



Mini Review

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Updates in the Treatment of Chronic Lymphocytic Leukemia with Targeted and Immunotherapies

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ABSTRACT

Chronic lymphocytic leukemia is a B cell malignancy characterized by proliferation of B cells and is most prevalent in elderly populations that has poor prognosis in advanced stages. Bruton tyrosine kinase inhibitors such as ibrutinib and BCL-2 inhibitors such as venetoclax are considered one of the standard front-line treatments as shown by several clinical trials. However, several targeted and immunotherapies are emerging. Sonrotoclax is a BH3 mimetic BCL2i has been tested in combination with Zanubrutinib in phase I dose escalation/dose expansion study and resulted in a uMRD4 rates of 78% at a 320mg dose in the peripheral blood. No disease progression at a median follow-up of 10 months resulted with no atrial fibrillation and grade 3 infections at 8% of patients. Two clinical studies describe the construction of CAR T cell therapies for the treatment of CLL. One study provided a protocol to recapitulate the TME of CLL to further precision medicine approaches for the disease with the aim of understanding resistance to targeted therapies. Another agent, VIP152, is a selective CDK9 inhibitor with pre-clinical in vitro and in vivo efficacy that phosphorylates RNA POLII by positive transcription elongation factor complex (P-TEFb). It is a heterodimeric protein complex composed of cyclin dependent kinase 9 (CDK9) and cyclin T1, producing dysregulated transcripts in CLL. CAR T cell therapies in two clinical studies describe constructions which are definite options, and combinations of BCL-2 and BTK inhibitors have been evaluated especially for double refractory disease.

Chronic lymphocytic leukemia is a B cell malignancy characterized by proliferation of B cells and is most prevalent in elderly populations that has poor prognosis in advanced stages. The development of therapy for this cancer was the result of understanding how tumors initiate, progress and respond to therapy. Oncogenic somatic and germline mutations in tumor suppressor genes are the primary drivers of cancers. These oncogenic alterations lead to an increase in proliferative signaling, bypassing replicative limit, as well as resistance to apoptosis and increase in genome instability. Tumors are characterized by intra and inter tumor heterogeneity. Based on an understanding of molecular cancer biology, targeted therapy treatments were developed targeting genes with oncogenic alterations and related signaling pathways¹. Bruton tyrosine kinase inhibitors such as ibrutinib and BCL-2 inhibitors such as venetoclax are considered one of the standard front-line targeted therapy treatments for CLL as shown by several clinical trials. CAR T cells are another category of therapy and are based on extracting T cells from patients, modifying them with a chimeric receptor that targets a particular tumor antigen and infusing ex vivo the modified T cells. They were further enhanced by the addition of a co-stimulatory domain augmenting expansion and persistence after infusion. Upon administration, CAR T cells target cancer cells through antigen recognition and result in tumor cell killing with specificity^{1,2}.

Immunosurveillance through the processes of elimination, equilibrium and escape describe the tumor immunological environment. The TME determines the immune therapeutic response and evasion. The treatment of cancer has undergone a major transformation with the introduction of drugs that modify the immune system to induce and increase anti-tumor activity. Innate immune cells such as dendritic cells are the antigen presenting cells of the immune system and trigger anti-tumor T cells. T cells and B cells are components of the adaptive immune system that eliminate tumor cells and foreign cells. Cancer immunotherapies enable the boosting of immunity for controlling the cancer and TME to allow for immune cells to precisely target and eradicate tumor cells at critical nodes². Targeted therapies such as Zanubrutinib and pirtobrutinib and immunotherapies in the categories of CAR T cell therapies and bispecific antibodies are being evaluated for CLL in cases of drug resistance to standard therapy. Most drugs target surface proteins such as CD19 and CD20. However, patients have reported refractory disease, leading to the need to develop novel therapies^{3,4}.

