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Targeted Therapy in Chronic Lymphocytic Leukemia

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Abstract

Despite a prevailing view that advances in cancer therapy will come through selective targeting of enzymes encoded by mutated oncogenes responsible for the neoplastic phenotype, recent advances in the treatment of patients with chronic lymphocytic leukemia (cLL) have instead exploited knowledge of its biology. indeed, cLL cells depend on interactions with cells and soluble factors present in the tumor microenvironment for proliferation and survival. B-cell receptor signaling and chemokine-receptor signaling play prominent roles. Elucidation of these signaling pathways has defined physiologic targets for drugs, such as ibrutinib, which inhibit Bruton tyrosine kinase and are therapeutically effective. The characteristic high-level expression of BCL2 in CLL that can enhance leukemia-cell survival has now become an Achilles heel targeted by clinically effective drugs such as venetoclax. Here we discuss advances in such targeted therapy and highlight other disease attributes, such as the distinctive expression of ROR1, which may be targeted for clinical benefit, alone or in combination with other targeted therapies.

Keywords

B-cell receptor signaling antagonists; BCL2 antagonist; cirmtuzumab; CLL; ibrutinib; leukemia microenvironment; ROR1; targeted therapy; venetoclax

Although chemotherapy[1–3] and, more recently chemoimmunotherapy[4–6] have been the mainstay for therapy of patients with chronic lymphocytic leukemia (CLL), the advent of targeted therapy has improved clinical outcomes and changed clinical practice. Such targeted therapies exploit our knowledge of the biology of CLL, which in some respects is a fastidious malignancy highly dependent on survival and growth factors elaborated by the leukemia microenvironment. Studies on such interactions have identified numerous targets for therapy (Fig. 1). Chronic lymphocytic leukemia cells also express distinctively high levels of BCL2, an antiapoptotic protein that plays an integral role in leukemia-cell survival. Targeting this protein also has proven to be highly effective in the treatment of patients with this disease.

The CLL Microenvironment

Chronic lymphocytic leukemia cells depend on interactions with cells and soluble factors present in the tumor microenvironment for proliferation and survival (Fig. 1).[7] The

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migration of CLL cells into the lymphoid tissue primarily is mediated through CXCR4 in response to CXCL12,[8] which is secreted mainly by nurse-like cells (NLCs, otherwise called lymphoma-associated macrophages) and mesenchymal-derived stromal cells.[9,10] Chronic lymphocytic leukemia cells also are attracted to lymph nodes via CCR7 in response to the chemokines CCL19 and CCL21, which are produced by high endothelial venules.[11,12] The basement membranes of high endothelial venules also express hyaluronan, which can interact with CD44, a signaling glycosaminoglycan expressed by CLL cells that can recruit membrane-associated receptor-tyrosine kinases or their substrates and thereby facilitate cell signaling.[13,14] It also might enhance the production of active matrix metallopeptidase 9.[15,16] Once in tissues, CLL cells can derive survival support from the same chemokines, as well as from additional factors elaborated by accessory cells in the CLL microenvironment. For example, CLL cells come in contact with NLCs that can promote CLL-cell survival through the production of CXCL12. Nurse-like cells also express BAFF (B *cell–activating factor of the TNF family)* and APRIL *(a proliferation-inducing ligand)*,[17] which can complement the survival stimulus afforded by CXCL12.[9] Nurse-like cell–CLL interactions also can promote CLL-cell survival through cognate interactions between CD31 and CD38, which are expressed on NLC and CLL cells, respectively.[18,19] In turn, CLL cells may secrete chemokines, such as CCL3 and CCL4,[20] which can recruit T cells and NLC-precursor cells (monocytes) to the CLL microenvironment. T cells in that microenvironment might become activated and provide CLL cells with proliferative signals through CD154-CD40 interactions, as well as through the secretion of multiple cytokines, such as interleukin 2 (IL-2), IL-4, IL-10, and IL-21.[21] In return, activated CLL cells secrete CCL3, CCL4, and CCL22, chemokines that can attract more $CD4^+$ T cells into the CLL microenvironment. Stromal cells also can contribute to CLL-cell survival via the secretion of CXCL12 and CXCL13[21] and. like NLCs, also via the production of various Wnt factors, including Wnt5a (wingless-type MMTV integration site family, member 5a),[22] which can interact with ROR1 (receptor tyrosine kinase-like orphan receptor 1) expressed by CLL cells.[23] Chronic lymphocytic leukemia-mesenchymal-derived stromal cells contact also can be established through vascular cell adhesion protein 1–CD49d interactions that contribute to CLL-cell survival.[24] In tissues, CLL cells can be exposed to environmental and/or self-antigens that trigger cell activation through interactions with the surface immunoglobulin (sIg) expressed by CLL cells.[25] Stimulation from ligation of sIg with antigen can amplify the responsiveness of CLL cells to the signals and factors provided by the CLL microenvironment.

