Perspectives on Precision Medicine in Chronic Lymphocytic Leukemia: Targeting Recurrent Mutations—NOTCH1, SF3B1, MYD88, BIRC3

Maciej Putowski 1,* and Krzysztof Giannopoulos 1,2

1 Department of Experimental Hematooncology, Medical University of Lublin, 20-093 Lublin, Poland; krzysztof.giannopoulos@gmail.com
2 Department of Hematology, St. John’s Cancer Center, 20-090 Lublin, Poland
* Correspondence: putowski.maciek@gmail.com; Tel.: +48-81-448-66-32

Abstract: Chronic lymphocytic leukemia (CLL) is highly heterogeneous, with extremely variable clinical course. The clinical heterogeneity of CLL reflects differences in the biology of the disease, including chromosomal alterations, specific immunophenotypic patterns and serum markers. The application of next-generation sequencing techniques has demonstrated the high genetic and epigenetic heterogeneity in CLL. The novel mutations could be pharmacologically targeted for individualized approach in some of the CLL patients. Potential neurogenic locus notch homolog protein 1 (NOTCH1) signalling targeting mechanisms in CLL include secretase inhibitors and specific antibodies to block NOTCH ligand/receptor interactions. In vitro studies characterizing the effect of the splicing inhibitors resulted in increased apoptosis of CLL cells regardless of splicing factor 3B subunit 1 (SF3B1) status. Several therapeutic strategies have been also proposed to directly or indirectly inhibit the toll-like receptor/myeloid differentiation primary response gene 88 (TLR/MyD88) pathway. Another potential approach is targeting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inhibition of this prosurvival pathway. Newly discovered mutations and their signalling pathways play key roles in the course of the disease. This opens new opportunities in the management and treatment of CLL.

Keywords: chronic lymphocytic leukemia; NOTCH1; SF3B1; MYD88; BIRC3

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in western countries. CLL is classified as a lymphoproliferative disorder characterized by accumulation of clonal B lymphocytes showing a characteristic immunophenotype (i.e., CD19+, CD20weak, CD23+) in the peripheral blood, bone marrow, lymph nodes and spleen [1]. The clinical course of CLL is highly heterogeneous, with the majority of patients following an indolent course with no or delayed treatment, while others experience aggressive disease with survival of few months [2]. The clinical heterogeneity of CLL reflects differences in the biology of the disease, including chromosomal alterations, gene mutations, specific immunophenotypic patterns and serum markers [3]. Despite significant progress in its management, CLL remains an incurable disease [4].

In the 1990s, cytogenetic abnormalities assessed by conventional karyotyping in CLL patients were found to be associated with shorter survival in a study by Juliasson et al. [5]. According to the cytogenetic model presented in 2000 by Döhner et al., CLL patients may be stratified based on the four most common chromosomal alterations (deletion of 13q14, deletion of 11q22-23, deletion of 17p12 and trisomy 12). Chromosomal alterations, assessed by FISH molecular karyotyping, have been detected in 82% of patients affected by CLL [6]. Of these, deletion of 13q14, occurring in 50–60% of cases, is the most frequent genetic lesion of CLL [6,7].
CLL cells express the B cell receptor (BCR) on their surface, which is a membrane bound form of the immunoglobulin molecule (Ig). Surface Ig expression plays a key role in survival and functioning of normal B cells, and also of many B cell lymphoproliferative disorders [2]. In 1999, it was independently reported by the Hamblin/Stevenson and Chiorazzi groups that somatic hypermutations present in rearranged immunoglobulin heavy variable (IGHV) genes in CLL predict a different clinical course [8,9]. Somatic mutations of IGHV gene (defined as <98% identity to the germline IGHV gene) occur in approximately half of CLL cases and are usually characteristic by more favourable prognosis. This contrasts with patients with unmutated CLL (IGHV gene sequences with a germline homology of 98% or higher), who have a more aggressive disease with worse prognosis [8,9].

Notably, 30% of CLL patients express quasi-identical BCR Ig, the so-called “stereotyped” receptors, and can be classified into subsets defined by distinctive sequence motifs within the Ig variable heavy complementarity-determining region 3 (VH CDR3). Stereotyped subsets are characterized by similar biological features, and similar disease course and outcome [10–12]. It has been suggested that subset classification can supersede general division into CLL patients with mutated and unmutated IGHV [13].

In recent years, the application of next-generation sequencing (NGS) techniques has demonstrated the high genetic and epigenetic heterogeneity in CLL [14]. The novel, previously unknown, mutations which were revealed include neurogenic locus notch homolog protein 1 (NOTCH1), splicing factor 3B subunit 1 (SF3B1), tumor protein p53 (TP53), myeloid differentiation primary response gene 88 (MYD88), ataxia telangietasia mutated (ATM), baculoviral IAP repeat containing 3 (BIRC3) and chromodomain-helicase-DNA-binding protein 2 (CHD2) [2,14–17]. These recurrent somatic mutations were found to be involved in key cellular pathways, such as DNA damage response, cell cycle regulation, apoptosis, RNA metabolism, NOTCH signalling, nuclear factor (NF)-kB signalling, chromatin remodelling and inflammatory BCR pathways [2,14–17]. Among these mutations, TP53, NOTCH1, SF3B1, and BIRC3 have been established as prognostic factors for the course of CLL and proposed to be incorporated in CLL prognostic scales [18–20]. The International Workshop on Chronic Lymphocytic Leukemia published in 2018 guidelines which included assessment of TP53 mutation in routine practice. As of today, evaluation of others molecular targets such as NOTCH1, SF3B1, and BIRC3 mutations is not an element of the routine prognostic work up in CLL. However, for clinical trials only, molecular testing is recommended before treating a patient on protocol [21].

Over the past decade, the implementation of the Bruton’s tyrosine kinase (BTK), phosphoinositide 3-kinase (PI3K) inhibitors and venetoclax overturned CLL treatment and replaced chemotherapy-based treatments for most CLL patients [22]. The consequent advances in understanding the clinical and biological heterogeneity of CLL and the development of new targeted therapies are leading us to an individualized, personalized approach [4].

