory CLL revealed 81 % of patients having ≥50 % decrease in lymph node and spleen size as well as a median PFS of 17 months [36]. The principal toxicities of idelalisib are autoimmune in nature: inflammatory colitis (8 %) and pneumonitis (5 %) [37]. These can be severe and potentially life-threatening and often preclude further therapy with this agent. Transaminitis is an additional concern. Apart from these, idelalisib's side effect profile is relatively mild.

In addition to single agent studies, idelalisib has been the subject of multiple combination trials. Phase III data of idelalisib + rituximab revealed improved ORR, PFS, and overall survival in patients with relapsed CLL who were unfit for chemotherapy regardless of high-risk genetic abnormalities [38•]—a trial which led to its FDA approval for this population. Notably, the FDA-approved labeling stipulates for "the treatment of patients with relapsed CLL, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities."

Unique combined immunotherapy/molecular therapy strategies are being employed with these agents' effect in high-risk CLL populations. For example, CD37-mediated signaling was shown to result in direct cytotoxicity that was further enhanced by idelalisib [39]. Stemming from this data, idelalisib plus an anti-CD37 monoclonal antibody has been shown in CLL cell lines to enhance pro-apoptotic activity [40], and there is an ongoing phase Ib trial utilizing TRU-016 in combination with idelalisib (https://clinicaltrials.gov/ct2/show/NCT01644253). In vitro data using a combination of idelalisib and GS-9973 (targeting Syk) have shown synergistic decreases in viability of bone marrow CLL cells which are known to be more resistant to cytotoxic chemotherapy [41]. This is encouraging considering the elimination of minimal residual disease is difficult.

Agents with even more selective PI3K-δ activity in vitro, including AMG-319 [42] and TGR-1202, are currently being investigated. It remains to be seen whether selectivity will temper the side effect profile as with BTK inhibitors.

Duvelisib (IPI-145)—Duvelisib inhibits both lymphocyte-specific isoforms of PI3K (p110-δ and p110-γ), whereas idelalisib only inhibits the δ isoform. Phase I data with this drug in both untreated and relapsed/refractory CLL patients showed clinical activity at all doses studied as well as activity in high-risk CLL patients. There was 98 % nodal response, ORR of 47 % (50 % in relapsed refractory disease), and relatively well-tolerated side effect profile [43].

Importantly, Dong et al. provided preclinical data that duvelisib has the ability to inhibit survival of CLL cells possessing the clinically important BTK p.C481S mutation [44] noted above to be problematic in some patients previously/currently treated with ibrutinib. Thus, duvelisib is currently being investigated as alternative for patients who have progressed on ibrutinib therapy.

SAR245408 (XL147)—Although as demonstrated delta and gamma isoform-specific inhibition has clinical benefit, other compounds that additionally target alpha and/or beta isoforms of PI3 kinase hold interest because of their potential ability to modulate the tumor microenvironment as well as limit compensatory upregulation of PI3K-alpha in the face of delta inhibition. One such agent is SAR245408, a potent and selective inhibitor of the alpha, gamma, and delta PI3K isoforms. Although it has shown clinical activity in relapsed/refractory CLL with PFS range between 15 and 22 months, most interestingly, it has led to a reduction in levels of chemokines involved in lymphocyte trafficking and a reduction of TNFR2 and IL-2Rα levels. The toxicity profile of this agent is limiting at this point with 100 % of the CLL patients undergoing grade 3 or 4 toxicities [45]. Other multi-PI3K inhibitors such as GS-9820 (a beta/delta inhibitor) and buparlisib (BKM-120) are being investigated in CLL as well in attempt to more completely understand and mitigate the upregulation of alternate PI3k isoforms. [http://clinicaltrials.gov (NCT02340780)].

Syk Inhibition

R406 and Fostamatinib (R788)—R406 is a competitive reversible Syk inhibitor for which in vitro data have demonstrated inhibition of *all* downstream kinases in BCR signaling [46]. Fostamatinib is an orally available prodrug of R406 with studies confirming

R406's downstream effects [47] and additionally demonstrating decreased levels of BCR, NF-κB, and MYC target gene transcripts in primary CLL tumor samples [48]. These effects interestingly seem to be isolated to malignant B cells: when given to *TCL1* transgenic mice, the leukemic cells underwent apoptosis while normal B cell development continued unimpeded [49].

The most recently published phase II data with fostamatinib demonstrated an ORR of 55 % and a PFS of 6.4 months [50]. This agent was well tolerated with minimal rare grade 3/4 toxicities [50], although it does demonstrate secondary (redistribution) lymphocytosis after starting therapy [50], suggesting that this phenomenon is a class effect of BCR inhibitors. Fostamatinib is now being considered for combination trials [41].

Entospletinib (GS-9973)—Entospletinib is another oral selective Syk inhibitor currently under investigation in CLL. Phase 2 data with this agent as monotherapy has demonstrated safety and an ORR of 61 % and estimated PFS at 24 weeks of 70 %. In the same study, all of the patients with a known 17p chromosomal deletion had a clinical response [51•]. Like fostamatinib, although trials will continue to confirm its monotherapy efficacy, it is primarily being considered in a dual targeted therapy approach.

