Review

Chronic Lymphocytic Leukemia: Prognostic/Predictive Factors in the Era of Novel Drugs

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Review

Chronic Lymphocytic Leukemia: Prognostic/Predictive Factors in the Era of Novel Drugs

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Simple Summary: The treatment of chronic lymphocytic leukemia has dramatically changed following the availability of new drugs with targeted mechanisms of action. Traditional and new prognostic and predictive factors are being investigated to individualize and guide these new treatments. In this review we discuss the clinical outcomes of principal clinical trials with novel agents in relation to genetic factors including IGHV mutational status, *TP53* abnormalities and the complex karyotype and to the new score systems that have been developed accordingly.

Abstract: Novel drugs profoundly changed the outcomes in CLL patients and traditional prognostic/predictive factors that were delineated in the era of chemo-immunotherapy need to be validated in the contest of these new targeted therapies. Currently, the most important prognostic genetic biomarkers are immunoglobulin heavy chain variable (IGHV) mutational status, genetic aberrations including del(17p)/*TP53* abnormalities and the complex karyotype. In this review we discuss the prognostic/predictive role of these genetic markers in relation to novel treatments. Moreover, we present and discuss the new score systems that were elaborated and validated in the era of new drugs. Given the deeper responses obtained with small molecules, new prognostic/predictive markers, including measurable residual disease, and validated prognostic scores could possibly be incorporated into routine prognostic scores, to better identify "very-high" CLL patients, who will need more effective treatments.

Keywords: chronic lymphocytic leukemia; BTK inhibitors; BCL-2 inhibitors; prognostic scores; predictive factors; *TP53* abnormalities; IGHV; complex karyotype

1. Introduction

Chronic lymphocytic leukemia (CLL) is a low-grade lymphoproliferative neoplasm characterized by the accumulation of clonal B-cells expressing CD5, CD19, CD20(dim), and CD23 in lymphoid organs and blood [1]. CLL represents the most prevalent type of hematological neoplasm in Western countries, and it is characterized by a relevant clinical heterogeneity, varying from an indolent course to a more aggressive one with shorter progression-free survival (PFS) and overall survival (OS) [2]. The clinical variability reflects CLL biological and molecular diversity. Thus, over the years, it has become necessary to identify tools that can help clinicians to better define the prognosis of the disease. Rai and Binet represent the history of prognostic models, which continued to be routinely used as staging systems. Both systems consider lymphocytosis, the presence of lymphadenopathy, hepatomegaly or splenomegaly, and the presence of anemia or thrombocytopenia. Rai staging system identifies three subgroups (low-, intermediate- and high-risk) characterized by different survival with low stage having a median survival of more than 10 years

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and high stage having 1,5 years [3]. Binet categorized patients into three subgroups (A, B, and C), with group C having the worst survival [4].

In the last decades, the advent of prognostic biomarkers made Rai and Binet staging systems too reductive in stratifying CLL patients. Currently, the most important prognostic biomarkers, routinely used in clinical practice are immunoglobulin heavy chain variable (IGHV) mutational status, cytogenetic aberrations, such as the deletion of 17p (del(17p)) and 11q (del11q), complex karyotype (CK) and mutations of *TP53*, *NOTCH1*, *ATM*, and *BIRC3* [5–12].

Unmutated status of IGHV relates to a higher rate of disease progression, shorter time to first treatment (TTFT), and survival. On the contrary, a mutated status confers the neoplasm to a more indolent course [5].

Mutations in *TP53*, a gene encoding for a tumor suppressor protein, alone or in combination with del(17p) were historically associated with a poor outcome, sustained by a shorter time to next treatment (TTNT) and decreased or lack of response to classical immune-chemotherapies, such as fludarabine-cyclophosphamide-rituximab (FCR) and bendamustine-rituximab (BR) [6,7]. It mainly occurs in the setting of relapsed-refractory (R/R) CLL patients. Affection of the *ATM* gene, which plays a central role in cell-cycle checkpoint activation and the DNA damage response, occurs in del(11q) and it can be found in 15–20% of CLL cases at diagnosis [8]. It is often associated with unmutated IGHV status and bulky disease. Combined with *TP53* alterations, del(11q) determines highly adverse outcomes in CLL patients, leading to clonal advantage in vitro and in vivo [9]. Treatment-naive CLL patients with del(11q) experience sustained remission with FCR in the absence of TP53 dysregulation, either because of mutation or deletion [10]. Another key prognostic marker is a complex karyotype, which is defined as the occurrence of three or more chromosomal abnormalities in one clone, occurring in up to 15% of patients, and is frequently linked to unmutated IGHV status. It is a stronger predictor than del(17p) of an inferior outcome in R/R CLL patients, also in the era of new small molecules [11].

Even if less used in daily clinical practice, the detection of mutations in *NOTCH1*, *ATM*, and *BIRC3* appears to be very useful in determining a CLL patient's prognosis. Indeed, the weight of *BIRC3* mutations is comparable to that possessed by *TP53* alterations, determining the survival of 29% at 10 years. *NOTCH1* and *ATM* mutations also negatively impact clinical course [12].

Regarding the significance of biochemical abnormalities as a prognostic indicator, serum β2-microglobulin (β2M) has been routinely considered a feasible biomarker, where elevated levels (>2.0 mg/L) correlate with a worse outcome [13,14]. Among cell surface markers, ZAP-70, CD38, and CD49d expression are associated with earlier disease progression, shorter TTFT, and unsatisfied response to chemo-immunotherapy [15,16].

To generate the so-called CLL International Prognostic Index (CLL-IPI), clinical, biological, and genetic parameters including age, clinical stage, *TP53* status, IGHV status, and serum 2M were examined in data from patients included in eight randomized clinical trials in 2016. The score allowed cases' stratification into four groups, all characterized by different outcomes, and became a surrogate of the prediction of OS and TTFT in newly diagnosed CLL patients [17,18]. The limitation of this score relies on the lack of validation in the setting of R/R CLL patients, especially in the era of new target therapies. Indeed, nowadays, the CLL treatment armamentarium drastically improved with the availability in daily clinical practice of new small molecules, which leads to precision medicine. Bruton-tyrosine-kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i) are effective in improving PFS and OS with manageable side effects, also in the setting of CLL patients harboring negative biological prognostic factors. Moreover, they improved the depth of response with benefits in terms of treatment-free remission [19]. The above-mentioned prognostic factors were delineated in the era of chemo-immunotherapy. It is, therefore, important to validate them in the scenario of target drugs. Moreover, given the deeper responses obtained with small molecules, new prognostic markers, such as the detection of measurable residual disease (MRD), could be possibly incorporated into routine prognostic scores, also to better identify "very-high" CLL patients, who need more effective treatments [20].