In this article, recent approaches to CLL will be described involving both a targeted-therapy framework and an immunotherapy-framework wherein advances due to cell-intrinsic drug-response and immune modulation are considered and evaluated through a combined tumor-cell directed strategy and microenvironment-directed strategy. Advances in cancer genomics targeting specific genetic mutations have further refined the strategy of targeting tumor cells. Targeting immune cells is the strategy focusing on immune cells within the TME that play a role in tumor progression as shown by the success of immune checkpoint blockade that alleviate the inhibition of effector T cells. However within the immunosuppressive TME there are regulatory T cells and exhausted T cells that limit the effectiveness of this strategy⁵.

The microenvironment in lymph nodes, spleen, and bone marrow is crucial for chronic lymphocytic leukemia (CLL) cells, acting as protective niches that promote survival, proliferation, and drug resistance through interactions with stromal cells, cytokines, chemokines, and T-cells. CLL cells actively reshape these tissues, creating supportive structures like proliferation centers in nodes and inducing supportive cells (e.g., M2 macrophages, regulatory T-cells) that shield them from therapy and immune attack, making these tissues key for disease progression.

Lymph Nodes (LNs): Act as “hubs” where CLL cells form proliferation centers, increasing Cyclin D2 expression and promoting cell division, supported by T-helper cells.

Bone Marrow (BM): Provides a protective niche, reducing drug sensitivity and impacting normal blood cell production as CLL cells accumulate.

Spleen: Enlarges (splenomegaly) due to infiltration, becoming a site for abnormal cell accumulation and function impairment. The microenvironment of CLL provides signals for its growth. Active cells are at lymphoid tissue sites whereas in the peripheral blood they become quiescent. In the lymphoid tissue, CD40L-presenting T helper cells, myeloid and stromal cells provide signals. This crosstalk promotes the microenvironment dependent CLL cells to survive and proliferate. BTK inhibitors halt disease progression by inducing lymphocytosis due to release of activated CLL from lymphoid tissue to PB and preventing migration back into lymphoid tissue. LN tissues promote CLL proliferation by BCR, CD40 and TLR signaling. In vivo BCR signalling activity is elevated in CLL cells and deregulation of this signalling leads to CLL disease progression. BCR triggers downstream signaling pathways including PI3K/AKT/mTOR, NF-KappaB, and MAPK/ERK that lead to CLL survival and proliferation.

CAR T cell therapies

Liso-cel is the first FDA-approved CAR T-cell therapy for CLL and is an option for some patients, especially after other treatments have been tried. Lisocabtagene maraleucel was evaluated in TRANSCEND CLL Cohort trial design (N=65): TRANSCEND CLL 004 was a Phase 1/2, open-label, multicenter, single-arm trial in adult patients with R/R CLL or SLL who had received at least 2 prior lines of therapy, including a BTKi and a BCL-2i. The primary endpoint was ORR (including CR and PR). Liso-cel demonstrated deep and durable complete responses, with 87.5% of CRs maintained at 18 months with an mPFS of 12 months.

ZUMA-8 evaluated the safety of brexucabtagene autoleucel (brexu-cel), a CD19-directed autologous chimeric antigen receptor (CAR) T-cell immunotherapy, for patients with R/R CLL. Patients with ≥ 2 prior lines of therapy (including a Bruton tyrosine kinase inhibitor) underwent leukapheresis, optional bridging therapy, and conditioning chemotherapy (fludarabine/cyclophosphamide) before infusion of 1×10^6 (cohort 1) or 2×10^6 (cohort 2) anti-CD19 CAR T cells per kg. Fifteen patients, median age of 63 years (range, 52-79), were administered treatment in separate arms 1 (n = 6), 2 (n = 3), 3 (n = 3), and 4A (n = 3). Median follow-up was 24.3 months. One DLT occurred in cohort 3 (grade 4 cytokine release syndrome). Grade ≥ 3 neurologic events were observed in 3 patients (20%). ORR was 47% (7/15) and CR was 7% including all patients in cohort 3 and seven of 15 patients responded. Expansion was observed in 4 patients including all 3 patients in cohort 3 (1 with CR). CAR T-cell expansion occurred in 4 patients (27%), “with an apparent weak inverse correlation with absolute lymphocyte count before apheresis.” No new safety signals were reported with CAR T-cell expansion and responses as shown in patients with low tumor burden⁷.

