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# Prognostic Markers in the Era of Targeted Therapies

Sorang Kang[a] Inhye E. Ahn[b]

[a]College of Medicine, Catholic University of Korea, Seoul, Republic of Korea; [b]Dana-Farber Cancer Institute, Boston, MA, USA



**Keywords**
Chronic lymphocytic leukemia · Prognostic markers · Targeted therapy

**Abstract**

***Background:*** Small molecules targeting Bruton's tyrosine kinase (BTK) and B-cell lymphoma-2 have become the standard of care for the treatment of chronic lymphocytic leukemia (CLL), replacing chemoimmunotherapy (CIT) in most clinical settings. Ongoing trials explore targeted combinations and minimal residual disease-driven treatment cessation. These dramatic shifts in the current and upcoming treatment landscape of CLL raise the need to reevaluate existing prognostic markers and develop novel ones. ***Summary:*** This review examines prognostic markers in CLL patients treated with standard and investigational targeted therapies. Specifically, initial treatment of *TP53* aberrant patients with a BTK inhibitor can achieve 70% progression-free survival (PFS) at 5 years, outperforming the 15% 5-year PFS with a CIT regimen containing fludarabine, cyclophosphamide, and rituximab (FCR). The prognostic implications of the immunoglobulin heavy chain variable gene (IGHV) mutation status have also changed. Unmutated IGHV is associated with inferior PFS and overall survival after FCR and inferior PFS with fixed-duration therapy with venetoclax and anti-CD20 monoclonal antibody but not with continuous BTK inhibitor treatment. ***Key Messages:*** (1) Genetic variables (e.g., *TP53* aberration, IGHV mutation, complex karyotype) have a prognostic significance in CLL patients treated with targeted therapy. (2) Understanding the prognostic and predictive values of these markers is critical for the development of a risk-adapted treatment strategy in CLL.


## Introduction

Chronic lymphocytic leukemia (CLL) is a disease of malignant B cells whose survival and proliferation are driven by the activation of the B-cell receptor (BCR) signaling pathway and overexpression of pro-survival proteins such as B-cell lymphoma-2 (BCL2). The current standard of care leverages these cellular mechanisms by targeting the BCR signaling pathway with a Bruton's tyrosine kinase (BTK) inhibitor (BTKi) or promoting cellular apoptosis with a BCL2 inhibitor (BCL2i) [1]. Ibrutinib, acalabrutinib, and zanubrutinib are covalent BTKis approved by the US Food and Drug Administration for the treatment of CLL. Venetoclax is the only BCL2i approved to date which is frequently used in combination with an anti-CD20 monoclonal antibody such as rituximab and obinutuzumab.

Treatment regimens incorporating targeted agents have dramatically improved the patient outcome and fundamentally changed the treatment landscape of CLL from chemoimmunotherapy (CIT) to targeted therapy. In randomized frontline trials comparing BTKi-based

karger@karger.com
www.karger.com/aha


Correspondence to:
Inhye E. Ahn, Inhye_Ahn@dfci.harvard.edu

Karger

regimens to CIT, progression-free survival (PFS) was significantly better with BTKis across the studies [2–6]. Additionally, overall survival (OS) benefit was observed in the ECOG E1912 study which compared ibrutinib and rituximab (IR) with fludarabine, cyclophosphamide, and rituximab (FCR) in fit, younger patients with treatment-naïve (TN) CLL (3-year OS: 99% for IR and 92% for FCR) [4]. The OS improvement continued to be observed in the recently updated data from the E1912 study at a median follow-up of 5.8 years [7]. Initial treatment with venetoclax plus obinutuzumab (VO) also improved PFS compared to chlorambucil and obinutuzumab among patients with older age or comorbidities [8–10]. More recently, the CLL13 study comparing venetoclax-based regimens with CIT in fit, younger TN CLL patients demonstrated higher rates of undetectable minimal residual disease (uMRD) and improved PFS in the VO-containing arms [11–13].

With shifts in treatment approaches and outcomes, changes in the prognostic significance of markers are inevitable. Genetic variables such as complex karyotype (CK) and selected driver gene mutations have gained prognostic importance, while clinical staging and age have become less critical in the context of targeted therapy. Not only the type of treatment but also the treatment duration can affect the role of prognostic markers. For instance, the attainment of uMRD has been associated with prolonged treatment-free survival after fixed-duration therapy with CIT. However, uMRD is uncommonly observed and does not impact long-term outcome during continuous BTKi monotherapy [9, 14, 15]. Critical to the development of a risk-adapted treatment approach in CLL is a precise understanding of the impact of each prognostic marker and its predictive value in selecting patients who might benefit from specific treatment approaches [16]. This review assesses established and emerging prognostic markers in CLL in relevance to targeted therapy.

## *TP53* Aberration

*TP53* gene, mapped at chromosomal band 17p13.1 and encoding p53 tumor suppressor protein, has a critical role in regulating cellular survival signals [17, 18], apoptosis [19, 20], and DNA repair machinery [21]. Most *TP53* mutations occur within the DNA binding domain of the gene (97%) [22, 23] and either the deletion of the short arm of chromosome 17 (del17p) or mutation of *TP53* has functional consequences as well as concurrent deletion and mutation of the gene [24, 25]. Herein, we refer to del17p and/or *TP53* mutation as *TP53* aberration.