2. NOTCH1 Mutation

The NOTCH1 gene encodes a member of the NOTCH family of proteins. The NOTCH1 receptor acts as a ligand-activated transcription factor that directly transduces extracellular signals leading to changes in gene expression in the nucleus, including MYC, TP53 and molecules of the NF-kB pathway [23–25]. The majority of NOTCH1 mutations disrupt the PEST domain of the protein, which is responsible for the proteasomal degradation of the of NOTCH1 receptor, resulting in a truncated, constantly active protein [7]. Additionally, recurrent mutations in the noncoding 3′UTR of NOTCH1 and rare, loss-of-function mutations in FBXW7, a ubiquitin ligase implicated in NOTCH1 turnover, have also been identified [15,17]. NOTCH1 signalling activation was confirmed to play a role in resistance to apoptosis and increased CLL cell survival [26–28]. In addition, recent studies revealed the alternative non-mutational mechanisms of NOTCH1 activation in CLL, indicating that constitutive activation of the NOTCH1 pathway in this leukemia is more frequent
than previously estimated by the incidence of genetic lesions [29]. Clinically, NOTCH1-mutated patients have been associated with more aggressive clinical presentations of the disease such as being chemorefractory and having a high risk of disease progression toward transformation into Richter syndrome. Affecting up to 10–15% of CLL patients at diagnosis, NOTCH1 mutations are an independent predictor of survival in CLL [27]. NOTCH1 mutations are more frequently detected in patients harbouring trisomy 12 and cases with unmutated IGHV genes [27]. CLL patients with NOTCH1 mutations do not benefit from rituximab-combining therapies, which may be related to lower levels of CD20 expression in NOTCH1 mutated cases [30,31], while a longer progression-free survival was demonstrated when treated with alemtuzumab [32]. Among anti-CD20 antibody therapies, obinutuzumab with higher efficacy compared to rituximab, has shown to overcome the refractoriness in CLL patients carrying NOTCH1 mutation [33].

The canonical NOTCH signalling pathway and potential pharmacological inhibitors are shown in Figure 1. Moreover, therapeutic strategy involving the administration of non-coding RNAs has emerged as a possible novel approach of targeting NOTCH signaling [34].

![Figure 1. NOTCH1 signaling pathway and potential inhibitory strategies.](image_url)

For this reason, targeting NOTCH signalling has emerged as a promising therapeutic strategy for CLL. Potential NOTCH1 signalling targeting mechanisms in CLL include secretase inhibitors (GSIs) and specific antibodies anti-NOTCH1 receptor. Lopez-Guerra et al. reported the antitumor effect of using the GSI PF-03084014 in combination with fludarabine in CLL cells carrying NOTCH1 mutations [35]. Additionally, the PF-03084014 and fludarabine combination impairs angiogenesis and CXCL12-induced responses associated with tumoral migration and invasion [23,35]. Moreover, GSIs were confirmed to have a therapeutic effect in T-cell acute lymphoblastic leukemia (T-ALL), where more than 50% of patients harbor NOTCH1 activating mutations [36]. The main limitations of the use of GSIs in clinical practice include non-selectivity and gastrointestinal toxicity [36]. Nevertheless, GSIs are still being explored in clinical trials with the aim of optimizing the dose regimen and reducing side effects through distinct formulations [37–39].
The other approach of targeting the NOTCH1 pathway is the use of antibodies to block NOTCH ligand/receptor interactions. Among different NOTCH ligands, delta-like ligands DLL4 and DLL1 play crucial roles in CLL, with DLL4 being the most potent stimulator of NOTCH signalling in NOTCH1-mutated CLL cases [40]. The specific antibodies against the specific NOTCH receptors have been already developed [41,42]. OMP-52M51, an anti-human NOTCH1 monoclonal antibody, was studied in xenograft models of T-ALL and demonstrated promising antitumor efficacy [43]. OMP-52M51 inhibits DLL4-induced Notch stimulation and cell proliferation and also reverses the Notch-induced MYC, CCND1, and NPM1 gene expression [44]. The study conducted by Lopez-Guerra et al. [40], suggested that DLL4 expressed by the tumor microenvironment activates NOTCH signaling in CLL. Based on this result, the protumour processes in CLL could be disrupted by specific NOTCH targeting.

3. SF3B1 Mutation

SF3B1 is a core component of the spliceosome, a complex of five small nuclear ribonucleoproteins RNA (snRNPs), the splicing machinery involved in the process of RNA editing through the removal of introns in protein-encoding genes [45]. The product of the SF3B1 gene is considered as an essential component that catalyses the removal of intronic sequences and ligates the exons into mature, functional mRNA [46]. The SF3B1 mutations lead to deregulation of the mRNA splicing process due to intron retention, exon skipping and abnormal splice site insertion. The functional consequences of SF3B1 mutations are associated with alteration of multiple cellular functions, including the DNA damage response, telomere maintenance and NOTCH pathway signalling [47].

Multiple bacterial-derived products and their synthetic analogs display antitumor activities and bind tightly to components of the spliceosome [48]. Together with other genes encoding splicing factors, SF3B1 is one of the most highly mutated genes in various hematological malignancies, including CLL. For this reason, drugs targeting the spliceosome are being sought. Among the first identified compounds displaying cytotoxic effects in tumor cell lines by an arrest in the G1 and G2/M phases of the cell cycle were FR901463, FR901464 and FR901465 (obtained from Pseudomonas spp.), GEX1 and pladienolides (Streptomyces spp.). Subsequently, synthetic analogs with improved stability and solubility were discovered such as spliceostatin A (SSA), meayamycin, sudemycins, E7107, and most recently, H3B-8800 [48–52].

The preclinical models have confirmed that splicing inhibitors are selectively lethal to tumor cells [53]. In a mouse model of leukemia, treatment with E7107 resulted in prolonged survival and reduced leukemic burden [54]. The oral analog of E7107, H3B-8800, inhibits cell growth in human AML cell lines and induces apoptosis preferentially in cells carrying the K700E SF3B1 mutation [53].

In CLL, in vitro studies characterizing the effect of exposure to FD-895, pladienolide B and SSA resulted in increased apoptosis of CLL cells regardless of SF3B1 status [15,55,56]. Similarly, promising effects both in vitro and in a xenograft model were observed with exposure to sudemycins, where even low doses of sudemycins provoked apoptosis of CLL cells. Sudemycin has also shown an enhanced antitumor response in combination with ibrutinib in CLL, which may be related to the alteration of BTK signaling [57].