Dasatinib—Dasatinib is a reversible pan-Src kinase inhibitor currently used primarily for chronic myelogenous leukemia but has been shown to inhibit BTK [52] and Syk [53] as well as prevent CD40-mediated anti-apoptotic changes in CLL [54]. Thus, a phase 2 trial was completed in patients with relapsed or refractory CLL which revealed partial responses in 20 % of patients. However, myelosuppression limited its use [53]. Nonetheless, there are at least two phase 2 trials being conducted with this agent in CLL currently registered at http://clinicaltrials.gov (NCT01441882; NCT01051115).

Cell Cycle Regulation

Eukaryotic cells are reliant on the cyclins and their complementary cyclin-dependent kinase proteins for progression through the cell cycle. Overexpression of cyclin D2 mRNA has been described in CLL cells [55], and activation of the BCR complex as described above has also been shown to increase cyclin D2 in murine B cells [56]. The expression of cyclin D1 was significantly stronger in the ZAP-70+ CLL cases leading to speculation that cyclin-D is a link between the BCR signaling in ZAP-70+ CLL and the cell cycle [9, 57].

Maintenance of the quiescent state by anti-apoptotic factors is a key part of CLL's escape from normal cell cycle. Mediating this, some Bcl-2 family of anti-apoptotic proteins are overexpressed in CLL [58, 59]. Pharmacologic disruption of these Bcl-2 family proteins could then render CLL cells again subject to programmed cell death.

Bcl2 Family Inhibition

Venetoclax (ABT-199; Formerly GDC-0199)—Although the anti-apoptotic Bcl-2 family of proteins has had a recognized role in malignant B cell survival for many years and represents a natural target, early attempts at Bcl-2 inhibition were met with frustration, the primary limitation being severe thrombocytopenia resulting from inhibition of Bcl-XL [60,

61]. Venetoclax was designed to spare Bcl-XL and is specific for the Bcl-2 protein thus avoiding this toxicity. Pre-clinically, ABT-199 demonstrated induction of apoptosis through activation of the mitochondrial pathway [62] in Bcl-2 reliant primary CLL samples. Additionally, tumor regression was achieved with ABT-199 as a single agent and in combination across four mouse xenograft models [63]. This agent is now garnering much interest as results from a phase 1b trial presented in June of 2015 EHA summit in which venetoclax was given with monthly rituximab infusions revealed an 84 % ORR with 41 % achieving a CR [64]. Phase 2 data from a trial on this same dosing schedule will likely be presented later in 2015. Venetoclax is being explored alone and in combination, including in patients resistant to ibrutinib, and overall represents a very exciting prospect for registration.

CDK Inhibitors

Alvocidib (Flavopiridol; Formerly HMR-1275)—Alvocidib (better known as flavopiridol) is a prototypical CDK inhibitor and among the earliest explored in CLL or other cancers. Intriguingly, despite CLL being relatively non-proliferative, flavopiridol was found to be very effective in CLL—largely a result of decreased transcription of anti-apoptotic Bcl-2 family proteins [65] rather than just regulation of CDK/cyclin control of cell cycle. Initial clinical trials of various flavopiridol regimens in CLL were disappointing, but the most notable results of these studies were its limiting side effect of hyper-acute tumor lysis (TLS) [66, 67]. Once safeguards against TLS were in place and the dosing strategy was revised to account for enhanced binding to human proteins [68], more successful outcomes were ultimately recorded with a pharmacokinetically designed schedule in a phase II trial of refractory and genetically high-risk CLL patients [69]. Importantly, response and PFS outcomes were non-inferior in high-risk disease subgroups.

Dinaciclib (SCH727965)—Dinaciclib is a more selective CDK inhibitor than alvocidib [70] with a therapeutic index more than ten times flavopiridol's in mice [71]. In vitro data have been encouraging regardless of CLL risk cytogenetics [72•]. Phase I data showed an ORR of 58 % including those with higher risk cytogenetic profiles as well as a median PFS of 1.3 years [73]. Phase I/II data from Ohio State (NCT01515176) and phase III data from an international study conducted by Merck (NCT01580228) are all expected to be published in 2016.

Other CDK Inhibitors: TG-02 and Palbociclib (PD-0332991)—Other CDK inhibitors in clinical development include TG-02 and palbociclib, both oral agents that differ in their spectra of specific CDKs inhibited. TG-02 is currently being studied in CLL, while palbociclib has the distinction of being the first FDA-approved CDK inhibitor for any disease. Although approved in breast cancer, preclinical work shows palbociclib may be effective in the related cancer mantle cell lymphoma (MCL) and should be explored in CLL.