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2. Prognostic and predictive factors in the era of new drugs

2.1. Clinical outcomes

RESONATE-2 is a phase 3 study including treatment-naïve CLL patients without del(17p) who underwent ibrutinib (Ibr) as monotherapy, which demonstrated robust rates of PFS and OS. In the trial, patients were randomized 1:1 to receive BTKi until disease progression or unacceptable adverse events or chlorambucil (Clb) for 12 cycles [21]. At a follow-up of 8 years, PFS was 59% for the Ibr cohort, dramatically higher than that observed in the Clb arm (9%). Long-term data still confirms the benefit of the small molecule even in the subset of patients harboring high-risk cytogenetics, such as del(11q) and unmutated IGHV status. A relevant rate of 7-year OS has been also observed (78%), with 42% of patients still in treatment with Ibr [22]. A multivariable analysis of baseline characteristics ensuring the continuation of Ibr was performed in recent research examining the features and clinical outcomes of patients with CLL receiving Ibr for up to 5 years in the RESONATE-2 trial [23]. None of the parameters considered, such as age ≤ 75 years, female sex, creatinine clearance ≥ 60 ml/min, *TP53* mutated, del(11)q, CLL history, LDH ≤ 250 U/L, absence of cytopenia, advanced Rai stage, β2M >3.5 mg/l and absence of bulky disease (< 5 cm) reached statistical significance.

E1912 trial compared the efficacy of the ibrutinib-rituximab (Ibr-R) regimen to FCR in a cohort of 529 treatment-naïve patients without del(17p). In the last update [24], in line with results from the original study [25], Ibr-R was demonstrated to be effective with longer PFS than that observed in the control group treated with chemo-immunotherapy. An evaluation of PFS by CLL-IPI risk category was also performed: CLL-IPI allowed to accurately stratify patients in terms of PFS in the FCR arm, while did not predict PFS as effectively as in the IR arm.

ALLIANCE trial is a three-arms phase 3 study which investigated the superiority of Ibr, alone or in combination with rituximab, over chemo-immunotherapy in previously untreated unfit CLL patients. The study population was well-balanced in terms of genetic features [26]. In the trial, patients were stratified according to Rai stage, Zap-70 methylation, and unfavorable FISH. From the last ad interim analysis, at a median follow-up of 55 months, improved PFS and OS were observed in the arms with Ibr and Ibr-R. The clinical benefit of the BTKi was unequivocal in all subgroups, regardless of its combination with anti-CD20 monoclonal antibody.

The ability to overcome unfavorable prognostic factors, peculiar to BTKi versus chemo-immunotherapy, was highlighted in the ELEVATE-TN trial [27], which compared the efficacy of acalabrutinib (Aca), alone or in combination with obinutuzumab (Obi), versus chlorambucil and Obi (Clb-Ob), in the setting of 675 treatment-naïve unfit patients, 14%, 13% and 14% of whom harboring del(17p) and/or *TP53*, respectively. At a median follow-up of 49.6 months [28], PFS was not reached in Aca-containing arms. In contrast, it was 27.8 months for the Clb-Obi cohort.

To demonstrate its non-inferiority in terms of PFS in the setting of R/R CLL patients, Aca was compared to Ibr in the ELEVATE-RR clinical study. The trial demonstrated that PFS and OS are comparable across prognostic subgroups, regardless of the number of previous treatments [29].

In patients treated with FCR, the achieving of MRD, defined as the number of clonal cells detectable in peripheral blood or bone marrow, has shown to be a significant predictive factor [30]. Indeed, several studies, over the years, demonstrated that MRD status after anti-leukemic therapy is a strong and independent predictor factor of PFS and OS [31]. Despite the high rate of complete response obtained with first-generation BTKi, Ibr as a single agent, the small molecule rarely allows CLL patients to achieve undetectable MRD (uMRD). Moreover, data regarding second-generation BTKis have not been reported so far. Rates increased with the combination of immunotherapy or chemo-immunotherapy. In fact, in the HELIOS trial, patients treated with BR-Ibr showed a rate of uMRD at 36 months of 26.3%, which correlated with a prolonged PFS [32], and in the ILLUMINATE trial [33], the association of Ibr-Obi also determined a high MRD negativity rate.

Bcl-2 inhibitor, venetoclax (Ven), in monotherapy, has been demonstrated to be very effective in achieving uMRD. Higher rates could be obtained when it is combined with an anti-CD20 monoclonal antibody. MURANO study evaluated the efficacy of that combination within 2-year fixed-duration

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therapy in the setting of R/R CLL patients [34]. The control arm was represented by BR. At the most recent follow-up (5 years) [35], Ven-R still shows its benefit in terms of PFS over BR.

Interestingly, the association of Ven-Obi in the setting of treatment-naïve patients within the CLL14 trial [36] appeared to be more effective in reaching a higher CR rate, and improving PFS, compared to the control arm (Clb-Obi), regardless of the presence of the classical biomarkers associated with poor prognosis [37].

Since MRD negativity is a strong surrogate of longer survival, the phase 2 CAPTIVATE trial, which evaluated the combination of Ibr-Ven in the setting of 164 treatment-naïve CLL patients, has been designed to investigate the efficacy of an MRD-driven anti-leukemic approach. With this approach over two-thirds of patients achieved an uMRD, including those with high-risk disease features. Indeed, it has been successfully demonstrated how MRD assessment could be a useful tool to guide treatment discontinuation [38].

The GLOW trial, at a median follow-up of fixed duration Ibr-Ven showed superior PFS versus Clb-Obi in untreated CLL who were older or had comorbidities. (HR 0.214 [95% CI 0.138–0.334]; p<0·0001); 42-month PFS rates were 74·6% (95% CI 65.0–82.0) for Ibr-Ven and 24·8% (16.5–34.1) for Clb-Obi. PFS rates 2 years after Ibr–Ven treatment were 93.0% (95% CI 82·4–97·3) in 58 patients with uMRD and 79·6% (60·1–90·3) in 31 patients with detectable MRD 3 months after the end of treatment, for patients who had a post-treatment disease evaluation visit (n=89). In the Clb—Obi group, PFS rates 2 years after treatment were 66.6% (49.4–79.1) in 41 patients with uMRD and 18.0% (8.5–30.3) in 47 patients with detectable MRD 3 months after the end of treatment [39].