*TP53* aberration is found in 5%–12% of TN CLL patients and up to 30% of relapsed or refractory (RR) CLL [26]. Prospective and retrospective studies demonstrated the strong negative impact of *TP53* aberration on CLL outcome, which manifests as primary resistance to or short duration of remission after CIT and inferior survival [27]. In studies investigating CLL driver genes in CIT-treated CLL patients, *TP53* mutation had a more negative impact on prognosis than any other mutations (i.e., *NOTCH1, SFB1*, *MYD88*, *BIRC3*) [28], increasing the risk of death by 4-fold [29–31]. Patients with *TP53* aberration have inferior PFS and OS after initial treatment with FCR compared to those with wild-type *TP53* (median PFS and OS: 15 and 42 months for the *TP53* aberrant group vs. 59 months and not reached for the wild-type *TP53* group, respectively) [27]. As a result, International Workshop on CLL (iwCLL) guidelines recommend assessment of *TP53* using both FISH and sequencing for all CLL patients before treatment initiation [32].

The outcome of *TP53* aberrant CLL markedly improved with targeted therapy (Table 1). In the RESONATE-17 study which exclusively enrolled RR patients with del17p, treatment with ibrutinib resulted in 2-year PFS and OS of 63% and 75%, respectively [33], which contrasted with the historical median PFS of 3 months when FCR was used in this population [34]. Response to a BTKi is particularly durable when it is given as initial therapy. In the NIH phase 2 study including 34 TN CLL patients with *TP53* aberration, continuous treatment with single-agent ibrutinib led to 5-year PFS and OS of 70% and 85%, respectively [35]. A pooled analysis of 89 TN, *TP53* aberrant CLL patients treated with ibrutinib demonstrated similar results (4-year PFS: 79%, 4-year OS: 88%) [36].

Long-term experience with BTKis has provided novel insights relevant to the role of *TP53* aberration in CLL. First, *TP53* aberration is associated with less durable response to a BTKi in RR CLL but not in TN CLL. The Alliance A041202 study is a three-arm randomized study testing two ibrutinib-containing regimens (ibrutinib with or without rituximab) and conventional CIT with bendamustine and rituximab (BR) in TN CLL [37]. At a median follow-up of 55 months, the study showed no difference in PFS based on the *TP53* aberration status within the two ibrutinib-containing arms, suggesting that ibrutinib can overcome the poor prognostic impact of *TP53* aberration in the frontline setting. However, *TP53* aberration continues to be associated with shorter PFS in RR CLL treated with ibrutinib (median PFS: 36–41 months) [14, 45]. Second, *TP53* aberration is associated

**Table 1.** Clinical outcome of CLL patients with or without *TP53* aberration

| Study | Treatment | *N*, all | N, *TP53* aberration* | Outcome | Ref |
|---|---|---|---|---|---|
| TN | | | | | |
| GCLL8 | FCR | 316 | 72 | Median PFS: 15 months with $TP53^{MUT}$ versus 59 months without $TP53^{MUT}$ (HR 3.2, $p < 0.001$); Median OS: 42 months with $TP53^{MUT}$ versus not reached without $TP53^{MUT}$ (HR 4.4, $p < 0.001$) | [27] |
| NIH *TP53* cohort | IBR | 34 | 34 (all) | 5 years PFS: 70%; 5 years OS: 85% | [35] |
| Pooled analysis of patients with *TP53* ab | IBR +/− CD20 mAb | 89 | 89 (all) | 4 years PFS: 79%; 4 years OS: 88% | [36] |
| Alliance A041202 | IBR+/−R | 364 | 34 | 4 years PFS not reported based on the *TP53* status; No PFS or OS difference in subgroups with or without *TP53* ab | [37] |
| SEQUOIA Arm D | ZANU | 109 | 109 (all) | 18 months PFS: 89%; 18 months OS: 95% | [38] |
| CLL14 | VO | 216 | 49 | 5 years PFS: 41% with *TP53* ab versus 66% without *TP53* ab; 5 years OS: 60% with *TP53* ab versus 86% without *TP53* ab | [10] |
| MDACC phase 2 | IV | 80 | 11 $TP53^{MUT}$; 14 del17p | PFS and OS not reported by the *TP53* status; BM-uMRD rate after cycle 24: 45% with $TP53^{MUT}$, 66% with del17p versus 66% for overall study population | [39] |
| CAPTIVATE | IV | 164 | 32 | PFS and OS not reported by the *TP53* status; Best BM-uMRD rate: 66% with *TP53* ab versus 72% without *TP53* ab | [40] |
| GLOW | IV | 106 | 7 | Outcome data not separately reported by the *TP53* status | [41] |
| CLL2-GIVe2 | IVO | 41 | 41 (all) | 2 years PFS: 95%; 2 years OS: 95% | [42] |
| DFCI | AVO | 68 | 41 | PFS and OS not reported by the *TP53* status; BM-uMRD rate at cycle 16: 83% with *TP53* ab versus 89% without *TP53* ab | [43] |
| BOVEN | ZVO | 47 | 2 | Outcome data not separately reported by the *TP53* status | [44] |
| RR | | | | | |
| RESONATE | IBR | 195 | 104 | Median PFS: 41 months with *TP53* ab versus not reached without *TP53* ab; Median OS: 62 months with del17p versus 68 months overall | [45] |
| ELEVATE-RR | ACA<br>IBR | 268<br>265 | 121<br>120 | Median PFS: 33 months with del17p versus 38 months overall<br>Median PFS: 28 months with del17p versus 38 months overall | [46] |
| ALPINE | ZANU<br>IBR | 327<br>325 | 45<br>50 | 2 years PFS: 73% with *TP53* ab versus 78% overall<br>2 years PFS: 55% with *TP53* ab versus 66% overall | [47] |
| MURANO | VR | 194 | 17 | Median PFS: 37 months with *TP53* ab versus 57 months without *TP53* ab; 5 years OS: 70% with *TP53* ab versus 82% overall | [48] |
| CLARITY | IV | 54 | 11 | Outcome data not separately reported by the *TP53* status | [49] |
| Mixed: TN and RR | | | | | |
| Pooled analysis of high risk CLL | ACA+/−O | 313 TN; 488 RR | 64 TN; 219 RR | 4 years PFS: 76–77% with *TP53* ab TN; 4 years OS: 89% with *TP53* ab TN; 3 years PFS: 54% with *TP53* ab RR; 3 years OS: 73% *TP53* ab RR | [50] |
| OSU | IVO | 25 TN; 25 RR | 3 TN; 1 RR | Outcome data not separately reported by the *TP53* status | [51] |