Inhibitors of B-Cell Receptor and Chemokine-Receptor Signaling

Drugs that interfere with B-cell receptor (BCR) signaling have clinical activity in the treatment of patients with CLL. Drugs such as ibrutinib and idelalisib target intracellular kinases that are activated in response to ligation of sIg and thereby catalyze the cascade of intracellular events leading to B-cell stimulation (Fig. 2). The kinases targeted by these drugs also are involved in chemokine-receptor signaling.[26–28] As such, use of these agents impairs the capacity of leukemia cells to recirculate between the blood and the protective microenvironmental niches present in lymphoid tissue. Because of this, treatment of CLL patients with these drugs generally results in rapid shrinkage of the lymph nodes and concomitant enhanced lymphocytosis, which abates over time as the circulating leukemia

cells gradually succumb to depravation from the survival signals afforded by the lymphoid-tissue microenvironment (Fig. 1).

Ibrutinib and Second-Generation "Brutinibs" That Inhibit Bruton Tyrosine Kinase

Clinical trials have demonstrated that continuous ibrutinib therapy provides for progression-free survival (PFS) that is superior to that of chemotherapy-based regimens. Such trials also have shown improvements in overall survival and/or outcome for patients who were treated with ibrutinib compared with matched patients who were treated with anti-CD20 antibodies,[29,30] chemotherapy,[31] or chemoimmunotherapy.[32,33] The improvement in survival is particularly apparent for patients who have CLL cells with del(17p), and/or inactivating mutations in *TP53*, which mitigate the efficacy of chemotherapy.[34] A phase III trial showed that treatment-naive fit patients who were able to tolerate more intensive chemoimmunotherapy had an improved median PFS when treated with ibrutinib and rituximab rather than fludarabine, cyclophosphamide, and rituximab,[35] long considered one of the most effective treatment regimens.[36] Similarly, treatment-naive patients 65 years or older had a superior median PFS when treated with ibrutinib than with bendamustine and rituximab (BR).[37] Patients treated with ibrutinib and rituximab in another arm of this same trial did not have a significant improvement in outcome,[37] making it difficult to justify using anti-CD20 monoclonal antibodies (mAbs) in combination with ibrutinib.[38] In view of the demonstrated clinical effectiveness of ibrutinib, the National Comprehensive Cancer Network committee on CLL/SLL has recommended primary consideration of single-agent ibrutinib as initial therapy for patients with CLL.[38]

Despite having excellent clinical activity, ibrutinib generally cannot eradicate the disease or induce durable responses in the absence of continuous therapy.[39,40] Prognosis may be poor for patients with aggressive disease who discontinue ibrutinib soon after initiation of therapy, owing to the potential for rapid disease progression upon cessation of therapy. Moreover, the proportion of patients who achieve a complete response (CR) to ibrutinib appears consistently below 7%.[29,41–44] As such, it generally is not recommended to discontinue therapy with ibrutinib unless there is demonstrated intolerance or resistance to therapy.

The need for continuous therapy is problematic for patients who experience even mild adverse effects with ibrutinib, such as diarrhea, onychoschizia, myalgias, arthralgias, hypertension, or increased bruising due to drug-induced impairment in platelet function.[45] The costs of continuous therapy also may poise a financial burden.[46] Some patients may note improvement in drug-related symptoms over time with continued therapy, especially if they have resolution of lymphadenopathy and lymphocytosis. However, the incidence of other adverse effects, such as drug-related hypertension or atrial fibrillation, may increase over time on therapy. Also, despite noted improvement in some immunologic parameters with therapy,[47] there are numerous reports of serious opportunistic infections occurring in patients on protracted ibrutinib therapy.[48–54]

Even with continuous therapy, remissions are not durable for all patients, particularly those with relapsed disease who have CLL cells with del(17p) and/or complex cytogenetics, for whom the estimated 30-month PFS on therapy is approximately 60%.[55] Furthermore, the proportion of patients wanting or electing to discontinue therapy with these agents appears higher in community practice than reported in clinical trials,[56,57] possibly due to the intolerance of patients facing lifelong therapy with even low-grade toxicity and/or the costs of therapy. In addition, even with continuous therapy, patients can develop drug resistance due to acquired mutations in genes encoding proteins involved in BCR signaling[58] or Richter transformation.[59,60]