Very recently, in untreated CLL patients the FLAIR phase 3 trial compared Ibr–Ven and Ibr monotherapy with FCR. The duration of Ibr–Ven therapy was defined by MRD status. After a median follow-up of 43.7 months, the estimated 3-year PFS was 97.2% (95% CI, 94.1 to 98.6) with ibr–Ven and 76.8% (95% CI, 70.8 to 81.7), with FCR with a hazard ratio for disease progression or death (Ibr–Ven vs. FCR) of 0.13 (95% CI, 0.07 to 0.24; P<0.001). In a subgroup analysis, the benefit of Ibr–Ven with respect to PFS and OS was seen across all subgroups except patients with mutated IGHV. The 3-year OS was 98.0% (95% Cl, 95.2 to 99.2) with Ibr–Ven and 93.0% (95% Cl, 88.9 to 95.6) with FCR. The adjusted odds ratio of having undetectable MRD at any time (Ibr–Ven vs. FCR) was 2.03 (95% CI, 1.43 to 2.89) in bone marrow and 3.91 (95% CI, 2.55 to 6.00) in peripheral blood while the adjusted odds ratio (Ibr–Ven vs. FCR) was 2.00 (95% CI, 1.26 to 3.16) for overall response and 1.51 (95% CI, 1.07 to 2.14) for complete response [40].

2.2. Genetics

2.2.1. IGHV mutational status (Table 1)

The prognostic relevance of IGHV mutational status was first demonstrated in 1999 by two seminal papers [5,41], in which it was shown that patients with an unmuted IGHV configuration (U-CLL), in comparison to mutated cases (M-CLL), had a shorter time to first treatment (TTFT), a more aggressive clinical course and a significantly decreased OS. The more aggressive course of U-CLL seems to have a biological assumption in that U-CLL are more responsive to antigenic engagement of B cell receptor, particularly within the proliferation centers, whereas M-CLL appears to have an anergic response to antigenic stimulation [42].

Thereafter, the prognostic and predictive role of the IGHV mutational status was confirmed in several trials using various chemoimmunotherapy (CIT) regimens [43–48].

Nowadays the availability of more effective new targeted agents including BTKi and BCL2i may question the prognostic and predictive significance of IGHV mutational status.

Ibr was evaluated in multiple randomized controlled trials (RCT) in both R/R and treatment naive (TN) settings.

In the RESONATE, a RCT demonstrating a significant benefit of Ibr to 12 cycles of ofatumumab in patients with R/R CLL (HR 0.103, 95% CI: 0.067-0.159, after a median follow up of 65.3 months PFS was superimposable between U-CLL and M-CLL cases treated with Ibr (HR 1.208, 95% CI 0.741-1.971) [49].

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Similarly, in the RESONATE-2 trial with up to 8 years of follow-up, among Ibr treated patients PFS was similar irrespective of IGHV mutational status (HR, 0.858; 95% CI, 0.437-1.686) [22].

In open-label, randomized, noninferiority, phase III trial comparing Aca and Ibr in patients previously treated with CLL the direct comparison Aca and Ibr demonstrated noninferior PFS with fewer cardiovascular adverse events but with no difference in terms of PFS between M-CLL and U-CLL (HR 0.60, 95% CI 0.28 to 1.31 and 1.09 95% CI 0.85-1.40, respectively) [29].

In a multinational, phase 3, head-to-head trial, Ibr was compared with Zanubrutinib (Zan), a BTK inhibitor with greater specificity, as treatment for R/R CLL/SLL. At a median follow-up of 29.6 months, Zan was found to be superior to Ibr with respect to PFS (HR.65; 95% CI, 0.49-0.86; P=0.002) and the PFS benefit in favor of Zan was also observed in other major prespecified subgroups, including U-CLL (HR 0.67 95% CI 0.47-0.87) but not M-CLL (HR0.63, 95% CI 0.54-1.23) [50].

Multiple RCTs compared Ibr +/- anti CD20 monoclonal antibody against CIT regimens in the frontline setting [25,26,33]; in these trials there was a significant PFS benefit in favor of Ibr in comparison to the control arm in high-risk patients, including those with U-CLL.

In the Phase III A041202 trial, comparing Ibr ± R vs BR for untreated older CLL patients, PFS significantly improved with Ibr and Ibr-R vs BR (HR for Ibr vs BR (HR 0.36, 95% CI: 0.26-0.52 and 0.36. 95% CI: 0.25-0.51, respectively with both 1-sided P <.001)[51] while when considering ZAP70-unmethylated disease status as a surrogate for U-CLL, PFS was longer among patients with M-CLL than among those with U-CLL (HR, 0.51; 95% CI, 0.32 to 0.81).No significant interaction between IGHV mutation status and the effect of treatment on PFS was observed [26,51].

The randomized E1912 trial, after a median follow-up of 5.8 years, showed that Ibr-R improved PFS in patients with both U-CLL (HR: 0.27; P < .001) and M-CLL with a 5 PFS of 75% and 83% , respectively. Concerning OS, a small but significant improvement was observed for patients on the Ibr-R arm and, although the power for this secondary analysis is limited, in patients with U-CLL (HR, 0.35; 95% CI, 0.15-0.80; P 5 .01) but not in those with M-CLL (HR, 0.72; 95% CI, 0.15-3.47; P 5 .68)[24].

The FLAIR study is an open-label, randomized, controlled, phase 3 trial comparing Ibr-R versus FCR for patients with previously untreated CLL. Patients with greater than 20% of their CLL cells having the del(17p) were excluded. In the interim analysis, front line treatment with Ibr-R significantly improved PFS compared with FCR but did not improve OS. In subgroup analyses, at 9 months the effect of Ibr-R on complete response was similar in U-CLL (FCR 57% [95% CI 50–64] and IR 21% [16–28]) and M-CLL FCR 62% [54–70]; IR 18% [12–25]) as well as the on overall response in U-CLL (FCR 87% [95% CI 80·89–91·01%]; IR 91% [85·73–94·41]) and M-CLL (FCR 88% [82·13–93·12]; IR 91% [84·64–94·73]). However, a PFS advantage for the Ibr-R treated group was observed in U-CLL (HR 0.41, 95% CI 0.28-0.61) but not in M-CLL (HR 0.64, 95% CI 0.35-1.17)[52].