Third-generation chimeric antigen receptor T cells (CAR-Ts) with their enhanced CAR design show improved efficacy over second generation CAR-Ts. A phase 1/2 trial evaluated escalating doses of HD-CAR-1, a third generation CAR targeting CD19 in R/R CLL. Patients must have failed in two therapy lines that included a pathway inhibitor or allogeneic HSCT. Nine patients received HD-CAR-1 at dose levels ranging from 1×10^6 to 200×10^6 .

Nine patients received HD-CAR-1 at dose levels ranging from 1×10^6 to 200×10^6 CART/m² noting that in-house HD-CAR-1 manufacturing was successful for all patients. One episode of CRS was observed with 6 patients (67%) achieving CR and 5/6 (83%) achieving undetectable MRD. 2-year PFS and OS were 30% and 69%, respectively. No cases of neurotoxicity were reported, and "HD-CAR-1 products of responders contained significantly more CD4+T cells compared to non-responders. In non-responders, a strong enrichment of effector memory-like CD8+T cells with high expression of CD39 and/or CD197 was observed. HD-CAR-1 demonstrated encouraging efficacy and exceptionally low treatment specific toxicity, presenting new treatment options for patients with r/r CLL."

The FCR regimen consists of rituximab, a chimeric, monoclonal antibody targeting CD20 and fludarabine, and was evaluated in a phase II trial in R/R CLL. "The regimen consisted of rituximab "375 mg/m² on day 1 of cycle 1 and 500 mg/m² on day 1 of cycles 2–6; fludarabine 25 mg/m²/day and cyclophosphamide 250 mg/m²/day were administered for 3 days each cycle." Among 280 patients, CR was achieved in 30% of patients with a PR of 30% and an ORR of 74%. The CLL8 (n=817) was a randomized phase III trial designed to compare FC with FCR in treatment-naïve CLL patients. "With a median follow up of 5.9 years, the PFS for FCR versus FC was 56.8 versus 32.9 months (hazard ratio (HR), 0.59; 95% confidence interval (CI), 0.50–0.69). Furthermore, there was a significant OS advantage: not reached for the FCR group versus 86 months for the FC group (HR, 0.68; 95% CI, 0.54–0.89). Major toxicities associated with this therapy were myelosuppression (which could be prolonged) and infectious complications⁸."

Combining BCL-2 and BTK inhibitors may be effective in CLL as shown by the AMPLIFY trial that evaluated acalabrutinib and venetoclax and revealed deep and durable responses. These two first-line treatments were administered over 14 months with acalabrutinib combined with venetoclax and the same drug pair combined with obinutuzumab. AV and AVO are compared to FCR or bendamustine-rituximab, thus making three treatment groups (n=867) randomized and followed over 40 months. The primary endpoint PFS was met with higher rate in the AV group versus standard CIT. "The estimated 36-month PFS for the three groups are: 76.5% for AV, 83.1% for AVO, and 66.5% for the standard treatment group." The ORRs

were over 92% for both experimental arms and the ORR for standard cohort was 75%. The AV regimen was also well tolerated and had improved OS versus the control arm and the AVO regimen had a very high rate of undetectable MRD of about 95%⁹.

Patients progressing after both classes of therapy (BTK inhibitors and BCL-2 inhibitors) (double-refractory) have limited options and poor prognoses. According to Shadman and Davids, "[i]n true double-refractory disease, noncovalent BTK inhibitors (eg, pirtobrutinib) and CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy (lisocabtagene maraleucel) are standard-of-care options. Pirtobrutinib induces rapid responses, though often of limited duration, underscoring the need for early consolidation planning with CAR-T or allogeneic stem cell transplant." CAR T cell therapy may warrant transplant referral and close monitoring. Emerging agents such as teclistamab, a bispecific antibody, are a possibility as well. BTK degraders and non-covalent BTK inhibitors are options and provide promise in future directions. In double-refractory CLL, an individualized strategy lends itself to optimized outcomes that integrate available treatments with innovative investigational agents. Optimizing outcomes in double-refractory CLL requires an individualized, nuanced strategy integrating available treatments with innovative approaches under investigation¹⁰.