Second-generation small molecule inhibitors of Bruton tyrosine kinase (BTK) share with ibrutinib the same root designation "brutinib." Among these are acalabrutinib,[61] ONO/GS-4059,[62] zanubrutinib (BGB-3111),[63] SNS-062,[64] and others. Each is touted to have a potentially higher therapeutic index than ibrutinib due to greater specificity for BTK and/or different mechanisms of action, potentially resulting in fewer "off-target" effects. Moreover, some of the drugs do not require covalent bonding with BTK and thus may be effective in patients who develop resistance to ibrutinib because of an acquired mutation in BTK, causing a C→S substitution at position 418 (BTK^{C481S}), which precludes the covalent bonding of ibrutinib to BTK.[58] Nonetheless, it does not appear that any one of the second-generation "brutinibs" will obviate continuous maintenance therapy.[64,65]

Idelalisib and Second-Generation "Lisibs" That Inhibit PI3K

Drugs that target BCR signaling by inhibiting the delta isoform of phosphoinositide 3 kinase (PI3Kδ) also have clinical activity (Fig. 2). As PI3Kδ also plays a critical role in chemokine-receptor signaling,[66] treatment with drugs that inhibit PI3Kδ also can cause early and dramatic reduction in lymph node size and concomitant enhanced lymphocytosis, which can be mitigated when used in combination with rituximab.

Idelalisib was the first to receive US Food and Drug Administration (FDA) approval for treatment of patients with CLL in combination with the anti-CD20 mAb, rituximab. This was based on the demonstration that addition of idelalisib to therapy with rituximab improved PFS and overall survival,[67] which was corroborated in long-term follow-up analyses.[68] Although highly effective, widespread use of idelalisib has been compromised by concerns over toxicity related to its propensity for causing immune dysregulation, resulting in autoimmunity (e.g., pneumonitis,[69] colitis[70]) or enhanced immune deficiency against opportunistic infection. The FDA recommended closure of clinical trials of frontline idelalisib due to the apparently higher incidence of hepatic toxicity observed in treatment-naive patients[71] and a higher number of infections and deaths in treatment-naive patients who received idelalisib and rituximab relative to that of matched patients who received comparator-arm therapy. This has diminished the chance that "lisibs" will achieve approval for use in frontline therapy of patients with CLL.

Second-generation small molecule inhibitors of PI3K also have been approved for treatment of patients with CLL. Duvelisib, which inhibits the gamma isoform of PI3K (PI3Kγ) and PI3Kδ, also has clinical activity. Clinical trials have demonstrated clinical activity similar to

that of idelalisib with a favorable safety profile, suggesting this drug may have a higher therapeutic index than idelalisib.[72–74] In September 2018, duvelisib was approved by the FDA for treatment of patients with CLL who have had at least 2 prior therapies.[75] Umbralisib (TGR-12032) also has been shown to have clinical activity, particularly in combination with ibrutinib.[76] However, combination of idelalisib with other kinase inhibitors (e.g., Syk) has resulted in unacceptable toxicity.[77]

Inhibitors of BCL2

Another category of drug recently approved for use in patients with relapsed CLL is venetoclax, a small molecule that functions as a BH3 mimetic to inhibit BCL2.[78] BCL2 is an antiapoptotic protein that is expressed by CLL cells at high levels,[79] thereby helping leukemia cells to mitigate spontaneous or drug-induced cell death by countering the activity of proapoptotic proteins, such as BAX, via their respective BH3 domains (Fig. 3). Cytotoxic drugs indirectly can tip the balance in favor of BAX and thereby induce apoptosis. Moreover, the cytotoxic activity of drugs, such as fludarabine, is largely due to their capacity to induce p53, which in turn induces expression of intrinsic inhibitors to BCL2, such as PUMA, freeing up proapoptotic proteins to induce cell death.[80] Leukemia cells that harbor del(17p) and/or have inactivating mutations in p53 fail to make such intrinsic BCL2 inhibitors in response to cytotoxic drugs and therefore are relatively insensitive to chemotherapy. The importance of BCL2 in maintaining CLL-cell survival is underscored by the capacity of venetoclax to induce fulminant tumor lysis in patients initiating therapy with this drug.[81]

Clinical trials have demonstrated venetoclax to be highly effective in the therapy of patients with relapsed and/or refractory CLL,[82] particularly those with CLL harboring del(17p),[83] effecting an overall response rate of 79%, with 8% achieving a CR. Combination therapy of venetoclax with an anti-CD20 mAb, such as rituximab or obinutuzumab, achieved even higher CR rates in patients who were treatment-naive or who had relapsed after other therapies.[84,85] Therapy eradicated detectable minimal residual disease (MRD) (at 10^{-4}) in approximately 50% of cases. Some of these patients achieved only partial responses, per iwCLL guidelines (due to persistence of lymph nodes ≥1.5 cm in diameter),[86] but had undetectable MRD in the blood or marrow; such patients also may have no detectable disease even in enlarged lymph nodes and have a median PFS comparable to that of patients who achieve a CR with undetectable MRD.[87]