The iLLUMINATE trial compared Ibr-Obi vs Clb-Obi as first line for CLL patients aged>65 years or with comorbidities. After a median follow up of 48 months there was a significant PFS benefit with Ibr-Obi vs Clb-Obi among U-CLL patients (HR=0.17; 95% CI: 0.10-0.29) while within the Ibr-Obi arm, the estimated PFS was 67% and 89% for U-CLL and M-CLL, respectively, with the PFS benefit that persisted after excluding patients with del(17p) (U-CLL: HR=0.17;95% CI: 0.09-0.30; M-CLL: HR=0.25; 95% CI: 0.08-0.74) [53].

Similar results in high-risk U-CLL were reported in RCTs comparing second generation BTKi (Aca and Zan to CIT [27,54].

Table 1. Efficacy outcomes based on IGHV mutational status.

Trial	Setting	Treatment	PFS M%/UM%; HR (95% CI)	OS M%/UM%; HR (95% CI)	ORR M%/UM%	CR M%/UM%	uMRD M%/UM%	Ref
RESONATE-2	TN	Ibr	At 7 y 68/58; 0.858 (0.437-1.686)	NA	88/95	33/34	NA	22
		Clb	At 7 y 17/2; NA	NA	NA	NA	NA	
	TN	Ibr+R	At 5 y 83/75;	At 5 y 97/95;	NA	NA	NA	24

 doi:10.20944/preprints202401.1747.v1

ECOG ACRIN E1912		FCR	NA At 5 y 68/33; NA	NA At 5 y 92/84; NA	NA	NA	NA	
Alliance A041202	TN	Ibr	At 2 y 84/79; NA	NA	NA	NA	NA	26
		Ibr+R	AT 2 y 87/71; NA	NA	NA	NA	NA	
		BR	At 2 y 77/56; NA	NA	NA	NA	NA	
FLAIR	TN	Ibr+R	At 3 y 91.6/87.8; NA	NA	At 9 m 91/91	At 9 m 18/21	NA	52
		FCR	At 3 y 90.5/74.2; NA	NA	At 9 m 88/87	At 9 m 62/57	NA	
iLLUMINATE	TN	Ibr+Obi	At 4 y 89/67; NA	NA	NA	NA	NA	51
		Clb+Obi	Median NA/15.2 m; NA	NA	NA	NA	NA	
ELEVATE-TN	TN	Aca+Obi	At 4 y 89/86; NA	NA	NA	NA	NA	28
		Aca	At 4 y 81/77; NA	NA	NA	NA	NA	
		Clb+Obi	At 4 y 62/4; NA	NA	NA	NA	NA	
CLL14	TN	Ven+Obi	Median: NE/57.3 m; 0.47 (0.25, 0.87)	At 5 y 86.6/80.5, 1.48 (0.73,3.03)	NA	NA	PB EOT: 74/79	36, 55, 55
		Clb+Obi	Median 54.5/26.9 m; 0.33 (0.22,0.48)	At 5 y 87/70.8; 2.24 (1.22,4.12)	NA	NA	PB EOT: 43/28	
CAPTIVATE	TN	Ibr-Ven	At 3 y 92/ 88; NA	At 3 y 100/98; NA	96/97	51.3/61.3	Best PB: 72/88	57
GLOW	TN	Ibr-Ven	At 42 m 90.0/69.8; 3.775 (1.133–12.576);	NA	NA	NA	At cycle 9 31.0/52.0	39
		Clb-Obi	At 42 m 43.1/15.0; 2·172 (1·289–3·660)	NA	NA	NA	NA	
FLAIR	TN	Ibr-Ven	At 3 y: 94.3/98.3 NA	At 3 y: 94.3/98.3 NA	NA	NA	Median time to (m) in BM 29/18	40
		FCR	At 3 y: 88.6/71.2 NA	At 3 y;88.6/71.2 NA	NA	NA	Median time to (ms) in BM 8.9/NR	
RESONATE	R/R	Ibr	Median 8.4/49.7 m; 1.208 (0.741-1.971)	NA	NA	NA	NA	48
		Ofa	NA	NA	NA	NA	NA	
ELEVATE R/R	R/R	Aca	At 40.9 m 70.4/40.9; NA	NA	NA	NA	NA	29
		Ibr	At 40.9 m 53.6/48.1; NA	NA	NA	NA	NA	
ALPINE	R/R	Zan	At 2 y 76/72; NA	NA	76/86	NA	NA	49
		Ibr	At 2 y: 74/60; NA	NA	69/75	NA	NA	
SEQUOIA	TN	Zan	At 2 y 83.4/88; NA	NA	NA	NA	NA	53

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		BR	At 2 y 77.2/62.8; NA	NA	NA	NA	NA	
MURANO	R/R	Ven+R	Median NE/52.2 m, 2.96 (1.64, 5.34)	At 5 y 92.3/80.7; 2.46 (0.85, 7.13)	NA	NA	PB EOT 43.4/45.5	35
		BR	Median 24.2/15.7 m; 1.79 (1.24, 2.58)	At 5 y 66.7/61.4; 1.13 (0.63, 2.03)	NA	NA	NA	

Abbreviations: PFS, progression free survival; OS, overall survival; ORR, overall response rate; CR, complete response; uMRD, undetectable minimal residual disease; PB, peripheral blood; EoT, end of treatment; BM, bone marrow; NA, not available; NE, not evaluable; NR, not reached; HR, hazard ratio; Ibr, ibrutinib; Clb, chlorambucil; Aca, acalabrutinib; Zan, zanubrutinib; BR, bendamustine-rituximab; R, rituximab; FCR, fludarabine-cyclophosphamide-rituximab; Ofa: Ofatumomab; Obi, obinutuzumab; Ven, venetoclax; y, years; m, months.

In the ELEVATE TN RCT, estimated median 24-month PFS was longer in patients treated with Aca-Obi than in those treated with Clb-Obi in U-CLL patients (Aca-Obi 91%, 95% CI 83–95%; vs Clb-Obi 31%, 22–40%), and in those with M-CLL (Aca-Obi 96%, 87–99%; vs Clb-Obi 76%, 61–86%)[27,28].