Subsequently, human phase I clinical trials of E7107 were conducted, initially in patients with advanced solid tumours. The therapeutic effect of stabilization of tumor growth was achieved, however the study was discontinued due to optical and gastrointestinal toxicity [58]. The other compound, a selective small molecule SF3B1 modulator, H3B-8800, has been studied in patients with myelodysplastic syndromes, acute myeloid leukemia and chronic myelomonocytic leukemia and found to have a good safety profile and tolerability. However, neither objective complete nor partial response, except laboratory and clinical improvement, was observed [59]. The actual, ongoing clinical trials involving newly designed molecules targeting mutations/pathways of NOTCH, SF3B, MYD88/TLR, BIRC3 are presented in Table 1.
Table 1. Ongoing clinical trials associated with targeting mutations/pathways in haematological malignancies.

| Gene/Pathway | Drug/Mechanism of Action | Phase | Conditions | Identifier |
|--------------|--------------------------|-------|------------|------------|
| NOTCH        | CB-103/pan-NOTCH inhibitor | I/II  | Metastatic Solid Tumours, Haematological Malignancies | NCT03422679 |
| SF3B         | JNJ-64619178/Inhibitor of PRMT5 | I     | Neoplasms, Solid Tumor, NHL, MDS | NCT03573310 |
|             | H3B-8800/Spliceosome inhibitor | I     | MDS, AML, CMML | NCT02841540 |
| MYD88 /TLR  | CA-4948/IRAK4 kinase inhibitor | I/II  | NHL, WM/LPL, CLL/SLL | NCT03328078 |
|             | CA-4948/IRAK4 kinase inhibitor | I/II  | AML, MDS | NCT04278768 |
|             | SD-101/TLR9 agonist         | I     | NHL | NCT03410901 |
|             | SD-101/TLR9 agonist         | I/II  | B cell lymphoma | NCT02927964 |
|             | Poly-ICLC/TLR3 agonist      | I/II  | Low grade lymphoma | NCT01976585 |
| BIRC3        | ASTX660/cIAP1 and XIAP inhibitor | I     | AML | NCT04155580 |
|             | ASTX660/cIAP1 and XIAP inhibitor | I/II  | T-cell lymphoma | NCT04362007 |
|             | ASTX660/cIAP1 and XIAP inhibitor | I/II  | Lymphomas | NCT02503423 |

Table includes ongoing studies registered at ClinicalTrials.gov (Accessed date 10 August 2021). Abbreviations: AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CMML: chronic myelomonocytic leukemia; IRAK4: IL-1R-associated kinase 4; MDS: myelodysplastic syndromes; MYD88/TLR: myeloid differentiation primary response gene 88 / toll-like receptor; NHL: non-Hodgkin lymphoma; NOTCH: neurogenic locus notch homolog protein; Poly-ICLC: Polynosinic-polycytidylic acid, and poly-L-lysine; PRMT5: protein arginine methyltransferase 5; SF3B: splicing factor 3B subunit; SLL: small lymphocytic lymphoma; TLR: toll-like receptor; WM/LPL: macroglobulinemia/lymphoplasmacytic lymphoma.

4. MYD88 Mutation

MYD88 is a cytoplasmic adaptor protein that plays an essential role in the innate and adaptive immune response. The protein encoded by the MYD88 gene is required for signal transmission by toll-like receptors (TLRs), except TLR3, and receptors for IL-1 as well as IL-18 [60,61]. After stimulation, MYD88 activates the NF-κB pathway and the mitogen-activated protein kinase (MAPK) pathway by forming a signalling complex that consists of various intermediary proteins, such as IL-1R-associated kinases (IRAKs) and tumor necrosis factor receptor-associated factors (TRAFs), most notably TRAF6 [62,63].

A single-nucleotide change (c.794T.C), is the most common mutation of MYD88 resulting in a change from leucine into proline at position 265 (L265P) [64]. The functional effects of the MYD88 mutation include increased NF-κB activity, increased JAK-STAT3 signalling and production of pro-inflammatory cytokines such as IL-6, IL-10, and IFN-β, as well as enhanced survival of lymphoma cells [64,65]. The MYD88 mutation has been found at high frequencies in cutaneous diffuse large B cell lymphoma (DLBCL; 69%), primary central nervous system lymphoma (38%), Waldenström’s macroglobulinemia (WM; almost 100% of cases) and activated B cell DLBCL (39%), indicating its role in the pathogenesis of lymphoid neoplasias [65,66]. In CLL, MYD88 mutations occur at a variable frequency of 1.5% to 10% and are found predominantly in patients with mutated IGHV and chromosome 13q deletions, both of which are associated with lower-risk disease [18,67–69]. However, multiple studies in CLL have shown the MYD88 mutation to have a favourable prognosis [70] or no association with the course of disease [18,67], whereas others have shown the MYD88 mutation to be associated with an unfavourable prognosis [68]. Thus, the functional role of MYD88 in CLL has not been fully elucidated.

Several therapeutic strategies have been proposed to inhibit the TLR/MYD88 pathway directly or indirectly by targeting IRAK1 and IRAK4 in the myddosome-complex, TAK1 in downstream signalling, BTK in the BCR pathway, TLR9 in the My-T-BCR supercomplex, and components of the concurrently activated PI3K/AKT/mTOR and HCK pathways.
pathways [63, 71, 72]. Although the BTK is not a MYD88 (L265P)-specific target and is not directly involved with the MYD88-derived protein complex, inhibition of BTK has been widely studied and revealed as the most successful therapy in CLL [71]. Nevertheless, MYD88-derived peptides can induce T-cell responses, which supports the idea of a potential T-cell receptor-based immunotherapy [63].

As for IRAK inhibitors, several studies with promising results identified two compounds, ND-2158 and ND-2110, which blocked IRAK4 in vitro and in xenografts with human DLBCL cell lines [72, 73]. A recent study conducted by Giménez et al. [74] has shown similar effects in CLL in both in vitro and in vivo models. The dose-dependent antitumor effect confirmed the importance of the MYD88/TLR pathway in CLL and suggests IRAK4 may be a therapeutic target for this disease. Additionally, the combination of an IRAK4 inhibitor with ibrutinib or venetoclax demonstrated superior antitumor activity [74, 75]. The preclinical tests of IMO-8400, an oligonucleotide specifically designed to inhibit ligand activation of TLR7/8/9 have shown inhibition of cell signalling and reduction of tumor growth [76]. Two phase I/II clinical trials (NCT02252146 and NCT02363439) in MYD88-positive DLBCL and WM patients have been performed, with the results showing that IMO-8400 is well tolerated [71]. More research is required to implement MYD88-derived treatment in the future.