The high rate of durable responses stimulated evaluation of fixed-duration therapy. The Murano study evaluated the outcome of patients with relapsed/refractory CLL who were treated for 24 months with venetoclax and rituximab (VR) or BR. A total of 389 patients were enrolled (194 in VR, 195 in BR). After a median follow-up time of 23.8 months, the PFS was much longer with VR (hazard ratio [HR], 0.19; $P < 0.0001$; median, not reached vs. 18.1 months). The benefit of VR was noted across all patient subgroups. The 2-year PFS was 82.8% for the VR group, which also enjoyed improved overall survival (HR, 0.48; $P = 0.018$). The improved outcome of patients treated with VR is even more apparent with longer-term follow-up.[88] With a median of 9.9 months (1.4–22.5 months) after completion of venetoclax therapy, both PFS and overall survival remained superior for the VR-treated

patients over that of patients treated with BR (HR, 0.16 [0.12–0.23] and 0.50 [0.30–0.85], respectively).

Upon demonstration that obinutuzumab could be administered safely to patients prior to the initiation of therapy with venetoclax,[85] a randomized study was conducted to compare the activity of this combination with that of chlorambucil and obinutuzumab in 432 patients 65 years or older who had comorbidities, which precluded them from receiving more aggressive forms of chemoimmunotherapy.[89] Patients received 6 cycles of obinutuzumab and twelve 28-day cycles of therapy with either venetoclax or chlorambucil. The percentage of patients with PFS at 24 months was significantly higher in the venetoclax-obinutuzumab treatment group (88.2% [95% confidence interval, 83.7–92.6]) than in the chlorambucil-obinutuzumab group (64% [95% confidence interval, 57.4–70.8]). Each treatment group had comparable rates of grade 3 or 4 neutropenia (52.8% vs. 48.1%, respectively). Based on these findings, the FDA and National Comprehensive Cancer Network guidelines committee recommended consideration of venetoclax and obinutuzumab as initial therapy.[38]

Despite the notable clinical activity of venetoclax, not all responses to this drug are durable, even with continuous therapy. The estimated 15-month PFS for patients with relapsed or refractory disease is 69%.[82] Patients who achieve only a partial response, or a CR with detectable MRD, generally relapse after the drug is discontinued[84] and/or develop drug resistance or even Richter transformation.[90,91] Also, despite the aforementioned use of drug combinations of venetoclax with anti-CD20 mAb and/or ibrutinib,[92] approximately a third of all patients fail to clear MRD even after 24 months of continuous therapy.

Some patients who develop resistance to venetoclax are found to have mutations in *BCL2* that impede the binding of venetoclax to the mutated BCL2 protein.[93] Other mutations affecting the capacity of venetoclax to inhibit BCL2 have been identified in the lymphoma cells of patients or lymphoma cell lines with acquired resistance to venetoclax.[94,95] Such mutations compromise the cytotoxic activity of venetoclax or second-generation BCL2 antagonists under development.[96]

ROR1

Targeting other survival-signaling pathways in CLL may allow for development of therapies that may be clinically effective, either alone and/or in combination with newly approved targeted therapies (e.g., ibrutinib, idelalisib, venetoclax).[7] One such survival-signaling pathway is triggered by activation of ROR1.

ROR1 is an oncoembryonic surface antigen, which is expressed by CLL cells[23,97,98] and by the neoplastic cells of many other types of cancer,[99] but not by virtually all normal adult tissues.[23,100,101] ROR1 can serve as a receptor for Wnt5a (Fig. 4),[23] which is found at high levels in the plasma of patients with CLL relative to that of healthy adults. Wnt5a induces ROR1 to recruit and activate Rho GTPases and enhance chemokine-directed migration, proliferation, and survival of CLL cells.[103] Furthermore, ROR1 signaling may promote development and progression of CLL.[104,105] Such signaling could be blocked by cirmtuzumab,[101] a humanized IgG1 mAb with high affinity and specificity for ROR1 that

was generated and selected based on its capacity to inhibit the survival-promoting effects of Wnt5a on CLL cells. A limited-duration phase I study of cirmtuzumab in patients with relapsed CLL showed this antibody had a long half-life, lacked dose-limiting toxicity, and was effective in blocking ROR1 signaling in vivo.[102] Transcriptome analyses revealed that treatment reversed cancer stem-cell gene expression signatures noted in the leukemia cells of patients prior to therapy.