In the SEQUOIA RCT Zan was compared to BR as frontline therapy in patients with TN CLL/SLL. At a median follow-up of 26.2 months (IQR 23.7–29.6), median PFS was significantly improved with Zan vs BR (HR 0.42 [95% CI 0.28 to 0.63]; p<0·0001) and in U-CLL (HR 0.24, 95% CI 0.13-0.43), while among patients with M-CLL the difference in PFS between the treatment groups was not significant (HR 0.67, 95% CI 0.36-2.33)[54].

Ven, the only BCL2i approved for the treatment of CLL, was investigated in a head-to-head comparison with CIT, both in frontline and R/R settings.

In R/R CLL, the MURANO study [34] showed that after 5 years of follow-up, Ven-R was superior to BR in all the prespecified subgroups, including U-CLL (HR for PFS 0.16, 95% CI 0.10-0.26). U-CLL and M-CLL patients treated with Ven-R exhibited similar a response rate, with an uMRD at the end of treatment (EOT) of 45.5% and 43.4% in U-CLL and M-CLL respectively. After 5 years of follow up, U-CLL patient had higher rate of MRD conversion with subsequent progressive disease (PD) (37.5% and 4.3%, in U-CLL and M-CLL, respectively), and a shorter median PFS in Ven-R arm (52.2 months vs NE, HR 2.96; 95% CI, 1.64-5.34, P=0.002) [35]. Moreover, in multivariate analysis M-CLL was independently associated with a reduced risk of relapse [35]. The inferior PFS in U-CLL treated with Ven-R, despite similar EOT uMRD, could be justified by a faster CLL regrowth after EOT in U-CLL than in M-CLL, indeed the median MRD doubling time was 192 days in M-CLL and 80 days in U-CLL [35]. M-CLL subgroup had a trend toward a superior OS without statistical significance (5 years OS 92.3% vs 80.7; HR 2.46: 95% CI, 0.85-7.13, p=0.0876).

In the CLL14 trial, Ven-Obi was superior to Clb-Obi in most high-risk subgroups, including U-CLL with a 5-year PFS of 55.8% in Ven-Obi arm vs 12.5% in Clb-Obi arm (HR 0.27, 95% CI 0.19–0.38) [55]. PFS was longer in M-CLL than in the U-CLL counterpart in both treatment arms (Ven-Obi arm: HR 0.47; 95% CI, 0.25 to 0.87; P =0.02 and Clb-Obi arm: HR 0.33; 95% CI, 0.22 to 0.48; P < 0.0001). In multivariate analysis, U-CLL and *TP53* abnormalities predicted for a worse PFS with a HR of 2.258 (95% CI 1.268-4.021) and 2.262 (95% CI 1.242-4.120. respectively [56]. U-CLL and M-CLL obtained similar rates of uMRD in Ven-Obi arm (79%, and 74% in U-CLL and M-CLL respectively) higher than those achieved in Clb-Obi arm (28% and 43%) [36], while MRD doubling time was not affected by IGHV mutational status only in Ven-Obi arm [57].Concerning OS there wasn't a significant difference in Ven-Obi treated patients based on IGHV mutational status (5-year OS 80.5% vs 86.6%; HR 1.48, 95% CI 0.73–3.03) [55].

In the CAPTIVATE study at 36-months, in the fixed duration Ibr-Ven cohort PFS rates for patients with U-CLL and M-CLL were 88% (95% CI, 80–93) and 92% (95% CI, 83–96), respectively with OS rates >95% in patients with and without high-risk features including those with U-CLL and M- CLL (OS 98%, 95% CI 92–99% and 100%, 95% CI 100-100, respectively). Unexpectedly, U-CLL showed deeper MRD responses than M-CLL with a best uMRD rates in peripheral blood of 88% (95% CI, 82–94) and 72% (95% CI, 62–82, respectively. Best uMRD rates in bone marrow were 73% (95% CI, 65–81) and 60% (95% CI, 49–71) for U-CLL and M-CLL, respectively, while in patients with U-CLL

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without del(17p)/*TP53* mutation, best uMRD rates in peripheral blood and bone marrow were 90% (95% CI, 84–96) and 80% (95% CI, 72–88), respectively [58]. Of interest, similar results were also obtained in the MRD cohort with an uMRD in 77% and 56% of U-CLL and M.CLL, respectively [38].

In the GLOW study, when assessing PFS per IGHV mutation status, 42-month rates in the Ibr–Ven group were 69.8% (95% CI 57.2–79.4) in U-CLL and 90.0% (72.0–96.7) in M-CLL (HR 3.775 [95% CI 1.133–12.576]; p=0.031). In patients with a post-treatment disease evaluation visit who received Ibr–Ven, and had M-CLL, PFS rates 2 years after treatment were 92.3% (56.6–98.9; one event) for 14 patients with detectable MRD and 100% (100–100; no events) for 13 patients with uMRD 3 months after the EOT. Among patients with U-CLL, PFS rates 2 years after treatment were 67.0% (37.9–84.7; five events) for 16 patients with detectable MRD and 89.9% (75.2–96.1; seven events) for 40 patients with uMRD 3 months after the EOT. In a post-hoc analysisuMRD was found, by cycle 9, in 52% and 31% of patients with U-CLL and M-CLL, respectively. Finally, in the Ibr-Ven cohort IGHV mutational status did not impact on OS both in univariate and multivariate analysis [39].

In the recently published FLAIR phase 3 trial in untreated CLL patients PFS was longer in patients with U-CLL (HR for disease progression or death, 0.07; 95% CI, 0.02 to 0.19) but not in those with M-CLL (HR, 0.54, 95% CI, 0.21 to 1.38). Results for OS appeared also to favor Ibr–Ven as compared with FCR in patients with U-CLL (HR for death, 0.23; 95% CI, 0.06 to 0.81) but not in those with M-CLL (HR, 0.61, 95% CI, 0.20 to 1.82). Of interest, median time to uMRD was shorter in patients with U-CLL vs those with m-CLL both in the PB and BM [40].

In conclusion, IGHV mutational status has no clear impact on BTKi response both in TN and R/R settings while in Ven + anti CD20 monoclonal antibody treatments IGHV mutational status could maintain a negative prognostic role for PFS and MRD kinetics mainly in R/R settings, as in TN patients treated with Ven-Obi the predictive significance of IGHV mutational status appears less prominent. Deep, durable responses and sustained PFS and OS were seen with fixed duration Ibr-Ven in patients with high-risk genomic features, including IGHV mutational status, with similar outcomes to those without high-risk features.