The phase 3 HELIOS study evaluated R/R CLL patients without deletion 17p (n = 578) that were randomized 1:1 to 420 mg daily ibrutinib or placebo plus ≤6 cycles of bendamustine plus rituximab (BR), followed by ibrutinib or placebo alone. mPFS at a median follow-up of 63.7 months was 65.1 months versus 14.3 months for the ibrutinib plus BR and placebo plus BR, respectively. [HR] 0.229 [95% (CI) 0.183–0.286]. Crossover was 63.3% of patients from the placebo plus BR cohort to ibrutinib treatment upon disease progression. An OS benefit was also seen in the ibrutinib plus BR arm versus placebo plus BR (HR 0.611 [95% CI 0.455–0.822]) (median not reached in either arm). No new safety signals emerged with safety profiles being consistent with those known for ibrutinib plus BR¹¹.

Obinutuzumab is a humanized CD20 antibody modified by glycoengineering to have unique structural and functional characteristics and is effective against CLL. When the glycoengineered Fc portion binds to the FcγRIII receptor on immune effector cells, its binding affinity is enhanced, resulting in increased antibody-dependent cellular cytotoxicity and phagocytosis. The type II antibody binding characteristics of the mAb to CD20 leads to "efficient induction of direct non-apoptotic cell death." The Galton trial examined 41 patients with CLL were administered the combination of obinutuzumab and central chemotherapy selected by the investigator. The ORR of obinutuzumab-bendamustine (G-B) was 90% (18/20) and the CR rate was

20%. When Obinutuzumab was combined with FC (G-FC), an ORR of 62% (13/21) and a CR rate of 10% resulted. "In the G-B group, the median follow-up period was 23.5 months while that of the G-FC group is 20.7 months, with no patients relapsed or died, which indicates that obinutuzumab with either B or FC has promising activity." CLL11 is a large randomized clinical trial that showed that an obinutuzumab-based regimen can significantly improve PFS and OS when compared with rituximab-based regimen for CLL while reducing the risk of death by 24%. The multicenter open-label phase III randomized trial included patients with CD20 positive CLL, "who were given obinutuzumab combined with chlorambucil (Chl) regimen (333 cases), rituximab combined with Chl regimen (330 cases) and Chl monotherapy regimen (238 cases). The results showed that the median follow-up was 59.4 months (nearly 5 years). Obinutuzumab combined with Chl regimen can reduce the risk of disease progression by 51% compared with rituximab combined with Chl regimen." The median PFS was 28.9 months and 15.7 months, respectively (HR=0.49), showing a reduction in the risk of death by 24%, and the median OS was 73.1 months (HR=0.76). The median time to start follow-up treatment was 56.4 months and 34.9 months, respectively (HR=0.58), and the negative conversion rate of MRD was 24% and 2%, respectively¹².

Vodarek et al "used multi-color flow cytometry, to prospectively measure absolute and relative numbers of CD4+ and CD8+ T-cells and their subsets in 45 patients with indolent untreated CLL, 86 patients indicated for first-line treatment, and 34 healthy controls" and in 55 patients the impact of CIT was analyzed. CLL progression was characterized by significantly elevated counts of most cell populations with a lower percentage of naïve T cells. "After treatment, the percentage of naïve T-cells further decreased at the expense of effector memory T-cells (TEM). In patients with indolent CLL, higher percentages of naïve CD4+ (p = 0.0026) and naïve CD8+ (p = 0.023) T-cells were associated with a longer time to first treatment (TTFT). The elevation of CD4+ central memory T-cells (TCM) (p = 0.27) and TEM (p = 0.003) counts and a higher percentage of CD4+ TEM (p = 0.0047), were linked with shorter TTFT. In treated patients, increased regulatory T-cells count was associated with shorter time to next treatment (TTNT) (p = 0.042), while higher CD4+ TCM count with shorter TTNT (p = 0.035) and shorter overall survival (p = 0.041)." Their results "indicate that naïve cell depletion and CD4+ TCM and TEM increases are detrimental to CLL patients' prognosis¹³"

Sonrotoclax is a BH3 mimetic BCL2i has been tested in combination with Zanubrutinib in phase I dose escalation/dose expansion study and resulted in a uMRD4 rates of 78% at a 320mg dose in the peripheral blood. There was no disease progression at a median follow-up of 10 months with no atrial fibrillation and grade 3 infections at in 8% of patients.