Studies indicate that the survival-signaling pathway triggered by Wnt5a via ROR1 is active in patients undergoing therapy with ibrutinib.[106] Although ibrutinib may mitigate the capacity of CLL cells to enter the protective leukemia microenvironment of lymphoid tissues, the factor triggering ROR1 signaling, namely, Wnt5a, can be found at high levels in the plasma of patients with CLL relative to healthy adults.[102,103] As such, stimulation of ROR1 signaling may transcend the leukemia microenvironment. Although ibrutinib can block BCR signaling because of its capacity to inhibit BTK, ibrutinib is not able to inhibit Wnt5a-induced ROR1-dependent activation of Rho GTPases, such as Rac1.[106] Such ancillary survival-signaling pathways could provide a lifeline to leukemia cells of patients undergoing therapy, thereby mitigating the capacity of BTK inhibitors to eradicate the disease. Consistent with this notion, treatment with ibrutinib and cirmtuzumab appeared more effective than treatment with either agent alone in clearing leukemia cells in preclinical studies.[106] This has fostered phase Ib/II clinical studies evaluating the combination of cirmtuzumab and ibrutinib in patients with CLL (ClinicalTrials.gov identifier).

Other studies indicate that targeting ROR1 may enhance the efficacy of venetoclax. The most common genetic lesion in CLL is loss or down-regulation of 2 microRNA, miR-15/16,[107,108] which were found to target *BCL2*[109] and, more recently, ROR1.[110] Deletion or down-regulation of miR-15/16 is conducive to high-level expression of *BCL2* and *ROR1*. Furthermore, leukemia cells that express the highest levels of surface ROR1 also are found to have the highest levels of cytoplasmic BCL2.[110] The anti-ROR1 mAb cirmtuzumab was found to enhance the cytotoxic activity of venetoclax for CLL cells in vitro,[110] indicating that targeting ROR1 and BCL2 may have additive, if not synergistic, activity in patients with this disease.

Because of its specificity, in vivo stability, long serum half-life, and potential capacity to concentrate conjugated drugs into lysosomal compartments, cirmtuzumab also appears suited to serve as the targeting moiety in anti-ROR1 antibody-drug conjugates (ADCs). Cirmtuzumab has been conjugated with monomethyl auristatin E to generate an ADC that preserves its high-affinity binding specificity for ROR1 and allows for ROR1-targeted intracellular release of monomethyl auristatin E.[111] This ADC is selectively cytotoxic for CLL cells that express ROR1 and can affect clearance of adoptively transferred ROR1-positive leukemia cells in preclinical models. This noted preclinical activity has fostered initiation of clinical studies evaluating this ROR1-specific ADC in patients with CLL or mantle cell lymphoma.

CONCLUSIONS

There have been tremendous improvements in therapy for patients with CLL with novel agents that target distinctive facets of its biology. Research defining the importance of the CLL microenvironment and BCR/chemokine-receptor signaling has ushered development of drugs such as ibrutinib, which has changed clinical practice. Research into mechanisms that promote survival of CLL cells has led to development of venetoclax, which also has potent clinical activity. Despite the success of these agents, challenges persist. The BCR-associated kinase inhibitors generally cannot eradicate the disease and thus generally mandate continuous therapy. Although venetoclax may effect deep remissions that allow for fixed-duration therapy, sizeable proportions of patients fail to clear detectable MRD even when treated with venetoclax in combination with anti-CD20 mAbs and/or other targeted therapies. Such patients may experience disease progression even in the setting of venetoclax therapy. Research on agents that can hit other survival factors produced by cells within the leukemia microenvironment may define novel targeted therapies that ensure a successful outcome for all patients requiring treatment for this disease.