ab, aberrations; ACA, acalabrutinib; AVO, acalabrutinib, venetoclax, obinutuzumab; BM-uMRD, bone marrow undetectable minimal residual disease; CD20 mAb, anti-CD20 monoclonal antibody; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del17p, deletion 17p; FCR, fludarabine, cyclyophosphamide, rituximab; HR, hazard ratio; IBR, ibrutinib; IV, ibrutinib, venetoclax; IVO, ibrutinib, venetoclax, obinutuzumab; M, months; MUT, mutation; *N*, number; O, obinutuzumab; OS, overall survival; PFS, progression-free survival; R, rituximab; Ref, reference; RR, relapsed or refractory CLL; TN, treatment-naive CLL; VO, venetoclax, obinutuzumab; VR, venetoclax, rituximab; Y, years; ZANU, zanubrutinib; ZVO, zanubrutinib, venetoclax, obinutuzumab. **TP53* aberration: *TP53* mutation or del17p.

with increased risks of clonal evolution and subsequent treatment resistance to BTKis. *BTK* and/or *PLCG2* mutations, found in up to 70%–80% of CLL patients who progress on a BTKi [52–54], occur three times more frequently among patients with *TP53* aberration than those without the aberration [55]. Third, the prognostic value of *TP53* aberration can change by the type and the allele frequency of the aberration. Approximately 30%–50% of *TP53* aberrant CLL presents as monoallelic *TP53* aberration (either deletion or mutation), which has been classically associated with inferior response to CIT [56–58]. A study by Brieghel et al. [59] demonstrated excellent outcomes with ibrutinib across patients with mono- and bi-allelic *TP53* aberration. Similarly, low-burden *TP53* mutations (variant allele frequency <10–15%) have been associated with poor outcome after CIT [60, 61], but not during treatment with a BTKi [62].

Selective BTKis with more favorable safety profiles than ibrutinib are approved for the treatment of CLL and continue to accumulate data specific to *TP53* aberration. Of these, zanubrutinib has been tested in a clinical trial with a large dedicated cohort of TN CLL patients with del17p ($n$ = 109) and achieved excellent initial response (18-month PFS: 89%) [38]. In RR CLL, the efficacy of acalabrutinib in *TP53* aberrant CLL was comparable to that of ibrutinib, a finding supported by the 54% 3-year PFS rate in a pooled analysis of 219 patients treated with acalabrutinib [50]. There are two randomized trials directly comparing more versus less selective BTKis in RR CLL, each of which included over 100 patients with *TP53* aberration. The ELEVATE-RR study compared acalabrutinib with ibrutinib in RR CLL including 120 patients with del17p, which showed a more favorable safety profile of acalabrutinib and no difference in PFS between the two treatment arms [46]. The ALPINE study comparing zanubrutinib and ibrutinib in RR CLL included 150 patients with *TP53* aberration and demonstrated more favorable 2-year PFS in the zanubrutinib arm (73%) than the ibrutinib arm (55%) [47].

The observed differences in the efficacy of BTKis are attributable to the differences in dosing and pharmacokinetic profiles of these agents. The twice-daily (BID) dosing can maintain higher BTK occupancy than the once-daily dosing of acalabrutinib [63] or zanubrutinib [64]. The BID dosing of zanubrutinib achieves 8-fold higher plasma drug exposure than ibrutinib and has a 2- to 4-fold longer half-life than acalabrutinib [65]. In the absence of data providing a head-to-head comparison of zanubrutinib and acalabrutinib, it is difficult to determine which one of the two selective BTKis is better in terms of efficacy and safety. It is also difficult to determine how much the differences in the pharmacokinetic properties of BTKis contribute to the differences in clinical outcomes. Overall, the current data support BTK inhibition as an important treatment strategy for CLL patients with *TP53* aberration and provide a strong rationale to use selective BTKis over ibrutinib, given improved tolerance to and more favorable safety profiles of selective BTKis.

Among patients treated with venetoclax-based regimens, *TP53* aberration continues to be associated with an inferior prognosis, although the patient outcomes are still markedly better than those with CIT. The CLL14 study is a randomized phase 3 trial comparing 1-year of VO and 6 cycles of chlorambucil and obinutuzumab in TN CLL [66]. At the median follow-up of 65 months, the 5-year PFS of the VO arm was 41% for a subgroup with *TP53* aberration and 66% for those without *TP53* aberration, raising concerns for the limited durability of remission in *TP53* aberrant CLL treated with fixed-duration therapy [10]. Treatment of RR CLL patients with a 2-year duration of venetoclax plus rituximab (VR) in the MURANO study also showed that the remission is less durable (4-year PFS: 33%) and less deep (uMRD in peripheral blood [PB] at the end of treatment: 36%) in the del17p subgroup compared to the overall study population (4-year PFS: 57%, PB uMRD at the end of treatment: 62%) [67]. Although the 5-year PFS of 41% on VO is seemingly lower than up to 70% 5-year PFS observed on a continuous BTKi, one should not directly compare the efficacy of these approaches without prospective randomized data. Current NCCN guidelines recommend both time-limited venetoclax plus anti-CD20 monoclonal antibody and continuous BTKi therapy as preferred regimens in CLL.