2.2.3. TP53 aberrations, genetic lesions, and cytogenetics

The first studies investigating the prognostic relevance of genetic aberrations in CLL were conducted in the 1980s using chromosome banding analysis (CBA) and led to the demonstration that a worse outcome was associated with the presence of clonal changes and with trisomy 12 and abnormalities involving chromosome 14q and with a complex karyotype as defined by the presence of 3 or more abnormalities [59]. However, in the following years, few studies used CBA for prognostication in CLL as no metaphases could be obtained in many patients and clonal aberrations were detected in only 40–69% of cases due to the low in vitro proliferative activity of the leukemic cells and the poor quality of the metaphases [60].

For these reasons interphase fluorescence in situ hybridization (iFISH) replaced CBA in the assessment of genetic aberrations as this technique does not require proliferating cells.

In 2000, Döhner using iFISH demonstrated that 82% of CLL patients harbor chromosomal aberrations, the most common being del13q, del11q, trisomy 12, and del(17p). These cytogenetic alterations were associated with different OS, with the worst prognosis in patients carrying del(17p) [61].

Subsequently, different technologies were developed for the studies of genomic abnormalities in CLL whose specific advantages, limitations and costs were recently reviewed [60,62–64].

Using next generation sequencing (NGS) techniques, in CLL were identified over 40 recurrently mutated driver genes [65], with mutations that may also involve non-coding regions [66]. However, despite the numerous genetic lesions with a proved pathogenic role, only *TP53* inactivating mutations demonstrated a validated negative prognostic and predictive impact on outcomes in the era of CIT [1].

Loss of function of *TP53* may be the result of the cooccurrence of *TP53* mutations and del(17p) in 60% of cases, while isolated 17p deletion or *TP53* mutations are observed in 10% and 30% of cases,

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respectively. Overall, the prevalence of *TP53* aberration is 10% in untreated patients but increases up to 40-50% in the R/R setting [67].

TP53 is a tumor-suppressor gene that regulates of the cellular response to DNA damage and can activate the apoptotic process in response to a severe DNA damage as during chemotherapy [67]. By contrast, targeted agents appear to have a p53-indipendent mechanism of action [68,69], that could, therefore, question the negative prognostic and predictive significance of *TP53* abnormalities.

Subgroup analyses of multiple RCTs comparing BTKi+/- anti CD20 to CIT suggest that the predictive role of *TP53* could be overcome in patients treated frontline with BTKi.

The iLLLUMINATE trial included 16% and 20% of patients with del(17p) and/or *TP53* mutation treated with Ibr-Obi and Clb-Obi respectively [33]. The Ibr+Obi treatment was associated with a significant PFS benefit in comparison to the control arm (HR=0.122; 95% CI: 0.051-0.294) with a PFS that was superimposable between patients with or without deletion del(17p)/*TP53* mutation (HR=0.93; 95% CI:0.32-2.69; P=0.895) [53].

In a pooled analysis across four studies: PCYC-1122e, RESONATE-2 (PCYC-1115/16), iLLUMINATE (PCYC-1130) and ECOG-ACRIN E1912 that included 89 patients with *TP53* aberrations receiving first-line treatment with single-agent Ibr (n = 45) or Ibr in combination with an anti-CD20 antibody (n = 44) with a median follow-up of 49·8 months, median PFS was not reached and PFS and OS rates at four years were 79% and 88%, respectively. Overall response rate was 93%, including complete response in 39% of patients [70].

In the ALLIANCE trial the study population was well-balanced in terms of genetic features. Specifically, the number of patients harboring del(17p)/*TP53* was 31, 24, and 30, respectively [26]. Adverse genetic prognostic factors, such as *TP53* mutations, del(17p), del(11q), or complex karyotype did not influence the efficacy of Ibr, while they still negatively impact the prognosis of patients treated with chemo-immunotherapy.

The effectiveness of first line Ibr was also evaluated in in a large series of 747 patients with CLL and *TP53* aberrations in a nationwide study with a 100% capture of patients. At 24 months, an estimated treatment persistence rate of 63.4% (95% CI 60.0%-67.0%) and a survival rate of 82.6% (95% CI 79.9–85.4%) were observed- Disease progression or death were the reasons for discontinuation in 182/397 patients (45.8%). These data confirm that Ibr is an effective first-line treatment for CLL and *TP53* aberrations in patients treated at large academic centers and community practice hospitals and that clinical characteristics at baseline including age, ECOG-PS and pre-existing heart disease, whereas ECOG ≥ 1, age ≥ 70 years and male sex may influence the effectiveness of ibr, whereas the experience of prescribing centers and multi-hit or single-hit *TP53* aberrations had no impact on outcome in this high-risk population [71].

In the ELEVATE-TN trial [27], the survival benefit was confirmed in high-risk cytogenetic subgroups, such as those with del(17p) and or mutated *TP53*, where the median PFS was not reached.

By contrast, when BTKi is used in R/R CLL patients, *TP53* deficiency seems to maintain its negative predictive significance on PFS. In the phase Ib/II PCYC-1102 trial, 34 R/R CLL patients with del(17p) were enrolled and treated with Ibr. Median PFS was 52 months overall, but only 26 months in patients with del(17p) (HR 3.549, 95% CI 1.357-9.282, p=0.010) with a trend for a reduced median OS in comparison to patients without *TP53* abnormalities (median OS of 57 months HR 3.353, 95% CI, 0.98-11.47) [72].

In the ELEVATE-RR clinical study, PFS and OS are comparable across patients harboring high-risk cytogenetics such as del(17p), del(11q), and complex karyotype or those patients with advanced disease, regardless of the number of previous treatments [29].

However, the negative predictive value of *TP53* disruption in R/R settings may be questioned by Zan, that in a head-to-head RCT with Ibr, showed a longer PFS in comparison to patients with *TP53* disruption who received Ibr (at 24 months PFS of 72.6% vs 54.6%, HR 0.53; 95% CI, 0.31 to 0.88) [50].