Future Directions and Potential Targets

ZAP-70 Inhibition

ZAP-70 overexpression in CLL cells enhances the BCR pathway [47, 74] and is a partial surrogate marker for *IGHV* mutational status. Preclinical data have demonstrated that the

EGFR inhibitor gefitinib induces apoptosis in ZAP-70 expressing CLL cells both when unstimulated and when the BCR complex is activated. Further, forced overexpression of ZAP-70 led to increased sensitivity to gefitinib-induced apoptosis [75]. The understanding of this mechanism is still in its infancy but holds much promise in terms of synthetic lethality and overcoming resistance in a parallel pathway component. Lead compounds for ZAP-70 inhibition are currently being generated.

Proteasome Inhibition

The proteasome mediates degradation of regulatory proteins of the p53, Bcl-2 [76] NF-κB [77], and cell cycle pathways; inhibition leads to build-up of protein substrates and apoptosis [78, 79]. Proteasome inhibition is an important strategy in the related diseases MCL and multiple myeloma but has failed thus far to translate to CLL. Despite promising preclinical data in which the second-generation proteasome inhibitor carfilzomib was shown to induce apoptosis of CLL cells (including those with 17p deletion) [80], phase I monotherapy data with carfilzomib revealed minimal clinical efficacy [81]. Recent combination drug screens revealed that carfilzomib's apoptotic effects may be enhanced in the presence of ibrutinib, displaying even more Annexin V/propidium iodide positivity than even ibrutinib plus venetoclax [82]. Carfilzomib may yet be employed in CLL but in rational combinations rather than as a single agent.

NOTCH1 Inhibition

Although not commonly considered in the early B cell lineage of lymphocyte differentiation, *NOTCH1* has been shown to promote terminal differentiation to antibody-secreting B cells [83]. Investigations have revealed *NOTCH1* mutations clustering in untreated CLL patients with trisomy 12; most of these cases possess an unmutated *IGHV* gene status and no other cytogenetic abnormalities [84, 85]. The consequences of this mutation are an accumulation of an active *NOTCH1* isoform sustaining deregulated signaling [86] leading to further NF-κB activation [87]. *NOTCH1* mutations have additionally been found in chemorefractory patients and importantly in those patients who have progressed to Richter's syndrome [88•]. Preclinical data demonstrate that inhibition of *NOTCH1* signaling with the γ-secretase inhibitor (GSI) PF-03084014 can trigger apoptosis [89], but overall this is an area that is not fully explored, in part due to clinical experience with GSIs for other diseases in which severe treatment-limiting gastrointestinal toxicities are seen. Given the critical role NOTCH signaling may play in proliferative centers and perhaps in transformation to Richter's syndrome wherein outcomes are universally poor, investigators will continue to pursue NOTCH inhibition in CLL.

Conclusions

The age of small molecule treatments for malignancy has ushered in new hope for patients who previously would not be considered candidates for therapy as well as the possibility of effective intervention without the need for chemotherapy. These agents alone and in combination with immunotherapy and cellular therapy will we believe replace our historical standards and improve outcomes in all patients, fit and unfit alike. The natural history of CLL affords researchers, clinicians, and patients many time points for risk stratification,

assessment of disease progression, and interventions, which will continue to translate into better more durable outcomes as well as understanding of treatment strategies for this disease, other hematologic malignancies, and solid tumors as well. Today, the most effective molecular targets are BTK, PI3K, and Bcl-2 family proteins as they are all positioned in critical points of cell signaling and sustenance. That there are already multiple FDA-approved orally administered agents targeting these vulnerabilities indicates that the field of oncology has undoubtedly entered a new age of understanding and intervention in CLL and there will be no turning back.

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Table 1

Non-chemotherapy agents recently under investigation in CLL discussed in this review paper are listed alongside their target and FDA status at the time of authorship

Drug class	Drug target	Drug/intervention	Status
Immunotherapy	CD20	Rituximab	FDA-approved
		Ofatumumab	FDA-approved
		Obinutuzumab	FDA-approved
	CD19	CAR-T cells	Investigational
		Blinatumomab	Investigational
	CD37	TRU-016	Investigational
Small molecule inhibitor	Syk	Fostamatinib (R788, R406)	Investigational
		Entosplentinib (GS-9973)	Investigational
	Src	Dasatinib	Approved but not in CLL
	PI3-kinase	Idelalisib (GS-1101, CAL-101)	FDA-approved
		Duvelisib (IPI-145)	Investigational
		SAR245408 (XL147)	Investigational
		Buparlisib (BKM-120)	Investigational
		GS-9820	Investigational
		AMG-319	Investigational
	BTK	Ibrutinib	FDA-approved
		ACP-196	Investigational
		BGB-3111	Investigational
	Cyclin-dependent kinase inhibitors	Alvocidib (flavopiridol)	Investigational
		Dinaciclib	Investigational
		TG-02	Investigational
		Palbociclib (PD-0332991)	Approved but not in CLL
	Bcl-2	Venetoclax (ABT-199)	FDA breakthrough
	ZAP-70	–	Compound development
	Proteasome inhibition	Carfilzomib	Approved but not in CLL
	NOTCH1	–	Investigational

–“various” or “unspecified compounds”