To overcome the limitation of established regimens, several studies are testing targeted combinations incorporating a BTKi and venetoclax with or without anti-CD20 monoclonal antibody coupled with MRD-guided treatment cessation. Several of these trials were enriched with *TP53* aberrant CLL. The CLL2-GIVe study exclusively enrolled 41 TN patients with *TP53* aberrant CLL and reported high rates of complete response (59%) and bone marrow (BM) uMRD (66%) at the end of combination therapy with ibrutinib plus VO (IVO) [42]. Two additional studies tested targeted triplet regimens replacing ibrutinib with a selective BTKi acalabrutinib (AVO) [68] or zanubrutinib (ZVO) [44]. Of these, AVO achieved high rates of BM uMRD in subgroups with (83%) or without *TP53* aberration (89%). The study testing ZVO had only 2 patients with *TP53* aberration. Studies testing the doublet regimen of ibrutinib plus venetoclax (IV) had relatively small numbers of patients

with *TP53* aberration, limiting one from drawing strong conclusions from these studies specific to the *TP53* subset. Despite the limitation, initial responses to IV were comparable between the overall study population and those with *TP53* aberration in several trials. For example, BM uMRD rate was 66% in the *TP53* aberrant subgroup and 68% in the overall study population of the CAPTIVATE study [40]. Other studies with a smaller number of patients with *TP53* aberration ($n$ = 7–18) reported BM uMRD rates ranging between 56% and 64% in TN CLL [39, 41] and 36% in RR CLL [49].

Outcome with a sequential combination of targeted therapy has been reported in two studies. In the study by Thompson et al. [69], ibrutinib-treated CLL patients with selected high-risk markers received venetoclax as an adjunct to ibrutinib (I + V). Over half of the patients in this study had *TP53* aberration (28 of 45 patients) and the rate of BM uMRD after 12 cycles of I + V was 57%. Another study by Scarfo et al. [70] tested the addition of ibrutinib to venetoclax in RR CLL patients who had detectable MRD after 12 cycles of initial treatment with venetoclax (V + I). Despite all patients in this study being previously treated with CIT and a third of the study population having *TP53* aberration (11 of 38 patients), 84% achieved uMRD in both PB and BM after a median of 7 months of V + I. Deep responses can be achieved with the addition of a PI3K inhibitor, umbralisib, and anti-CD20 antibody, ublituximab, to ibrutinib (77% PB uMRD at best response); however, this study included only 2 patients with del17p, and the FDA has withdrawn approval for umbralisib due to safety concerns [71].

The key lesson learned from the recent studies in CLL is that the combination of targeted agents increases the likelihood of uMRD in high-risk CLL, and the MRD-driven treatment cessation is feasible for patients with *TP53* aberration. In a pooled analysis of 51 patients with *TP53* aberration treated with ibrutinib or venetoclax plus anti-CD20 monoclonal antibody regimens across 3 trials, a third of the patients were able to stop therapy after achieving uMRD and had median PFS of 2 years after MRD-guided treatment cessation [72]. Further studies are needed to determine the duration of deep remission in *TP53* aberrant CLL, the best regimen that can provide durable disease control in this subgroup, and its relevance to treatment-free survival and OS.

### Complex Karyotype

CK is defined by the detection of 3 or more chromosomal abnormalities in the metaphase cytogenetics performed with cytokine or CpG oligonucleotide stimulation. Some of the abnormalities that are well-known and relevant to the prognosis of CLL include deletion of 6q, 11q, 13q, and 17p, and trisomy 12 [73], which can be sensitively detected by interphase FISH. Cytogenetics can help identify copy number changes and chromosomal rearrangements affecting regions not covered by the conventional CLL FISH panel. In a large retrospective study including 5,290 CLL patients, CK (≥3 abnormalities) was found in 15% of the patients and was associated with shorter OS [74]. Intriguingly, not all patients with CK had an adverse outcome in this study. Approximately 10% of the patients with CK had trisomies commonly affecting chromosome 12 or 19 and had excellent survival. Further, the study revealed highly CK with ≥5 abnormalities had a stronger negative impact on survival than ≥3 abnormalities.

The prognostic relevance of CK in 456 BTKi-treated patients has been reported by the group at Ohio State University (OSU) [75, 76]. This study demonstrated that CK was a continuous variable that increased the risk of progression or death on ibrutinib by 7% with each additional abnormality. The OS difference was more pronounced in subgroups with ≥5 abnormalities compared to ≥3. Another study by Thompson et al. [77] also demonstrated inferior event-free survival and OS associated with CK (≥3 abnormalities) in 88 RR patients treated with ibrutinib-based regimens (median EFS and OS: 19 and 25 months for the CK group vs. 39 months and not reached for the non-CK group, respectively). It is important to note that most (78%) of the patients in the OSU study and all patients in the study by Thompson et al. [78] had RR CLL at the time of ibrutinib initiation. Smaller data exist for the prognostic role of CK in TN CLL patients treated with a BTKi. In the GIMEMA LLC1114 study including 98 TN CLL patients treated with ibrutinib, CK (≥3 abnormalities) was associated with inferior PFS.