5. **BIRC3 Mutation**

The BIRC3 gene encodes a member of the inhibitor of apoptosis (IAP) family of proteins, c-IAP2. BIRC3 has been identified as a negative regulator of the MAP3K14 serine-threonine kinase and the alternative noncanonical NF-κB signaling pathway [77]. BIRC3 mutations, accounting for 2% to 10% of CLL patients, are associated with high-risk disease, shorter progression-free survival (PFS) and overall survival (OS) [78, 79]. There is an association between the BIRC3 mutations and unmaturated IGHV genes, trisomy 12 and deletion of 11q in CLL patients [78]. Functionally, BIRC3 mutation led to constitutive NFkB activation, which may contribute to the mechanism of resistance to treatment in leukemia and tumor growth through downregulation of the TP53 protein via MDM2 [80]. CLL patients harbouring BIRC3 mutations more commonly develop chemoresistance characterized by fludarabine resistance [78]. Additionally, BIRC3 mutations incidence is rare at the time of diagnosis, but in fludarabine-refractory patients is increased to approximately 25% [19]. The CLL14 phase 3 clinical showed a shorter progression-free survival in the chlorambucil-obinutuzumab arm versus venetoclax-obinutuzumab, reinforcing the role of BIRC3 mutations as a biomarker of chemoresistance [81]. In these patients, other treatments, such as cyclin-dependent kinase inhibitor, BTK inhibitor, B cell lymphoma 2 inhibitor, alemtuzumab and corticosteroids might be considered [82].

BIRC3 disrupting mutations in CLL lead to constitutive NF-κB pathway activation promoting proliferation and survival [83]. BIRC3 has no relevant role in physical inhibition of caspases resulting in direct inhibition of apoptosis but regulates NF-κB signalling [84]. Targeting NF-κB and inhibition of this prosurvival pathway represent a possible strategy for the treatment of CLL patients [85]. In vitro studies have shown that low or absent BIRC3 expression was associated with increased survival of CLL cells [86]. Silencing Map3K14 (also known as NIK–NF-κB-inducing kinase) decreased the levels of NFκB, which was followed by reduced viability of BIRC3-mutated cells [87]. Physiologically, BIRC3 catalyses MAP3K14 protein ubiquitination leading to proteosomal degradation [88]. With this regard, targeting Map3K14—the centrally activating kinase—remains under investigation [88]. Two NIK inhibitors (AM-0216 and AM-0650) demonstrated activity in myeloma cells with NIK-dependent activation of NF-κB [89]. However, the potential of NF-κB inhibitors in targeting the BIRC3 abnormalities requires further validated studies.

6. **Conclusions**

The mutational landscape in CLL is changing the understanding and management of the disease. Newly discovered mutations and their signalling pathways play key roles
in the course of the disease. The novel biomarkers should be considered in terms of prognosis as well as predictive factor. Nowadays, assessment of molecular abnormalities may contribute to the choice of treatment strategy. NOTCH1, SF3B1 and BIRC3 mutations are negative prognostic markers in CLL. Moreover, rituximab should be avoided in NOTCH1 mutated patients, while BIRC3 mutation is highlighted as a marker of chemorefractoriness. Ongoing studies directly affecting molecular pathways may open new opportunities in the management and treatment of CLL. Further research on the efficacy and safety of novel drugs is necessary to develop targeted, personalized therapy in CLL patients.

Author Contributions: Conceptualization, M.P. and K.G.; methodology, M.P.; writing—original draft preparation, M.P. and K.G.; writing—review and editing, M.P. and K.G.; supervision, K.G.; funding acquisition, K.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Polish Scientific Centre funds of grant NCN 2018/29/B/NZ5/02706.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations
APH-1/2: anterior pharynx-defective-1/2; CSL: CBF1/Su(H)/Lag-1; DLL: delta-like ligand; HAT: histone acetyltransferase; HES: hairy and enhancer of split-1; JAG: Jagged ligand; mAb: monoclonal antibody; MAML1: Mastermind-like 1; NICD: Notch intracellular domain; NRARP: Notch-regulated ankyrin-repeated protein; SKIP: ski-interacting protein; TACE, TNF-α-converting enzyme (also known as ADAM17).

References
1. Hallek, M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. Am. J. Hematol. 2017, 92, 946–965. [CrossRef]
2. Scarfo, L.; Ferreri, A.J.; Ghia, P. Chronic lymphocytic leukaemia. Crit. Rev. Oncol. Hematol. 2016, 104, 169–182. [CrossRef]
3. Yun, X.; Zhang, Y.; Wang, X. Recent progress of prognostic biomarkers and risk scoring systems in chronic lymphocytic leukemia. Biomark. Res. 2020, 8, 40. [CrossRef]
4. Montserrat, E.; Bauman, T.; Delgado, J. Present and future of personalized medicine in CLL. Best Pract. Res. Clin. Haematol. 2016, 29, 100–110. [CrossRef]
5. Juliusson, G.; Oscier, D.G.; Fitchett, M.; Ross, F.M.; Stockdill, G.; Mackie, M.J.; Parker, A.C.; Castoldi, G.L.; Guneo, A.; Knuttila, S.; et al. Prognostic subgroups in B-cell chronic lymphocytic leukemia defined by specific chromosomal abnormalities. N. Engl. J. Med. 1990, 323, 720–724. [CrossRef]
6. Döhner, H.; Stilgenbauer, S.; Benner, A.; Leupolt, E.; Kröber, A.; Bullinger, L.; Döhner, K.; Bentz, M.; Lichter, P. Genomic aberrations and survival in chronic lymphocytic leukemia. N. Engl. J. Med. 2000, 343, 1910–1916. [CrossRef] [PubMed]
7. Condoluci, A.; Rossi, D. Genetic mutations in chronic lymphocytic leukemia: Impact on clinical treatment. Expert Rev. Hematol. 2019, 12, 89–98. [CrossRef] [PubMed]
8. Damle, R.N.; Wasił, T.; Fais, F.; Ghioatto, F.; Valetto, A.; Allen, S.L.; Buchbinder, A.; Budman, D.; Dittmar, K.; Kolitz, J.; et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999, 94, 1840–1847. [CrossRef] [PubMed]
9. Hamblin, T.J.; Davis, Z.; Gardiner, A.; Oscier, D.G.; Stevenson, F.K. Unmutated Ig V (H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999, 94, 1848–1854. [CrossRef]
10. Stamatopoulos, K.; Belessi, C.; Moreno, C.; Boudjograh, M.; Guida, G.; Smilevska, T.; Belhoul, L.; Stella, S.; Stavroyianni, N.; Crespo, M.; et al. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: Pathogenetic implications and clinical correlations. Blood 2007, 109, 259–270. [CrossRef] [PubMed]
11. Rosenquist, R.; Ghia, P.; Hadzidimitriou, A.; Sutton, L.A.; Agathangelidis, A.; Balikas, P.; Darzentas, N.; Giudicelli, V.; Lefranc, M.P.; Langerak, A.W.; et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: Updated ERIC recommendations. Leukemia 2017, 7, 1477–1481. [CrossRef]
12. Baliakas, P.; Hadzidimitriou, A.; Sutton, L.A.; Minga, E.; Agathangelidis, A.; Nichelatti, M.; Tsanousa, A.; Scarfò, L.; Davis, Z.; Yan, X.J.; et al. Clinical effect of stereotyped B-cell receptor immunoglobulins in chronic lymphocytic leukaemia: A retrospective multicentre study. *Lancet Haematol*. **2014**, *1*, e74–e84. [CrossRef]