Rogers et al showed that the triplet combination of ibrutinib, venetoclax and Obinutuzumab demonstrated uMRD4 rates of 67% in treatment naïve and 50% in R/R patients after 14 cycles of therapy in a phase 2 study. As reported by Davids et al, the combination of acalabrutinib, venetoclax and obinutuzumab showed high activity in a single arm phase 2 trial however the primary endpoint was not met (MRD in the BM, 38%). After study amendment, the ORR was 98%, CR rate was 48%, and the uMRD4 was 86% in PB and BM at a median follow up of 35 months. 3-year PFS and OS were 93% and 99% respectively, with 3% patients reporting atrial fibrillation and 27% of patients reporting hypertension. Grade 1-2 headache, fatigue and nausea were observed¹⁴.

Molica et al discuss the complexity in developing prognostic models and risk stratification for CLL due to its tumor heterogeneity and novel targeted therapy treatments in their state of the art update article. The CLL International Prognostic Index or CLL-IPI was groundbreaking in its incorporation of pooled data from eight phase II trials including prognostic factors TP53 mutation status and cytogenetic abnormalities. Two new prognostic models BALL and CLL4 were developed in response to novel targeted approaches utilized. Both BALL and CLL4 incorporate LDH levels and serum beta2-microglobulin and have superior prognostic performance after validation studies on patients treated with ibrutinib. Combining BTK inhibitors, BCL2 inhibitors and anti-CD20 mAbs might provide superior long-term control for both low risk and high risk patients. CLL-IPI remains the standard for asymptomatic cohorts with incorporation of 5-year treatment survival data in a meta-analysis of 5,206 patients, however a new model the CLL-WONT (Without Need of Therapy) is becoming accepted as an innovative strategy for newly diagnosed and asymptomatic patients who can undergo less frequent monitoring and optimize healthcare resource allocation. The Personalized Stepwise Dynamic Predictive Algorithm (PSDPA) considers the dynamic nature of CLL with considerable inter-patient heterogeneity and unpredictable course and is a prognostic model that incorporates time-dependent patient data by dynamically updating a patient's personalized risk score as new clinical and biological data become available. The model can potentially enhance the accuracy of treatment predictions and aid clinicians in tailoring treatment and interventions in real time¹⁵.

Two clinical studies describe the construction of CAR T cell therapies for the treatment of CLL. A third generation anti-CD19 CART (HD-CAR-1) harboring two costimulatory domains manufactured academically was evaluated in a phase1/2 study for R/R CLL with dose escalation performed on 9 heavily pretreated patients, with the novel design hypothesized to mediate enhanced and faster expansion

along with longer CART persistence. Eligible patients include those who failed two therapy lines of at least one pathway inhibitor (cBTK1 and one venetoclax-based regimen) and AHCT. Adverse events included one Grade 3 CRS and no neurotoxicity events (no ICANS) with six patients (67%) achieving CR and 5 or 83% achieving undetectable MRD, with the conclusion that the treatment was well tolerated. At a median follow-up of 27 months, 2-year PFS and OS were 30% and 69% respectively. Responders upon analysis presented with more CD4+ T cells while non-responders had an enrichment of effector memory CD8+ T cells. This study was considered an advancement in CAR T cell treatment of CLL since CARTs from these patients typically have signs of exhaustion and decreased cytokine production resulting in insufficient leukemia suppression. Increased expansion and enhanced persistence were also observed. The investigators concluded that while there was deepened CRs observed with HD-CAR-1 the responses were less durable than those observed in the TRANSCEND CLL trial. However the low incidence of adverse events was suggestive of potential clinical success in this small sample size, warranting further exploration in this otherwise refractory patient population¹⁶.