TP53 deficiency seems to maintain its negative predictive relevance in patients during fixed duration Ven treatments. In the MURANO trial, Ven-R treatment was associated to a PFS benefit in patients with del(17p) and/or *TP53* mutation in comparison to the BR arm (median PFS of 37.4 vs 13.4

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months, HR 0.26, 95% CI 0.16-0.42) although in Ven-R arm patients without del(17p) and/or TP53 mutation showed a better PFS than those with del(17p) and/or *TP53* mutation (median PFS 56.6 vs 37.4 months, HR 2.04, 95% CI 1.32-3.15; P=0.001). In Ven-R arm, the rate of uMRD at the EOT seemed also to be impaired by the presence of del(17p) (23.5% vs 43.2% in patients without 17p deletion) with all patients with del(17p) experiencing PD vs 22.2% in patients without del(17p) [35]. Furthermore, *TP53* mutational status was identified as covariates related to MRD growth rate, with a median MRD doubling time of 101 days in patients with wild type *TP53* and 66 days in those mutated TP53 (p=0.012). In the Ven-R arm, patients with del(17p) and/or *TP53* mutation had also a significantly reduced OS (5 years OS 70.2% Vs 88.7% in those without *TP53* disruption, p=0.0059) [35].

The adverse prognostic significance of *TP53* abnormalities was also confirmed in patients treated up front with fixed duration Ven-Obi regimen. In the CLL14 trial, patients with del(17p) and/or *TP53* mutation had a longer PFS if treated with Ven-Obi than with Clb-Obi (5-year-PFS 40.6% vs 15.6%; HR 0.48, 95% CI 0.24–0.94), with a high rate of uMRD at EOT (68%) [36,56]. However, in the Ven-Obi arm patients with *TP53* abnormalities had a shorter PFS than those without *TP53* abnormalities (5-year PFS of 40.6% vs 65.8% respectively, HR 2.37, 95% CI 1.34–4.17 and 17p deletion (regardless of TP53 mutational status) and lymph node size ≥5 cm were the only variables significantly associated to a shorter PFS in multivariable analysis. In both arms, OS was shorter in the presence of del(17p) and/or *TP53* mutation (Ven-Obi: 5-year OS 60.0% vs 85.7%; HR 2.96, 95% CI 1.44–6.09; Clb-Obi: 5-year OS 54.2% vs 80.7%; HR 2.65, 95% CI 1.39–5.04) [56].

Finally, in the CAPTIVATE trial, the fixed duration Ibr-Ven treatment showed, at 36 months, a slightly lower PFS for the subsets of patients with del(17p)/*TP53* mutation in comparison to that without del (17p)/*TP53* mutation (81%, 95% CI, 61–92 and 91%, 95% CI, 85–94, respectively). OS was 96 % (95% CI 77–100) and 99% (95% CI 95–100 the patients with and without del(17p)/*TP53* mutation, respectively. Best uMRD rates in peripheral blood were 83% (95% CI, 69–97) and 82% (95% CI, 76–88) for the subsets of patients with and without del(17p)/*TP53* mutation, respectively, while best uMRD rates in bone marrow were 45% (95% CI, 27–63) and 72% (95% CI, 65–79) for the subsets of patients with and without del(17p)/*TP53* mutation, respectively, [58].

In conclusion, based on the results of the CLL14 and MURANO RCTs, Ven-based regimens were shown to improve the outcome of CLL patients with del(17p) and/or *TP53* mutation, although *TP53* disruption still appeared to be a predictor of inferior PFS and OS with these fixed duration therapies.

Since the years 2000s, CBA has gained a second youth due to the use of CpG oligonucleotides and IL2 for in vitro metaphase stimulation. Through this technology metaphases could be obtained in over 98% of patients, with chromosomal aberrations detected in 83% of cases [73]. CBA has also demonstrated to be informative in nearly one third of cases without cytogenetic abnormalities by standard 4 probes FISH analysis [74]. In addition, CBA can also identify CLL cases harboring a complex karyotype (CK) that is defined by the presence of at least three cytogenetic abnormalities in the same clone and that may be considered a genetic marker of chromosomal instability [75]. In the era of CIT, a CK, which is present in nearly 10-15% of CLL untreated patients, was associated to a shorter TFT, PFS or OS and it was an independent adverse prognosticator also in the subgroup of high risk CLL [75]. However, there is is still no consensus on the definition of a CK in CLL, although recently a large retrospective analysis concluded that a CK as defined by the presence of ≥3 chromosomal abnormalities should not be axiomatically considered unfavorable in CLL and rather a high cytogenetic complexity with ≥5 chromosomal aberrations represented a prognostically adverse, independently of other biomarkers [76].

The introduction of novel agents in CLL treatment questioned the predictive role of a CK. Thompson et al reported that a CK was observed in 21/56 of cases R/R CLL treated with ibr-based regimens and with an evaluable karyotype, and that in multivariable analysis a CK was a stronger predictor than del(17p) for a shorter event-free survival (EFS) (HR 6.6, 95% CI 1.7-25.6, P = 0.006), and OS (HR 5.9, 95% CI 1.6-22.2, P = 0.008) [77].

By contrast the Phase Ib/II PCYC-1102 and the RESONATE trials did not find any independent adverse prognostic role for a CK in R/R CLL patients treated with Ibr [49,71] while, in a phase 2 study, after a median follow up of 41 months, despite a high ORR (90%), a shorter median PFS of 33 months

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compared to a median PFS not reached in the whole cohort was observed in 20 R/R CLL patients with CK treated with the second generation BTKi Aca [78].

In the frontline setting there are conflicting data. In the ALLIANCE trial, there wasn't a significant impact of CK on PFS (HR 1.01, 95% CI 0.68-1.51, P=0.95) [(26], whereas in the Phase 2 GIMEMA LLC1114 trial, CK was significantly associated to a shorter PFS in multivariable analysis (p=0.09) [78]. However, more recently, in one of the largest retrospective analyses including 456 CLL patients treated with Ibr, reported that in multivariable analysis karyotypic complexity treated as a continuous variable was an independent predictor of PFS (HR 1.07; 95% CI, 1.04-1.10; P < .0001) and OS (HR, 1.09; 95% CI, 1.05-1.12; P < .0001), both in TN and R/R cases [11]. Finally, a phase 1/2 multicenter study, evaluating Aca in TN CLL patients, patients with CK (n=12) obtained an ORR of 100% and after a median follow up of 53 months, with PFS and OS that were superimposable between patients with or without CK [80].