13. Baliakas, P.; Agathangelidis, A.; Hadzidimitriou, A.; Sutton, L.A.; Minga, E.; Tsanousa, A.; Scarfò, L.; Davis, Z.; Yan, X.J.; Shanafelt, T.; et al. Not all IGHV3-21 chronic lymphocytic leukaemias are equal: Prognostic considerations. *Blood* **2015**, *125*, 856–859. [CrossRef]

14. Fabbri, G.; la-Favera, R. The molecular pathogenesis of chronic lymphocytic leukaemia. *Nat. Rev. Cancer* **2016**, *16*, 145–162. [CrossRef]

15. Tripathi, R.; Lee-Verges, E.; Higashi, M.; Gimenez, N.; Rosich, L.; Lopez-Guerra, M.; Colomer, D. New drug discovery approaches targeting recurrent mutations in chronic lymphocytic leukaemia. *Expert Opin. Drug Discov.* **2017**, *12*, 1041–1052. [CrossRef]

16. Rossi, D.; Fangazio, M.; Gaidano, G. The spectrum of genetic defects in chronic lymphocytic leukaemia. *Mediterr. J. Hematol. Infect. Dis.* **2012**, *4*, e2012076. [CrossRef] [PubMed]

17. Puente, X.S.; Benavente, M.; Ait-Akhannouch, M.; Villamor, N.; Gutiérrez-Abril, J.; Martín-Subero, J.I.; Munar, M.; Rubio-Pérez, C.; Jares, P.; Aymerich, M.; et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. *Nature* **2015**, *526*, 519–524. [CrossRef] [PubMed]

18. Putowski, M.; Podgórska, M.; Piróg, M.; Knap, J.; Zalesa, J.; Zurawski, K.; Karczmarszcz, A.; Włosiuk, P.; et al. Prognostic impact of NOTCH1, MYD88, and SF3B1 mutations in Polish patients with chronic lymphocytic leukaemia. *Pol. Arch. Intern. Med.* **2017**, *127*, 238–246. [CrossRef] [PubMed]

19. Rossi, D.; Fangazio, M.; Rasi, S.; Vaisitti, T.; Cresta, S.; Chiaretti, S.; Del Giudice, I.; Fabbri, G.; Bruscaggin, A.; et al. Disruption of BIRC3 associates with fludarabine chemorefractoriness in TP53 wild-type chronic lymphocytic leukaemia. *Blood* **2012**, *119*, 2854–2862. [CrossRef] [PubMed]

20. Rossi, D.; Khiabanian, H.; Spina, V.; Ciardullo, C.; Bruscaggin, A.; Famà, R.; Rasi, S.; Monti, S.; Deambrogi, C.; De Paoli, L.; et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukaemia. *Blood* **2014**, *123*, 2139–2147. [CrossRef] [PubMed]

21. Hallek, M.; Cheson, B.D.; Catovsky, D.; Caligaris-Cappio, F.; Dighiero, G.; Döhner, H.; Hillmen, P.; Keating, M.; Montserrat, E.; Catovsky, D.; et al. Treatment of chronic lymphocytic leukemia. *N. Engl. J. Med.* **2008**, *358*, 2274–2294. [CrossRef] [PubMed]

22. Aster, J.C.; Pear, W.S.; Blacklow, S.C. Notch Signaling in Leukemia. *Annu. Rev. Pathol.* **2008**, *3*, 587–613. [CrossRef]

23. Puente, X.S.; Pinyol, M.; Quesada, V.; Conde, L.; Ordóñez, G.R.; Villamor, N.; Escaramis, G.; Jares, P.; Beà, S.; Gómez-Diaz, M.; et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature* **2011**, *475*, 101–1005. [CrossRef]

24. Rosati, E.; Sabatini, R.; Rampino, G.; Tabilio, A.; Di Ianni, M.; Fettucciari, K.; Bartoli, A.; Coaccioli, S.; Scerpanti, I.; Marconi, P.; Constitutively activated Notch signaling is involved in survival and apoptosis resistance of B-CLL cells. *Blood* **2009**, *113*, 856–865. [CrossRef] [PubMed]

25. Rossi, D.; Rasi, S.; Fabbri, G.; Spina, V.; Fangazio, M.; Forconi, F.; Marasca, R.; Laurenti, L.; Bruscaggin, A.; Cerri, M.; et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukaemia. *Blood* **2011**, *119*, 521–529. [CrossRef] [PubMed]

26. Rossi, D.; Banfi, S.; Fabbri, S.; Fabbri, G.; Spina, V.; Fangazio, M.; Forconi, F.; Marasca, R.; Laurenti, L.; Bruscaggin, A.; Cerri, M.; et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukaemia. *Blood* **2011**, *119*, 521–529. [CrossRef] [PubMed]

27. Rosati, E.; Sabatini, R.; Rampino, G.; Tabilio, A.; Di Ianni, M.; Fettucciari, K.; Bartoli, A.; Coaccioli, S.; Scerpanti, I.; Marconi, P.; Constitutively activated Notch signaling is involved in survival and apoptosis resistance of B-CLL cells. *Blood* **2009**, *113*, 856–865. [CrossRef] [PubMed]

28. Fabbri, G.; Holmes, A.B.; Viganotti, M.; Scuoppo, C.; Belver, L.; Herranz, D.; Yan, X.J.; Kieso, Y.; Rossi, D.; Gaidano, G.; et al. Common nonmutational NOTCH1 activation in chronic lymphocytic leukaemia. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 2911–2919. [CrossRef]

29. Bittolo, T.; Pozzo, F.; Bomben, R.; D’Agaro, T.; Bravin, V.; Bulian, P.; Rossi, F.M.; Zucchetto, A.; Degani, M.; Macor, P.; et al. Mutations in the 3’ untranslated region of NOTCH1 are associated with low CD20 expression levels chronic lymphocytic leukemia. *Haematologica* **2017**, *102*, 305–309. [CrossRef]