CK has been investigated in TN and RR patients treated with VO-containing regimens. The CLL13 study was a four-arm trial randomizing over 900 TN patients to CIT, VR, VO, or IVO, which reported that CK ≥5 abnormalities were associated with significantly shorter PFS across all treatment arms [79, 80]. Three or four abnormalities resulted in a shorter PFS with CIT (HR 2.49, $p$ = 0.003), but not with the venetoclax-based treatment arms. Interestingly, 8q and 18q translocations showed significantly inferior PFS, providing data for the first time on specific chromosomal regions of clinical significance. The CLL14 study led to distinct conclusions on the role of CK in TN CLL patients treated with VO [81]. The CK subgroup with ≥3 abnormalities had a trend toward

inferior PFS and OS without reaching statistical significance (2-year PFS and OS: 79% and 88% with CK vs. 91% and 93% without CK). Only 10 patients in this study had high CK (≥5), and the outcomes were not significantly different in this subgroup. In RR CLL, CK was assessed using array comparative genomic hybridization (sCGH) in the MURANO study [48]. Patients with ≥3 abnormalities by aCGH had markedly inferior PFS (42 months) than those without (60 months), highlighting the prognostic importance of CK in RR CLL patients treated with VR. A smaller study using conventional cytogenetics also reported a higher risk of disease progression associated with CK (≥3) in RR CLL (HR 6.6, $p = 0.005$) [82].

CK is not as frequently tested as other prognostic markers in CLL, which limits further investigation and incorporation of this marker in novel prognostic models [83]. Data are sparse for the biological implication and the prognostic role of individual chromosomal loci beyond those commonly detected by FISH. Improved utilization of cytogenetics in clinical practice, systematic analyses of large clinical datasets, and reliable laboratory models representative of karyotypic complexity are needed to further our understanding of CK in CLL.

### Immunoglobulin Heavy Chain Variable Region Gene Mutation

Somatic hypermutation of the immunoglobulin heavy chain variable region gene (IGHV) occurs during affinity maturation of B cells at the germinal center [84]. In CLL, IGHV mutation dichotomizes CLL into two distinct biological and clinical phenotypes. Mutated IGHV (M-IGHV), defined by ≥2% divergence from the consensus germline sequence, is characterized by high-affinity binding of the BCR, a more indolent clinical course, and more durable remission after CIT [85, 86]. Treatment with FCR, for instance, can achieve long-lasting remission in young and fit patients with M-IGHV (12.8-year PFS: 54% with M-IGHV, 9% with unmutated IGHV [U-IGHV]) [87, 88].

Intriguingly, a group of patients with IGHV3-21 usage breaks the conventional IGHV classification. While most of these patients are categorized as M-IGHV, their clinical course mimics that of those with U-IGHV [89]. Nearly half of these patients have a stereotyped pattern of immunoglobulin gene usage called subset 2, which is defined by the presence of IGHV3-21 and additional characteristics of IGHV including short CDR3 sequence (9 amino acids) and acidic amino acid in the landmark location (most frequently aspartate) [90]. Recent studies demonstrated a high incidence of point mutations affecting the immunoglobulin light chain gene IGLV3-$21^{R110}$ in subset 2, which induces autonomous BCR signaling through the interaction of neighboring BCRs [91, 92]. While subset 2 and IGLV3-$21^{R110}$ mutation define a unique biological subgroup [74], detailed testing of the IGHV stereotype and the light chain gene sequences has not been widely adopted in clinical practice, and the prognostic role of these markers in the context of targeted therapy remains unclear.

The prognostic value of IGHV mutation has changed with targeted therapy with notable differences in the durability of response to continuous and time-limited treatments. Continuous BTKis lead to high rates of initial responses and durable disease control irrespective of IGHV status [5, 93]. In contrast, fixed-duration venetoclax-based therapy has shown marked differences among IGHV subgroups in the duration of treatment-free remission and PFS after treatment cessation [8]. Median PFS was approximately 5 years for TN patients with U-IGHV after VO therapy and not reached for those with M-IGHV in the CLL14 study [66].

Trials testing targeted combinations identified notable differences in MRD kinetics by IGHV status. Patients with U-IGHV are highly sensitive to IV doublet therapy, leading to faster attainment and higher rates of uMRD than those with M-IGHV [40, 94]. However, the uMRD in patients with U-IGHV was not durable, and MRD conversion from undetectable to detectable disease occurred at a rate of approximately 10% per year for the U-IGHV subgroup after stopping the IV combination [95]. Overall, IGHV mutation status is an important prognostic marker associated with remission duration and MRD kinetics among patients receiving time-limited targeted therapy.

### Minimal Residual Disease

uMRD is defined by <1 CLL cell per 10,000 leukocytes ($<10^{-4}$) based on multicolor flow cytometry, real-time quantitative polymerase chain reaction (PCR), or NGS-based IGH sequencing [96]. Multicolor flow cytometry is a widely available method with sensitivity limited to $10^{-4}$. The NGS method is highly sensitive ($10^{-6}$) but requires a baseline sample to identify disease-specific IGHV sequences prior to MRD testing. The PCR method is also sensitive ($10^{-5}$) but labor-intensive due to its requirement for patient-specific primers. Initial evidence for MRD as a post-treatment prognostic marker was generated in the context of CIT. Nearly half of the TN patients treated with

FCR achieved BM uMRD and those who attained uMRD had significantly longer PFS and OS than patients with detectable disease (shown in Table 2) [97, 98].