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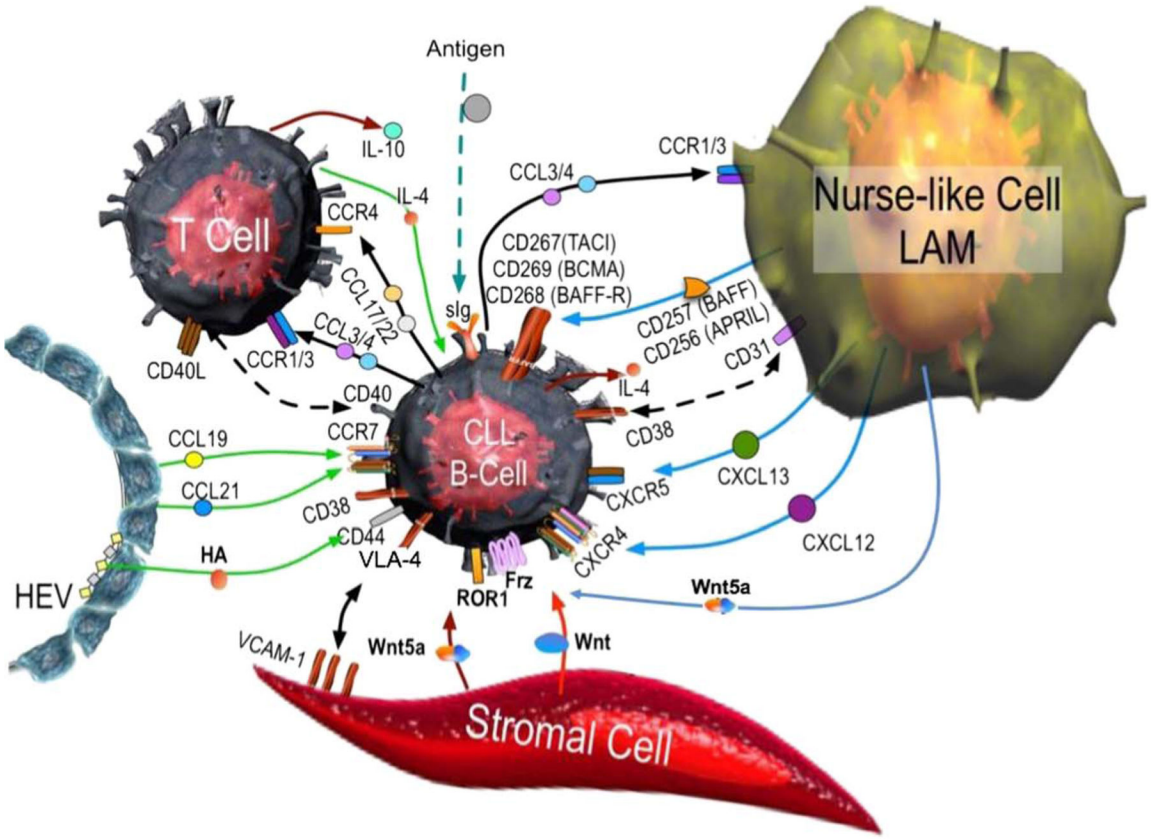

FIGURE 1.
Cross-talk and survival-signaling pathways within the leukemia microenvironment.