30. Estenfelder, S.; Tausch, E.; Robrecht, S.; Bahlo, J.; Goede, V.; Ritgen, M.; van Dongen, J.J.M.; Langerak, A.W.; Fingerle-Rowson, G.; Kneba, M.; et al. Gene Mutations and Treatment Outcome in the Context of Chlorambucil (Cib) without or with the Addition of Rituximab (R) or Obinutuzumab (GA-101, G)—Results of an Extensive Analysis of the Phase III Study CLL11 of the German CLL Study Group. *Blood* **2016**, *128*, 3227. [CrossRef]
34. Pepe, F.; Balatti, V. Role of Non-Coding RNAs in the Development of Targeted Therapy and Immunotherapy Approaches for Chronic Lymphocytic Leukemia. J. Clin. Med. 2020, 9, 593. [CrossRef]
35. López-Guerra, M.; Xargay-Torrent, S.; Rosich, L.; Montrave-A.; Roldán, J.; Matas-Céspedes, A.; Villamar, N.; Aymerich, M.; López-Otin, C.; Pérez-Galán, P.; et al. The γ-secretase inhibitor PF-03084014 combined with fludarabine antagonizes migration, invasion and angiogenesis in NOTCH1-mutated CLL cells. Leukemia 2015, 1, 96–106. [CrossRef]
36. Hales, E.C.; Tabb, J.W.; Mathrery, L.H. New insights into Notch1 regulation of the PI3K-AKT-mTOR1 signaling axis: Targeted therapy of γ-secretase inhibitor resistant T-cell acute lymphoblastic leukemia. Cell Signal. 2014, 1, 149–161. [CrossRef]
37. Andersson, E.R.; Lendahl, U. Therapeutic modulation of Notch signalling—are we there yet? Nat. Rev. Drug Discov. 2014, 13, 357–378. [CrossRef]
38. López-Nieva, P.; González-Sánchez, L.; Cobos-Fernández, M.A.; Córdoba, R.; Santos, J.; Fernández-Piqueras, J. More Insights on the Use of γ-Secretase Inhibitors in Cancer Treatment. Oncologist 2021, 26, 298–305. [CrossRef]
39. Huang, D.; Qiu, J.; Kuang, S.; Deng, M. In Vitro Evaluation of Clinical Candidates of γ-Secretase Inhibitors: Effects on Notch Inhibition and Promoting Beige Adipogenesis and Mitochondrial Biogenesis. Pharm. Res. 2020, 37, 185. [CrossRef]
40. López-Guerra, M.; Xargay-Torrent, S.; Fuentes, P.; Roldán, J.; González-Farré, B.; Rosich, L.; Silkenstedt, E.; García-León, M.J.; Lee-Vergés, E.; Giménez, N.; et al. Specific NOTCH1 antibody targets DLL4-induced proliferation, migration, and angiogenesis in NOTCH1-mutated CLL cells. Oncogene 2020, 39, 1185–1197. [CrossRef]
41. Aste-Amézaga, M.; Zhang, N.; Lineberger, J.E.; Arnold, B.A.; Toner, T.J.; Gu, M.; Huang, L.; Vitelli, S.; Vo, K.T.; Haytko, P.; et al. Characterization of Notch1 antibodies that inhibit signaling of both normal and mutated Notch1 receptors. PLoS ONE 2010, 5, e9094. [CrossRef][PubMed]
42. Wu, Y.; Cain-Hom, C.; Choy, L.; Hagenbeek, T.J.; de Leon, G.P.; Chen, Y.; Finkle, D.; Venook, R.; Wu, X.; Ridgway, J.; et al. Therapeutic antibody targeting of individual Notch receptors. Nature 2010, 464, 1052–1057. [CrossRef]
43. Agunsdei, V.; Minuzzo, S.; Frasson, C.; Grassi, A.; Axelrod, F.; Satyal, S.; Gurney, A.; Hoey, T.; Seganfredo, E.; Basso, G.; et al. Therapeutic antibody targeting of Notch1 in T-acute lymphoblastic leukemia xenografts. Leukemia 2014, 28, 278–288. [CrossRef][PubMed]
44. Silkenstedt, E.; Arenas, F.; Colom-Sanmartí, B.; Xargay-Torrent, S.; Higashi, M.; Giró, A.; Rodriguez, V.; Fuentes, P.; Aulitzky, W.E.; van der Kuip, H.; et al. Notch1 signaling in NOTCH1-mutated mantle cell lymphoma depends on Delta-Like ligand 4 and is a potential target for specific antibody therapy. J. Exp. Clin. Cancer Res. 2019, 38, 446. [CrossRef]
45. Zakrzewska, E.; Pirog, M.; Purkot, J.; Giannopoulos, K. Novel prognostic molecular factors: A quantum leap in the field of chronic lymphocytic leukemia. Folia Histochem. Cytobiol. 2017, 55, 95–106. [CrossRef]
46. Yoshimi, A.; Abdel-Wahab, O. Molecular Pathways: Understanding and Targeting Mutant Spliceosomal Proteins. Clin. Cancer Res. 2017, 23, 336–341. [CrossRef]
47. Wang, L.; Brooks, A.N.; Fan, J.; Wan, Y.; Gambe, R.; Li, S.; Hergert, S.; Yin, S.; Freeman, S.S.; Levin, J.Z.; et al. Transcriptomic Characterization of SF3B1 Mutation Reveals Its Pleiotropic Effects in Chronic Lymphocytic Leukemia. Cancer Cell. 2016, 30, 750–763. [CrossRef][PubMed]
48. Bonnal, S.; Vigevani, L.; Valcarcel, J. The spliceosome as a target of novel antitumour drugs. Nat. Rev. Drug Discov. 2012, 11, 847–859. [CrossRef][PubMed]
49. Fan, L.; Lagiisetti, C.; Edwards, C.C.; Webb, T.R.; Potter, P.M. Sudemycins, novel small molecule analogues of FR901464, induce alternative gene splicing. ACS Chem. Biol. 2011, 6, 582–589. [CrossRef]
50. Sakai, T.; Sameshima, T.; Matsufuji, M.; Kawamura, N.; Dobashi, K.; Mizui, Y. Pladienolides, new substances from culture of Streptomyces platensis Mer-11107. I. Taxonomy, fermentation, isolation and screening. J. Antibiot. 2004, 57, 173–179. [CrossRef][PubMed]
51. Kotate, Y.; Sagane, K.; Ota, W.; Mimori-Kiyosue, Y.; Shimizu, H.; Uesugi, M.; Ishihama, Y.; Iwata, M.; Mizui, Y. Splicing factor SF3b as a target of the antitumour natural product pladienolide. Nat. Chem. Biol. 2007, 3, 570–575. [CrossRef][PubMed]
52. Seiler, M.; Yoshimi, A.; Darman, R.; Chan, B.; Keaney, G.; Thomas, M.; Agrawal, A.A.; Caleb, B.; Csibi, A.; Sean, E.; et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nat. Med. 2018, 24, 497–504. [CrossRef][PubMed]
53. Brierley, C.K.; Steensma, D.P. Targeting Splicing in the Treatment of Myelodysplastic Syndromes and Other Myeloid Neoplasms. Curr. Hematol. Malig. Rep. 2016, 11, 408–415. [CrossRef][PubMed]
54. Lee, S.C.; Dvinge, H.; Kim, E.; Cho, H.; Micol, J.B.; Chung, Y.R.; Durham, B.H.; Yoshimi, A.; Kim, Y.J.; Thomas, M.; et al. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. Nat Med. 2016, 22, 672–678. [CrossRef][PubMed]
55. Kashyap, M.K.; Kumar, D.; Villa, R.; La Clair, J.J.; Benner, C.; Sasik, R.; Jones, H.; Ghia, E.M.; Rassenti, L.Z.; Kipps, T.J.; et al. Targeting the spliceosome in chronic lymphocytic leukemia with the macroline FD-895 and pladienolide-B. Haematologica 2015, 100, 945–954. [CrossRef]
56. Larrayoz, M.; Blakemore, S.J.; Dobson, R.C.; Blunt, M.D.; Rose-Zerilli, M.J.; Walewska, R.; Duncombe, A.; Osier, D.; Koide, K.; Forconi, F.; et al. The SF3B1 inhibitor spliceostatin A (SSA) elicits apoptosis in chronic lymphocytic leukaemia cells through downregulation of Mcl-1. Leukemia 2016, 30, 351–360. [CrossRef][PubMed]
57. Xargay-Torrent, S.; López-Guerra, M.; Rosich, L.; Montraveta, A.; Roldán, J.; Rodriguez, V.; Villamar, N.; Aymerich, M.; Lagisetti, C.; Webb, T.R.; et al. The splicing modifier modulator denucin induces a specific antitumor response and cooperates with ibrutinib in chronic lymphocytic leukemia. Oncotarget 2015, 6, 22734–22749. [CrossRef] [PubMed]