Unlike CIT, uMRD is uncommonly observed among patients on BTKi monotherapy. Attainment of low- ($<10^{-2}$) versus high-level ($\geq 10^{-2}$) MRD was not associated with differences in PFS during BTKi therapy [14]. The addition of an anti-CD20 monoclonal antibody [3, 5] or CIT [100–102] to a BTKi can improve the uMRD rate. In the ELEVATE-TN study, the addition of obinutuzumab to acalabrutinib improved 4-year PFS by nearly 10% and the rate of PB uMRD by 28% [103]. Initial treatment with venetoclax-based regimens substantially increases the rate of PB uMRD to 76% (PCR method) [10]. In the CLL14 study, attainment of uMRD at the end of fixed-duration VO therapy was associated with higher PFS and OS compared to patients with detectable MRD (4-year post-treatment PFS and OS: 77% and 89% with uMRD vs. 36% and 64% without uMRD, respectively). Similar to the TN population, RR patients treated who achieved uMRD after treatment with VR had superior OS than those with detectable disease (3-year post-treatment OS: 95% with uMRD vs. 73% without uMRD) [48]. Taken together, post-treatment uMRD predicts durable remission and improved survival in patients treated with fixed-duration therapy containing venetoclax and anti-CD20 antibody.

Targeted combinations can achieve high rates of uMRD as well (Table 2). In TN CLL treated with IV doublet, approximately half of the patients achieved BM uMRD and the uMRD rate was higher in the U-IGHV subgroup (56–77%) than the M-IGHV subgroup (~50%) [39, 40]. The BM uMRD rate in RR CLL treated with IV is over 10% lower than that observed in the TN population (36% in RR) [49]. Triplet combination can further increase the BM uMRD rate in TN CLL with reported rates at 66–78% with IVO [42, 51], 78–89% with AVO [68], and 89% with ZVO [44]. Extended follow-up and serial assessment of the MRD status are needed to better characterize uMRD as a post-treatment prognostic marker in the setting of targeted combination therapy.

## Other Factors

### *Integration of Prognostic Markers*

CLL International Prognostic Index (CLL-IPI) is a widely used, weighted scoring system integrating clinical (age, clinical stage), molecular (IGHV, *TP53* aberration status), and serologic markers (beta-2 microglobulin [B2M]) for risk stratification of previously untreated CLL patients [31]. While CLL-IPI was developed in the era of CIT and its survival data are irrelevant to current practice, it remains to be a useful tool to predict time to first therapy since the criteria for treatment initiation have not changed in CLL.

Several studies reported novel prognostic tools more relevant to targeted therapy. CLL-BALL utilizes B2M, lactate dehydrogenase (LDH), hemoglobin, and time from the last treatment to stratify patients into groups with distinct OS [104]. However, this model did not test PFS as an endpoint and patients in the discovery dataset received heterogeneous treatments including ibrutinib, idelalisib, and CIT. To overcome these limitations, CLL4 has been developed from over 800 patients treated with ibrutinib [83]. This model selected four factors: *TP53* aberration status, prior treatment status, B2M, and LDH, based on machine-learning algorithms and conventional multivariable analysis. The high-risk group defined by CLL4 had the shortest PFS and OS and the highest incidence of *BTK/PLCG2* mutations as well as Richter's transformation. The study also has limitations related to the lack of integration of CK and the inclusion of prior treatment status as a factor that can limit its applicability to patients receiving BTKis as initial therapy. Further research is needed to integrate novel molecular markers in the risk stratification of CLL and develop prognostic tools relevant to venetoclax-based therapy.

### CD49d

CD49d is a surface molecule of the integrin heterodimer α4 subunit which mediates leukocyte adhesion via very late antigen 4 (VLA-4). It is critical for leukocyte interaction through inside-out activation triggered by the BCR signaling pathway [105, 106], and its expression promotes the microenvironment-mediated proliferation of CLL cells, leading to a poor prognosis [107]. CD49d expression is assessed by flow cytometry, with >30% expression set as a cutoff for positivity [108]. In a study of 2,972 CLL patients conducted in the era of CIT, CD49d positivity was associated with inferior survival (10-year OS: 62% for CD49+ CLL vs. 84% for CD49d− CLL) [109]. Smaller data exist for ibrutinib-treated CLL patients which also demonstrated inferior PFS associated with CD49d positivity (HR 3.32, $p = 0.009$) [108]. There are no data on the prognostic role of CD49d in patients treated with venetoclax-based therapy.

### Deletion 11q and/or ATM Mutation

Inactivation of ataxia telangiectasia mutated (*ATM*) gene with mutation or deletion of chromosome 11q (del11q) decreases response to DNA double-strand breaks and increases the risk of lymphoid malignancies [110]. While patients with del11q or *ATM* mutations had