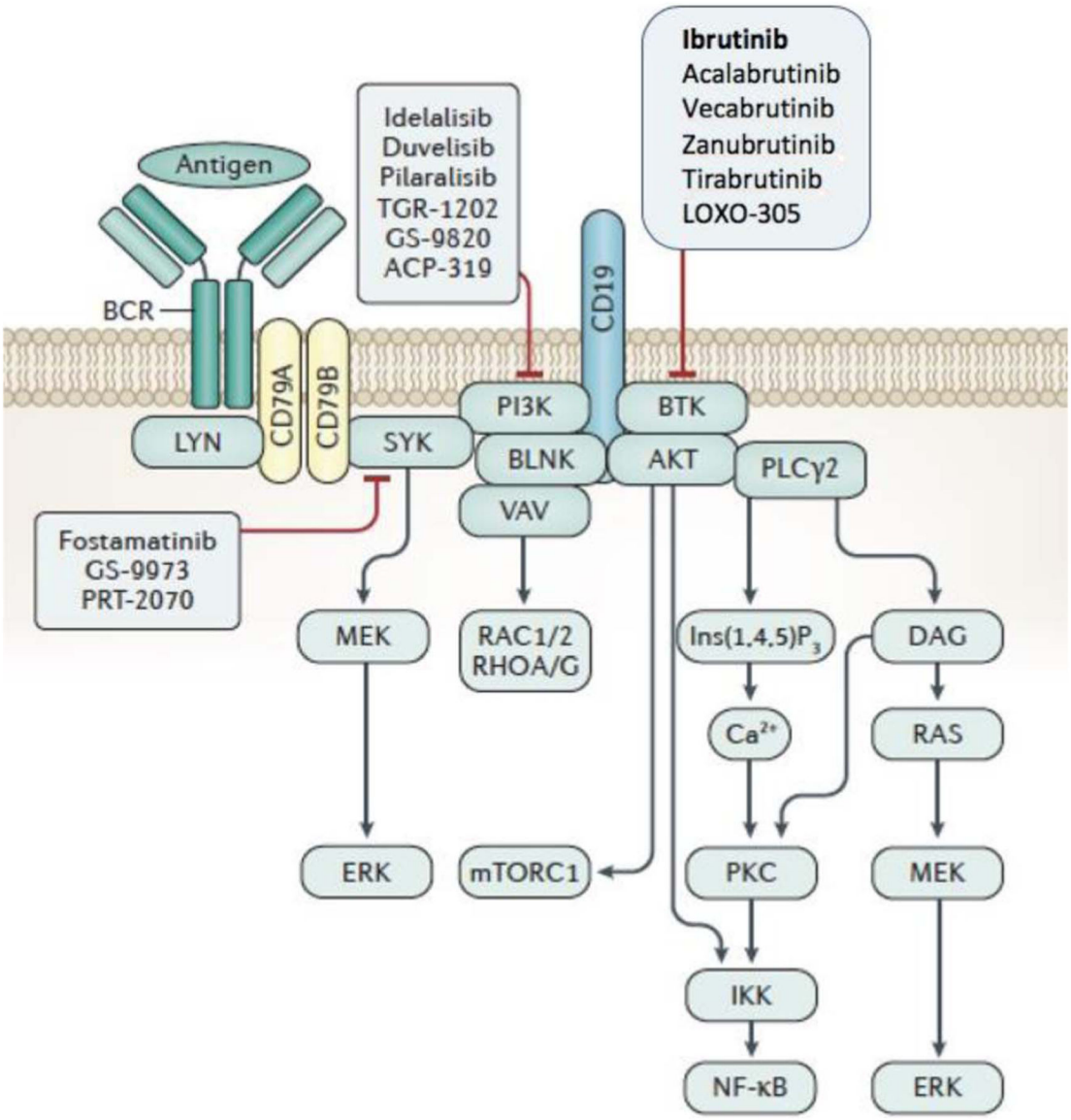

FIGURE 2.

B-cell receptor signaling triggers formation of a multicomponent “signalosome,” which can activate BTK, AKT, PI3K, PLCγ2, and BLNK, and CD19, a coreceptor important for PI3K activation. Inhibitors target enzymes in this signaling pathway. Modified from Kipps et al.[7]

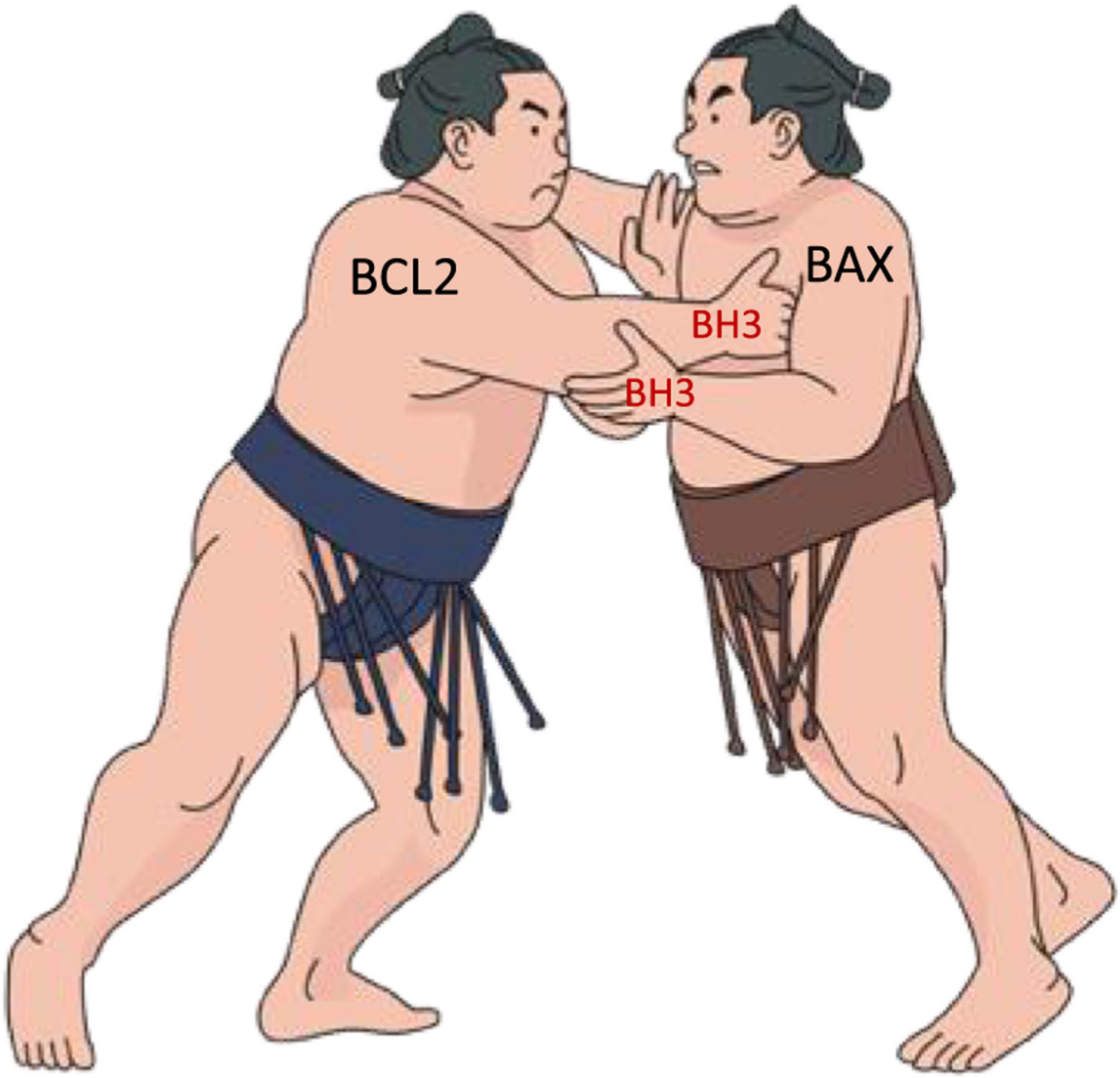

FIGURE 3.