58. Eskens, F.A.; Ramos, F.J.; Burger, H.; O’Brien, J.P.; Piera, A.; de Jonge, M.J.; Mizui, Y.; Wiemer, E.A.; Carreras, M.J.; Baselga, J.; et al. Phase I pharmacokinetic and pharmacodynamic study of the first-in-class spliceosome inhibitor E7107 in patients with advanced solid tumors. Clin. Cancer Res. 2013, 19, 6296–6304. [CrossRef] [PubMed]

59. Steensma, D.P.; Wernke, M.; Klimk, V.M.; Greenberg, P.L.; Font, P.; Komrokji, R.S.; Yang, J.; Brunner, A.M.; Carraway, H.E.; Ades, L.; et al. Results of a clinical trial of H3B-8800, a splicing modulator, in patients with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML) or chronic myelomonocytic leukemia (CMML). Blood 2019, 134, 673. [CrossRef]

60. Saikh, K.U. MyD88 and beyond: A perspective on MyD88-targeted therapeutic approach for modulation of host immunity. Immunol. Res. 2021, 69, 117–128. [CrossRef]

61. Iwasaki, A.; Medzhitov, R. Regulation of adaptive immunity by the innate immune system. Science 2010, 327, 291–295. [CrossRef] [PubMed]

62. Rawlings, D.J.; Schwartz, M.A.; Jackson, S.W.; Meyer-Bahlburg, A. Integration of B cell responses through Toll-like receptors and antigen receptors. Nat. Rev. Immunol. 2012, 12, 282–294. [CrossRef] [PubMed]

63. Yu, X.; Li, W.; Deng, Q.; Li, L.; His, E.D.; Young, K.H.; Zhang, M.; Li, Y. MYD88 L265P Mutation in Lymphoid Malignancies. Blood Cancer J. 2019, 9, 174. [CrossRef] [PubMed]

64. Wang, J.Q.; Jeelall, Y.S.; Ferguson, L.L.; Horikawa, K. Toll-Like Receptors and Cancer: MYD88 Mutation and Inflammation. Oncotarget 2015, 6, 2337–2348. [CrossRef] [PubMed]

65. Yu, X.; Li, W.; Deng, Q.; Li, L.; His, E.D.; Young, K.H.; Zhang, M.; Li, Y. MYD88 L265P Mutation in Lymphoid Malignancies. Blood Cancer J. 2019, 9, 174. [CrossRef] [PubMed]

66. Rawlings, D.J.; Schwartz, M.A.; Jackson, S.W.; Meyer-Bahlburg, A. Integration of B cell responses through Toll-like receptors and antigen receptors. Nat. Rev. Immunol. 2012, 12, 282–294. [CrossRef] [PubMed]

67. Baliakas, P.; Hadzidimitriou, A.; Agathangelidis, A.; Rossi, D.; Sutton, L.A.; Kminkova, J.; Scarfo, L.; Pospisilova, S.; Gaidano, G.; Stamatopoulos, K.; et al. Prognostic relevance of MYD88 mutations in CLL: The jury is still out. Blood 2015, 126, 1043–1044. [CrossRef]

68. Qin, S.C.; Xia, Y.; Miao, Y.; Zhu, H.Y.; Wu, J.Z.; Fan, L.; Li, J.Y.; Xu, W.; Qiao, C. MYD88 mutations predict unfavorable prognosis in Chronic Lymphocytic Leukemia patients with mutated IGHV gene. Blood Cancer J. 2017, 7, 651. [CrossRef]

69. Shuai, W.; Lin, P.; Strati, P.; Patel, K.P.; Routbort, M.J.; Hu, S.; Wei, P.; Khoury, J.D.; You, M.J.; Loghavi, S.; et al. Oncogenically active MYD88 in chronic lymphocytic leukemia. Nature 2011, 470, 115–119. [CrossRef] [PubMed]

70. Wang, J.Q.; Jeelall, Y.S.; Horikawa, K. Emerging targets in human lymphoma: Targeting the MYD88 mutation. Blood Lymphat. Cancer 2013, 3, 53–61.