**Table 2.** Rates of undetected minimal residual disease in bone marrow

| | Study | Treatment | Population | MRD testing method and timepoint | IGHV status | BM uMRD unless otherwise specified | Ref |
|---|---|---|---|---|---|---|---|
| CIT | CLL8 | FCR | 210 TN | FC at EOT | M-IGHV<br>U-IGHV | 50%<br>41% | [97] |
| | MDACC FCR300 | FCR | 300 TN | FC at EOT | M-IGHV<br>U-IGHV | 51%<br>33% | [88] |
| Continuous BTKi | NIH phase 2 | IBR | 53 TN + 33 RR | FC, best MRD | M-IGHV<br>U-IGHV | 10%<br>4% | [14] |
| | iLLUMINATE | IBR-O | 113 TN | FC, best MRD | Overall study population | 25% | [99] |
| BCL2i + anti-CD20 mAb | CLL14 | VO | 216 TN | ASO-PCR at EOT | M-IGHV<br>U-IGHV | 74% (PB uMRD)<br>79% (PB uMRD) | [66] |
| | MURANO | VR | 194 RR | FC at EOT (24C) | M-IGHV<br>U-IGHV | 43% (PB uMRD)<br>46% (PB uMRD) | [48] |
| BTKi + BCL2i doublet | MDACC phase 2 | IV | 80 TN | FC at EOCT (24C) | M-IGHV<br>U-IGHV | 67%<br>54% | [39] |
| | CAPTIVATE | IV | 159 TN | FC, best MRD | M-IGHV<br>U-IGHV | 53%<br>64% | [40] |
| | GLOW | IV | 106 TN | NGS at EOCT (15C) | M-IGHV<br>U-IGHV | 41%<br>60% | [41] |
| | CLARITY | IV | 54 RR | FC at EOCT (24 months) | Overall study population | 36% | [49] |
| | Scarfo et al. | IBR added to V | 38 RR | FC at EOCT (12C) | Overall study population | 84% (both PB and BM uMRD) | [70] |
| BTKi + BCL2i + anti-CD20 mAb triplet | CLL2-GIVe | IVO | 41 TN | FC at EOT (15C) | Overall study population | 66% | [42] |
| | DFCI phase 2 | AVO | 37 TN | FC at EOCT (24C) | Overall study population | 84% | [68] |
| | BOVEN | ZVO | 39 TN | FC, best MRD | Overall study population | 89% | [44] |
| | OSU | IVO | 25 TN + 25 RR | FC at EOCT (14C) | Overall study population | 67% in TN, 50% in RR | [51] |

ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; AVO, acalabrutinib, venetoclax, obinutuzumab; BCL2i, B-cell lymphoma-2 inhibitor; BM, bone marrow; BTKi, Bruton's tyrosine kinase inhibitor; C, cycles; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; EOCT, end of combination therapy; EOT, end of therapy; FC, flow cytometry; FCR, fludarabine, cyclophosphamide, rituximab; IBR, ibrutinib; IGHV, immunoglobulin heavy chain variable gene; IV, ibrutinib, venetoclax; IVO, ibrutinib, venetoclax, obinutuzumab; M: months; mAb, monoclonal antibody; M-IGHV, mutated IGHV; MRD, minimal residual disease; NGS, next generation sequencing; O, obinutuzumab; PB, peripheral blood; Ref, reference; RR, relapsed or refractory CLL; TN, treatment-naive CLL; U-IGHV, unmutated IGHV; uMRD. undetectable minimal residual disease; V, venetoclax; VO, venetoclax, obinutuzumab; VR, venetoclax, rituximab; ZVO, zanubrutinib, venetoclax, obinutuzumab.

poor prognoses on CIT [111–113], targeted agents dramatically improved the outcome of this population, leading to PFS and OS comparable to [48, 93] or even longer than those without del11q [114]. Del11q and *ATM* mutation are no longer considered adverse prognostic factors for patients receiving targeted therapy.

Serologic Markers

Serologic markers of disease activity in CLL include B2M and LDH. Elevated B2M and LDH at pre-treatment are associated with poor prognosis in CLL treated with CIT and targeted therapy including BTKi- and venetoclax-based regimens [31, 83, 104, 115]. The