Markl et al constructed a precision therapy CAR T molecule targeting IGLV3-21^{R110} expressing cell lines and primary CLL cells in high risk patients, but neither cells expressing the non-pathogenic IGLV3-21^{G110} light chain nor polyclonal healthy B cells. Their construct exhibited tumor lysis activity in vitro and in vivo models as well as a humanized form that also was effective in their proof-of-concept study. Usual targets of CAR T cell therapies include CD19, CD20, CD22 and BCMA that consist of B lymphocyte surface activation markers. However, they lead to the elimination of B lineage cells, a major drawback while making patients clinical management complicated by the incidence of infections. As a response, the authors engineered a construct targeting a recurrent oncogenic point mutation on malignant CLL cells in the BCR light chain IGLV3-21^{R110} mutation and showing selectivity for engineered and primary cell lines as well as observed efficacy in vitro and in vivo. Anti-IGLV3-21^{R110} CAR T cells displayed in vitro epitope-selective tumor cell lysis and was found to be selective “against the R110 point mutation through co-culture of NALM-6 Luc-R110 cells with HD- α R110-mCAR1 T cells showing epitope-selective lysis of IGLV3-21^{R110}-expressing lymphoid target cells, while control NALM-6 Luc cells were unaffected.” Bioluminescence imaging displayed a substantial decrease of NALM-6 Luc-R110 outgrowth “in mice treated with HD- α R110-mCAR1 T cells, accompanied by prolonged survival and disease eradication in 17% of treated mice.” Additionally, epitope selective lysis of the IGLV3-21^{R110} expressing cells was shown through culturing of α R110-mCAR2 T cells, but not non-pathogenic IGLV3-21^{G110}. This

lysis was not replicated in the model with CD19-directed CAR T cells (α CD19- mCAR) with co-incubation of human T cells.

These constructs also displayed no B cell toxicities in vitro or in vivo. Tumor lysis as shown by the substantial decrease of NALM-6 Luc-R110 was suggestive of the anti-IGLV3-21^{R110} CAR T construct effectively targeting the IGLV3-21^{R110} expressing cells. The authors conclude on the “[p]otential clinical applications of IGLV3-21R110-targeting CAR T cells [that] range from treatment of relapsed/refractory disease to consolidation after insufficient response to standard first-line CLL treatment. Future studies will need to investigate whether IGLV3-21R110 mutated CLL patients respond to such CD19 CAR T cells at all¹⁷.”

Hermansen et al in a study provided a protocol to recapitulate the TME of CLL to further precision medicine approaches for the disease with the aim of understanding resistance to targeted therapies. In a culture of primary CLL cells containing fibroblasts, spontaneous apoptosis is prevented and anti-apoptotic signals are stimulated. They showed in a case study of a CLL patient that the ex vivo sensitivity to venetoclax has a correlation with its in vivo response, with treatment vulnerabilities further defined. Their TME models proposes to be compatible with ex vivo drug sensitivity testing for the clinical implementation of functional precision medicine approaches. Ligands APRIL, BAFF, and CD40L in the culture form key transient stimuli of primary CLL cells provided by T cells in the tumor leading to anti-apoptosis as shown by the presence of Mcl-1, Bcl-xL, and Bcl-2. However, progressive disease on ibrutinib resulted in the case study. “These findings suggest that the protocol can facilitate functional precision medicine in CLL. We showed that ex vivo sensitivity to targeted therapies, measured either at the protein level or as cell viability, associated with in vivo responses to the respective treatments¹⁸.”

Sher et al showed that an agent VIP152 is a selective CDK9 inhibitor with pre-clinical in vitro and in vivo efficacy that phosphorylates RNA POLII by positive transcription elongation factor complex (P-TEFb), a heterodimeric protein complex composed of cyclin dependent kinase 9 (CDK9) and cyclin T1, producing dysregulated transcripts in CLL. VIP152 was found through their experiments to inhibit P-TEFb assembly, disrupt binding partners and reduce disease burden in preclinical models with improved OS by inducing cell death, suggesting that VIP152 can be a novel treatment for CLL. VIP152 inhibited up to 95.3% of CDK9 activity at 100 nM. In CLL, 17pdel and TP53 are associated with decreased survival and resistance from effective treatment, and cell lines harboring these mutations were also susceptible to the cytotoxic activity of the agent. In both treatment naïve and refractory BTKi/Venetoclax