Cartoon depicting a wrestler representing the antiapoptotic protein BCL2 holding in check the wrestler representing the proapoptotic protein BAX via handholds, which represent the BH3 domains of each protein. Inhibition of BCL2 by binding its BH3 domain frees up the proapoptotic proteins, allowing for release from mitochondria of cytochrome c, which results in apoptosis.

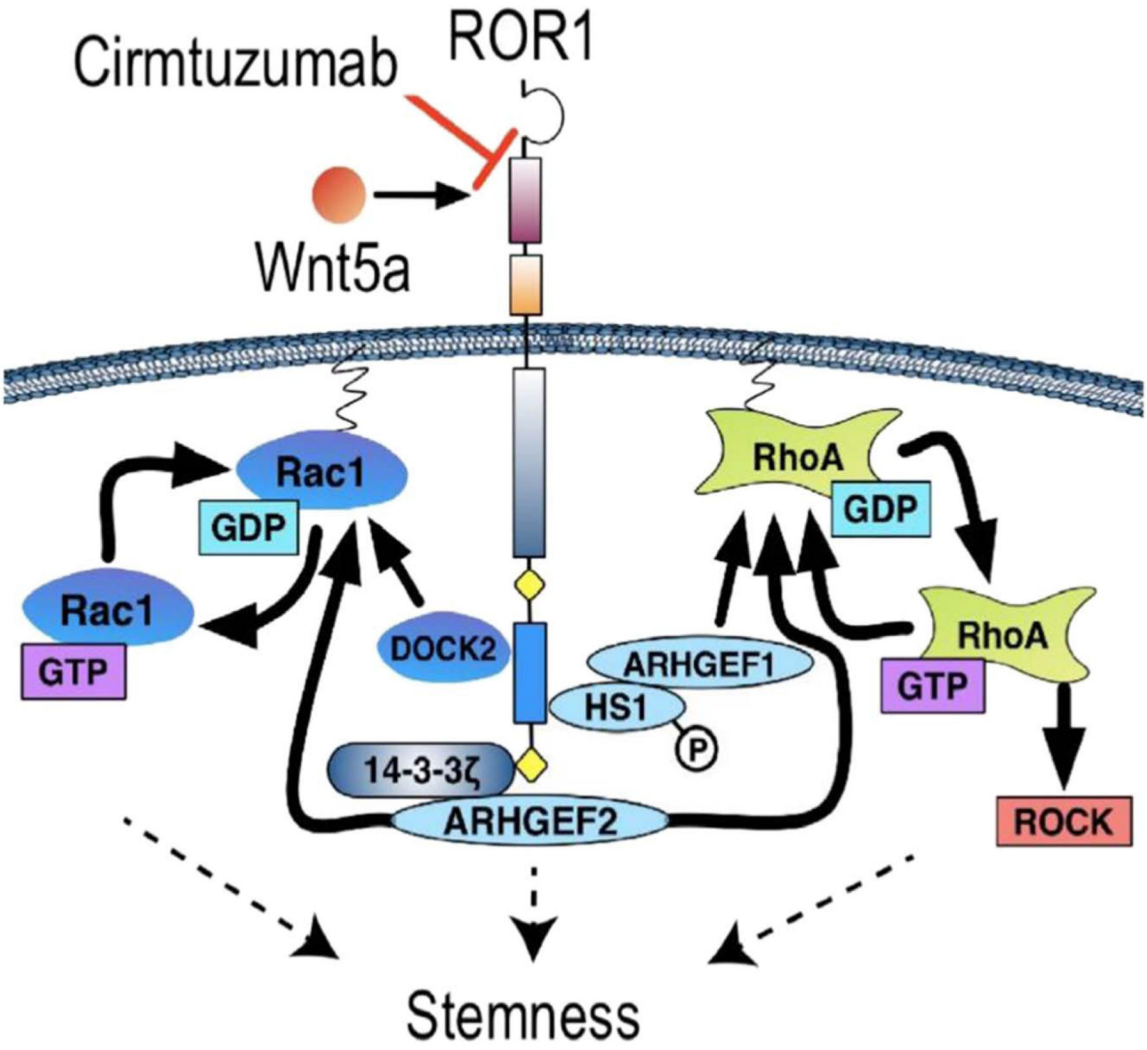

FIGURE 4.
ROR1 signaling in CLL. Adapted from Choi et al.[102]