71. de Groen, R.A.L.; Schrader, A.M.R.; Kersten, M.J.; Palo, S.T.; Vermaat, J.S.P. MYD88 in the driver’s seat of B-cell lymphomagenesis: From molecular mechanisms to clinical implications. Haematologica 2015, 100, 2825–2837. [CrossRef] [PubMed]

72. Martínez-Trillos, A.; Pinyol, M.; Navarro, A.; Aymerich, M.; Jares, P.; Juan, M.; Rozman, M.; Colomer, D.; Delgado, J.; Giné, E.; et al. Mutations in TLR/MYD88 pathway identify a subset of young chronic lymphocytic leukemia patients with favorable outcome. Blood 2014, 123, 3790–3796. [CrossRef]

73. de Groen, R.A.L.; Schrader, A.M.R.; Kersten, M.J.; Palo, S.T.; Vermaat, J.S.P. MYD88 in the driver’s seat of B-cell lymphomagenesis: From molecular mechanisms to clinical implications. Haematologica 2015, 100, 2825–2837. [CrossRef] [PubMed]

74. Weber, A.N.R.; Cardona, G.Y.; Cinà, O.; Reinhardt, H.C.; Pezzuto, A.; Wolz, O.O. Oncogenic MYD88 mutations in lymphoma: Novel insights and therapeutic possibilities. Cancer Immunol. Immunother. 2018, 67, 1797–1807. [CrossRef] [PubMed]

75. Kelly, P.N.; Romero, D.L.; Yang, Y.; Shaffer, A.L.; Chaudhary, D.; Robinson, S.; Miao, W.; Rui, L.; Westlin, W.F.; Kapeller, R.; et al. Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmunity disorders and lymphoid malignancy. J. Exp. Med. 2015, 212, 2189–2201. [CrossRef]

76. Giménez, N.; Schulz, R.; Higashi, M.; Aymerich, M.; Villamar, N.; Delgado, J.; Juan, M.; López-Guerra, M.; Campo, E.; Rosich, L.; et al. Targeting IRAK4 disrupts inflammatory pathways and delays tumor development in chronic lymphocytic leukemia. Leukemia 2020, 34, 100–114. [CrossRef]

77. Dadashian, E.L.; McAuley, E.M.; Liu, D.; Shaffer, A.L.; Young, R.M.; Iyer, J.R.; Kruhlak, M.J.; Staudt, L.M.; Wiestner, A.; Herman, S.E.M. TLR Signaling Is Activated in Lymph Node-Resident CLL Cells and Is Only Partially Inhibited by Ibrutinib. Cancer Res. 2019, 79, 360–371. [CrossRef]

78. Weil, L.; Staudt, L.; Wiestner, A.; Herman, S.E.M. TLR Signaling Is Activated in Lymph Node-Resident CLL Cells and Is Only Partially Inhibited by Ibrutinib. Cancer Res. 2019, 79, 360–371. [CrossRef]

79. Brenner, L.; Arbe, R.D.; Sullivan, T. IMO-8400, an antagonist of toll-like receptors 7, 8, and 9, in development for genetically defined B-cell lymphomas: Safety in phase 1 and phase 2 clinical trials. Blood 2014, 124, 3101. [CrossRef]

80. Zarnegar, B.J.; Wang, Y.; Mahoney, D.J.; Dempsey, P.W.; Cheung, H.H.; He, J.; Shibata, T.; Yang, X.; Yeh, W.C.; Mak, T.W.; et al. Noncanonical NF-kappB activation requires coordinated assembly of a regulatory complex of the adaptors cIAP1, cIAP2, TRAF2 and TRAF3 and the kinase NIK. Nat. Immunol. 2008, 9, 1371–1378. [CrossRef] [PubMed]

81. Chiaretti, S.; Marinelli, M.; Del Giudice, I.; Bonina, S.; Picciocchi, A.; Messina, M.; Vignetti, M.; Rossi, D.; Di Maio, V.; Mauro, F.R.; et al. NOTCH1, SF3B1, BIRC3 and TP53 mutations in patients with chronic lymphocytic leukemia undergoing first-line treatment: Correlation with biological parameters and response to treatment. Leuk. Lymphoma 2014, 55, 2785–2792. [CrossRef] [PubMed]
80. Lau, R.; Niu, M.Y.; Pratt, M.A. cIAP2 represses IKK- mediated activation of MDM2 to prevent p53 degradation. *Cell Cycle* 2012, 11, 4009–4019. [CrossRef]

81. Tausch, E.; Bahlo, J.; Robrecht, S.; Schneider, C.; Bloehdorn, J.; Schrell, S.; Galler, C.; Al-Sawaf, O.; Fink, A.M.; Eichhorst, B.; et al. Genetic markers and outcome in the CLL14 trial of the GCLLSG comparing front line obinutuzumab plus chlorambucil or venetoclax in patients with comorbidity. *HemaSphere* 2019, 3, 4. [CrossRef]

82. Rozovski, U.; Hazan-Halevy, I.; Keating, M.J.; Estrov, Z. Personalized medicine in CLL: Current status and future perspectives. *Cancer Lett.* 2014, 352, 4–14. [CrossRef]

83. Gaidano, G.; Rossi, D. The mutational landscape of chronic lymphocytic leukemia and its impact on prognosis and treatment. *Hematology Am. Soc. Hematol. Educ. Program.* 2017, 1, 329–337. [CrossRef]

84. Silke, J.; Vucic, D. IAP family of cell death and signaling regulators. *Methods Enzymol.* 2014, 545, 35–65.

85. Mansouri, L.; Papakonstantinou, N.; Ntoufa, S.; Stamatopoulos, K.; Rosenquist, R. NF-κB activation in chronic lymphocytic leukemia: A point of convergence of external triggers and intrinsic lesions. *Semin. Cancer Biol.* 2016, 39, 40–48. [CrossRef]

86. Asslaber, D.; Wacht, N.; Leisch, M.; Qi, Y.; Maeding, N.; Hufnagl, C.; Jansko, B.; Zaborsky, N.; Villunger, A.; Hartmann, T.N.; et al. BIRC3 Expression Predicts CLL Progression and Defines Treatment Sensitivity via Enhanced NF-κB Nuclear Translocation. *Clin. Cancer Res.* 2019, 25, 1901–1912. [CrossRef]

87. Diop, F.; Moia, R.; Favini, C.; Spaccarotella, E.; De Paoli, L.; Bruscaggin, A.; Spina, V.; Terzi-di-Bergamo, L.; Arruga, F.; Tarantelli, C.; et al. Biological and clinical implications of BIRC3 mutations in chronic lymphocytic leukemia. *Haematologica* 2020, 105, 448–456. [CrossRef][PubMed]

88. Sun, S.C. The noncanonical NF-κB pathway. *Immunol. Rev.* 2012, 246, 125–140. [CrossRef][PubMed]

89. Demchenko, Y.N.; Brents, L.A.; Li, Z.; Bergsagel, L.P.; McGee, L.R.; Kuehl, M.W. Novel inhibitors are cytotoxic for myeloma cells with NFκB inducing kinase-dependent activation of NFκB. *Oncotarget* 2014, 5, 4554–4566. [CrossRef]