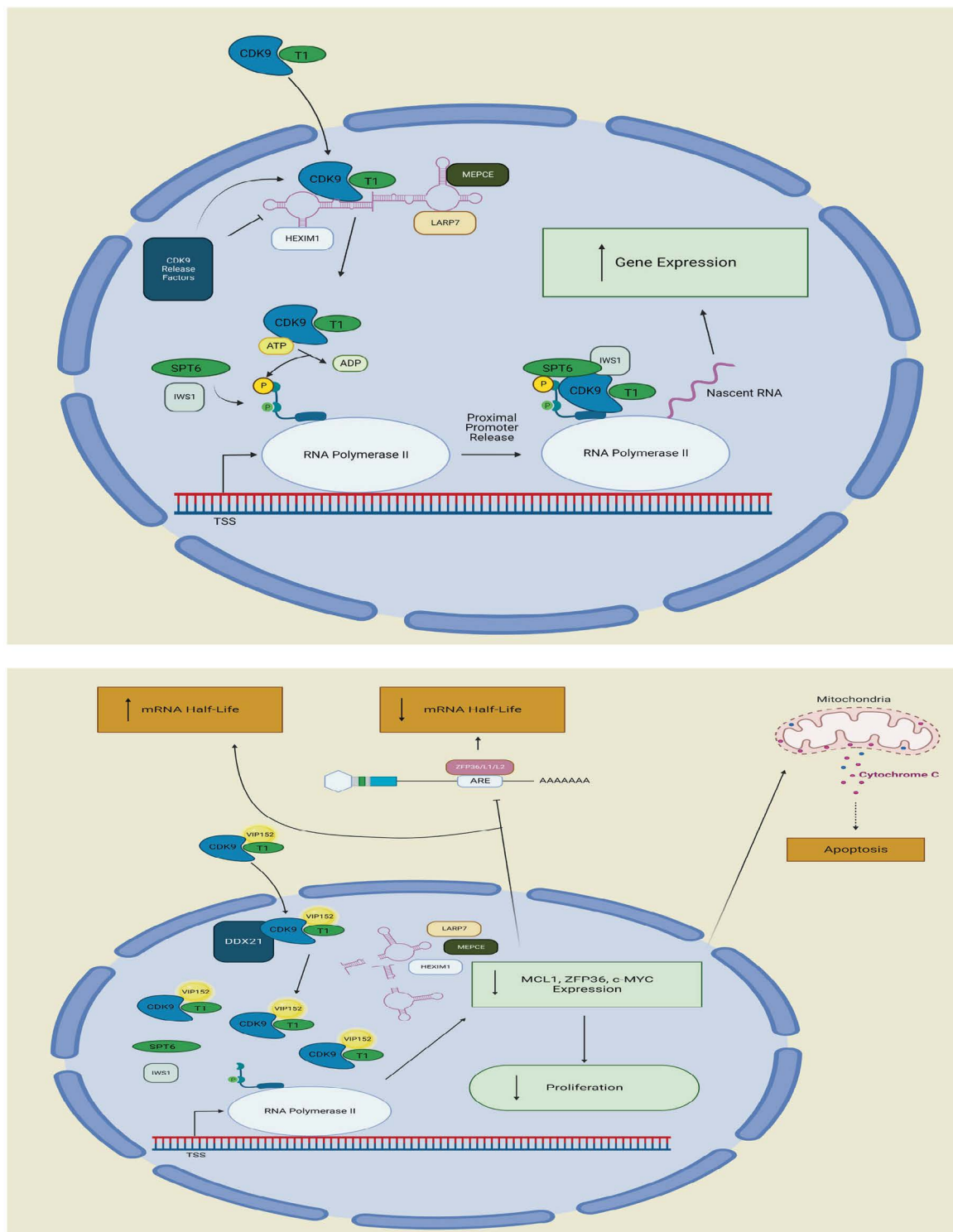


Figure 1: VIP152 Mechanism of Action (adapted from Sher et al²)