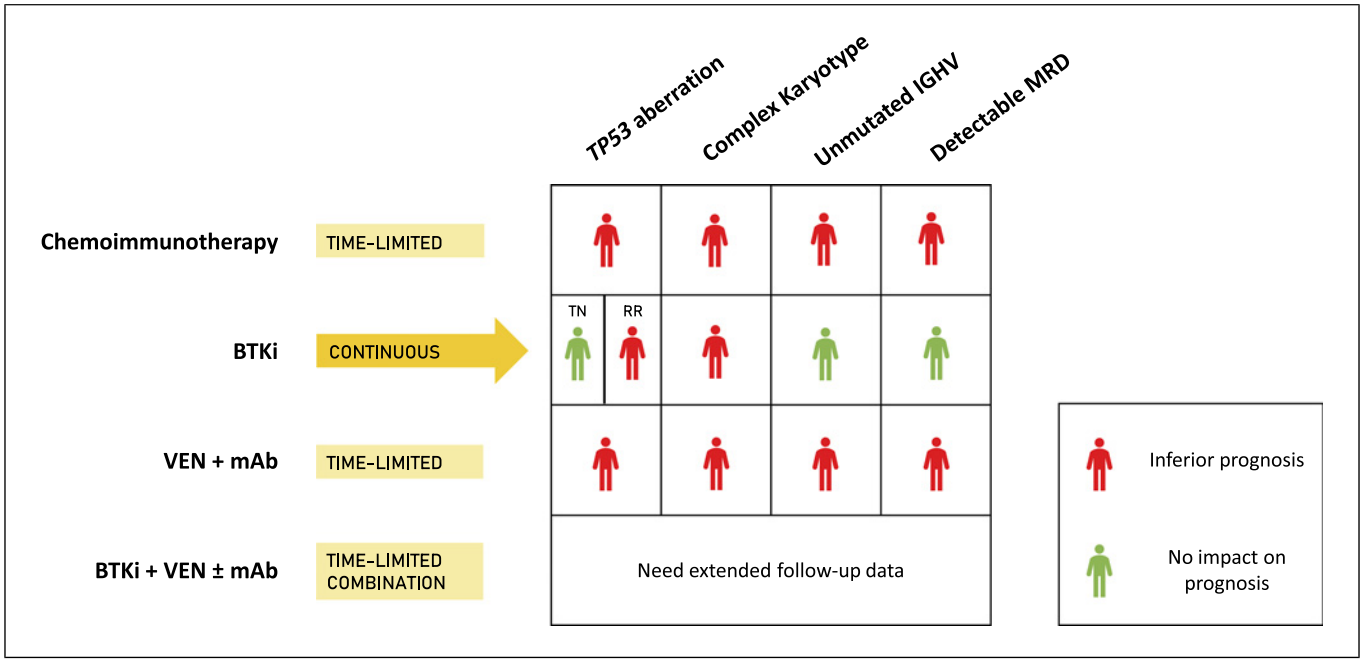


**Fig. 1.** Impact of prognostic factors by treatment regimens. Summarizes how the prognostic value of *TP53* aberration, CK, immunoglobulin heavy chain variable region gene mutation status, and minimal residual disease changed with targeted therapies. *TP53* aberration refers to deletion 17p and/or *TP53* mutation. BTKi, Bruton's tyrosine kinase inhibitor; IGHV, immunoglobulin heavy chain variable gene; mAb, anti-CD20 monoclonal antibody; MRD, minimal residual disease; RR, relapsed or refractory CLL; TN, treatment-naive CLL; VEN, venetoclax.

serologic markers dynamically change over time and with therapy. To our knowledge, no studies have investigated the prognostic value of serial monitoring of serologic markers.

Patient-Specific Factors

Patient-specific factors, particularly age and comorbidities, can predict risks associated with CLL therapy and assist in individualized treatment decisions. Age at diagnosis has long been recognized as an independent predictor of survival in CLL, with younger age being associated with a more aggressive disease course and shorter life expectancy compared to the age-matched general population [116, 117]. Moreover, selected comorbidities affecting vascular, upper gastrointestinal, and/or endocrine systems are linked to decreased OS and shorter time to treatment in large datasets of over 4,000 patients with CLL [118, 119]. While older patients may have relatively indolent disease courses, the presence of an increased burden of comorbidity has been shown to significantly impair tolerance to disease- and treatment-related complications and decrease survival [120]. However, these findings were generated when CIT was the prevailing treatment choice and may be less relevant during targeted therapy. Several trials have specifically demonstrated safety and excellent tolerance to the established targeted therapy regimens in older adults or those with comorbidities. For instance, the Alliance A041202 study enrolled patients with age 65 years or older and showed lower incidences of high-grade adverse events with ibrutinib compared to BR. The CLL14 study also enrolled relatively older patients (median age 72 years) with a cumulative illness rating scale (CIRS) score greater than 6 or impaired renal function (creatinine clearance <70 mL/min) and demonstrated VO was well tolerated in this population [10]. Based on these data, patients with older age and comorbidities should be considered for the current standard of care therapy with a BTKi or VO.

Additional patient-specific factors most relevant to the selection of targeted therapy include history of cardiovascular disease, history or increased risk of serious bleeding, and drug-drug interaction [1]. Because BTKis are associated with hypertension, arrhythmia, and sudden cardiac deaths, patients with a prior history of cardiac disease or uncontrolled hypertension are generally recommended to avoid this therapeutic class or at least use a selective BTKi [121–123]. Bleeding is a common side effect of all BTKis that occurs in similar frequencies in

selective and less selective BTKis. Although grade 3 or higher bleeding on a BTKi is rare (<5%), patients with a history of serious bleeding events (i.e., intracranial hemorrhage, large hematoma) or those on coumadin should avoid BTKis [124]. Drug-drug interaction is relevant to all targeted therapy and providers should carefully review concurrent medications. Both BTKis and venetoclax require dose reduction during the use of moderate CYP3A inhibitors and dose interruption when strong CYP3A inhibitors or inducers are used. Venetoclax also requires 50% dose reduction during treatment with a P-gp inhibitor [1].

## Conclusion

The introduction of targeted therapy for the treatment of CLL has generated new questions related to the present value of prognostic markers in this disease (shown in Fig. 1). Initial treatment with a BTKi can overcome the poor prognostic value of *TP53* aberration in TN CLL. *TP53* aberration continues to be a negative prognostic factor for RR CLL patients receiving BTKi therapy and TN and RR patients treated with venetoclax-based, time-limited therapy. CK is linked with unfavorable outcomes across targeted agents. The prognostic value of CK becomes stronger when a higher cutoff of 5 or more abnormalities is used instead of the conventional cutoff of 3. IGHV mutation remains an important prognostic marker predictive of the durability of remission after time-limited targeted therapy, but not with continuous BTKi treatment. These data align with the current iwCLL guidelines, which recommend testing of IGHV mutation status, FISH, and *TP53* sequencing as mandatory tests at pre-treatment and karyotyping as a desirable test in the setting of clinical trials [32]. The NCCN guidelines also recognize these tests and list CK as a well-defined prognostic marker (CLL, version 2.2023). To develop an individualized, genomically driven treatment strategy in CLL, further research is needed to validate prognostic markers in predicting treatment response and disease progression, to create risk-adapted strategies that incorporate predictive markers for patient and treatment selection, and to develop reproducible and widely applicable biomarkers for clinical use.

## Conflict of Interest Statement

S.K.: no conflict of interest. I.E.A.: consulting – BeiGene.


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## Author Contributions

S.K. and I.E.A. reviewed the literature and wrote the manuscript.

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