cell lines, harboring poor cytogenetic markers (del(11)(q22q23) and trisomy 12, VIP152 sensitivity shown at an IC50 of <100nM in the treatment naïve sample and 50% killing with IC50 of 1µM in R/R sT samples. VIP152 was also shown to disrupt P-TEFb canonical binding partners since increase in CDK9 isoforms and cyclin T1 were observed following treatment and proteomics showed an increase in

the release of P-TEFb in association with POLII, disrupting its kinase cascade activity. Mice in the VIP152 treatment group had also showed better OS compared with vehicle with a median survival of 46 days. 50% killing of R/R samples by VIP152 was enabled by an increase in P-TEFb release in association with POLII, disrupting its canonical binding proteins and leading to CDK9 isoform increase. As

the authors conclude “VIP152 demonstrates superior on-target and off-target properties with no measured weight loss in treatment groups. The tolerability and highest selectivity of VIP152 suggests that it will have an improved therapeutic index compared with these other inhibitors vs 32 days respectively. the disruption in binding of CDK9 to RNA Polymerase II machinery after treatment are strong evidence of how VIP152 exerts its effect. Through these data and by also demonstrating the in vivo efficacy and tolerability of VIP152, we maintain that VIP152 represents an attractive therapeutic option for the treatment of CLL⁴.”

To further characterize resistance mechanisms in the CLL TME, Avsec et al created an in vitro model of venetoclax-resistance CLL to investigate the molecular mechanisms that cause them. They showed that by inhibiting the p38 MAPK immunoproteasome, resistance to venetoclax is overcome since it is overexpressed in this cell line, inducing apoptosis. Cell death is indicative of the release of venetoclax resistance removing the Bcl-2 blockade through p38 MAPK immunoproteasome pharmacological inhibition via ONX-0914 administration. Selective pharmacological inhibitor ONX-0914 was found to resensitized MEC-1 VERO cells to venetoclax. P38 MAPK is overexpressed in venetoclax-resistant CLL cells and the anti-apoptotic activity of Bcl-2 is blocked. They hypothesized further that the MEK/ERK1/2 pathway and the JNK pathways also play roles in resistance to venetoclax and showed that p38 MAPK inhibitor overcomes resistance to venetoclax in patient-derived CLL cells, shown by adding a p38 MAPK inhibitor to the cell lines. “To test this, MEC-1 VERO cells were treated with 2.5 μM venetoclax alone and in combination with 25 and 50 μM BIRB796 or 25 and 50 μM SB203580 for 24 h. The viabilities of these cells were then determined using propidium iodide and flow cytometry. The viability of the MEC-1 VERO cells treated with 2.5 μM venetoclax and 25 μM BIRB796 decreased from 88% (vehicle control) to 76% and 72%, respectively... Pharmacological inhibition of p38 MAPK abolished the stimulating and resistance-promoting properties of IFNγ in CLL cells, thus restoring the cytotoxicity of venetoclax.” [19].

Discussion

Other oncogenic pathways have been implicated in drug resistance in CLL and newer investigational agents will be also evaluated in vitro and in preclinical models. Prognostic models are continually being updated as targeted therapies become more refined in their development to address resistance. CAR T cell therapeutic strategies are segueing from the experimental stage to clinical implementation, as shown in this review.. Mechanisms underlying resistance and drug therapy are further revealed by multi-omics analysis. Genomics, transcriptomics and proteomics will play crucial roles in revealing biomarkers and understanding how genomic biomarkers, differentially expressed genes

and protein biomarkers will lead to improved treatments and clinical outcomes. Liquid biopsy, including circulating tumor DNA and cell free DNA, with its prognostic and predictive capabilities will also prove pivotal by minimal residual disease measurements. Further studies may need to explore how clinical outcomes could be advanced by precision medicine approaches and development of cancer immunotherapies designed to target hematologic malignancies.

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Conflict of Interest

P.H. has stock ownership in Abbvie, which did not influence the descriptions, analysis or conclusions in this paper.

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