The predictive role of CK was also evaluated in CLL patients treated with Ven fixed duration therapy. In the MURANO trial evaluating genome complexity (GC) was with array comparative genomic hybridization (aCGH), low (three to four aberrations) and high (five or more aberrations) were associated to a higher rate of MRD positivity at EOT (p= 0.042) [81] and a higher rate of uMRD conversion with subsequent PD [35]. Although VenR was superior to BR in every subgroup of patients, after a median follow up of 5 years, in VenR arm genomic complexity negatively affected PFS (HR 2.5; 95% CI, 1.56-4; p<0.0001) but not OS (HR 1.52; 95% CI, 0.64-3.57; p=0.3) [35].

In the frontline setting, the CLL14 trial showed that CK maintained its adverse significance in the Clb-Obi arm; whereas in the Ven-Obi arm patients with CK had similar efficacy outcome than patients without CK, as no statistically significant differences were observed concerning uMRD, PFS and OS. CK didn't have a predictive relevance also if highly CK (five or more chromosomal aberrations) was compared to intermediate CK (three or four chromosomal aberrations) [82].

By contrast, the phase 3 GAIA/CLL13 trial, that evaluated different Ven containing arm to CIT in a population of fit TN patients without *TP53* aberration, in the pooled Ven arms, a multivariable analysis identified a highly CK (HR, 1.96; 95% CI, 1.03-3.72; P = .041), but not a CK, as independent adverse prognosticators for PFS [83]. Of interest, the presence of translocations, and particularly the unbalanced translocations, was also independently associated with an inferior PFS (HR 3.83, 95% CI 2.30-6.39, p<0.001) in the Ven arms as previously observed in single center series of patients mainly treated with CIT [84]. The CLL 13 data on CK are particularly relevant because achieved in the absence of TP53 disruptions, a factor frequently associated to CK [85].

In conclusion, the data on prognostic and predictive role of a CK appear to be still conflicting mainly because of the relatively low number of patients included in the various trials with different settings, inclusion criteria and treatments. Larger population-studies will address this issue [86] although the actual guidelines [1] and the recent recommendations released on behalf of the European Research Initiative on CLL (ERIC) [61] still recommend that CBA should be performed only in the context of clinical trials and not in the routine practice.

3. Score systems

The first attempt to validate CLL-IPI in the context of patients treated with small molecules was performed by Soumerai et al. (Table 2)[87]. The authors evaluated CLL-IPI in the context of 897 CLL R/R patients, enrolled in randomized phase 3 trials, receiving idelalisib (Idela)-based regimens or chemo-immunotherapy ± placebo. The primary endpoint of the study was OS. The median number of prior therapies was three. Up to 82% of the population had an unmutated IGHV status, while nearly one-third harbored high-risk cytogenetic lesions. After calculating the CLL-IPI risk score, patients were positioned to 1 of 4 CLL-IPI risk groups: low (score 0–1), intermediate (score 2–3), high (score 4–6), and very high (score 7–10). With a median follow-up of 21.4 months, the CLL-IPI scoring system separated patients into low- (2.2%), intermediate- (12.8%), high- (48.7%), and very high (36.2%) risk groups. CLL-IPI confirmed its ability to predict OS, satisfying the main endpoint of the study. Indeed, the 24-month OS rate was dramatically different between the intermediate-, high-, and very-high CLL-IPI risk groups, resulting in 88.3% for intermediate-, 69.8% for high-, and 52.5% for

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very high risk. On the contrary, there was no significant difference in terms of OS rate between the low- and intermediate- CLL-IPI risk (93.3 vs. 88.3%). The next step was to determine the impact of Idela on the CLL-IPI scoring system and it was found that it is also prognostic for OS in patients who underwent Idela-based treatment. Another aim of the study was to investigate, through a multivariable analysis, whether CLL-IPI risk factors were independently prognostic for OS in the R/R setting, given their validation in treatment-naïve one. In particular, age >65, B2M >3.5mg/L, IGHV unmutated, and del(17p) and/or *TP53* were independently prognostic for OS, but Rai I-IV or Binet B/C staging systems were not. This suggests how each risk factor had a relatively different contribution. Finally, the authors delineated a modified CLL-IPI to optimize the CLL-IPI scoring system in the setting of R/R patients. Indeed, a modification of the cut-off for the clinical stage (Rai III-IV and Binet C) was performed. Therefore, 3 groups of patients were identified: low- (score 0–1), intermediate- (score 2–3), and high-risk (score 4–5). The so-modified CLL-IPI stratified patients into low- (10.5%), intermediate- (51.3%), and high-risk (38.2%) groups, and was prognostic for OS.

Another robust attempt to validate the CLL-IPI scoring system in patients with R/R CLL, or patients treated with novel target therapies was operated by an international collaboration proposing a survival risk score based on simple and accessible biochemical and clinical parameters, the so-called BALL score [88]. The study included nearly 2500 R/R CLL patients treated with chemo-immunotherapy or novel agents (Ibr, Idela, Ven). The authors identified four factors that have an independent prognostic weight on OS: β2M (≥5mg/L), lactate dehydrogenase (LDH) (>upper limit of normal - ULN), hemoglobin (<110 g/L for women or <120 g/L for men) and time to initiation of last therapy (<24 months). Three different prognostic groups were identified: low- (score 0–1), intermediate- (score 2–3), and high-risk (score 4). All of them were characterized by a different OS. One of the advantages of the study was to identify potentially high-risk patients for whom available therapies could be ineffective and clinical trial participation encouraged.

An example of a real-world application of the BALL score was carried out by an Italian multicenter working group on CLL ("Campus CLL") [89]. In particular, the Italian group developed a survival risk score for Ibr, the so-called SRSI, able to predict OS in the setting of R/R CLL patients treated with Ibr outside clinical trials and compared it with the BALL score calculated in the same cohort. In univariable analysis, sex, age, hemoglobin levels, Binet stage, β2M and LDH levels, time from last therapy, IGHV mutational status, and del(17p) were considered. Among them, in the multivariate analysis, only anemia, elevated β2M, and LDH levels negatively impacted OS. After assigning a weighted point to each factor, three risk groups were identified: low (score 0), intermediate (score 1-3), and high risk (4-5), dramatically characterized by different 2-year OS, (95.3%, 81% and 60.6%, respectively). Specifically, 214 patients were classified as low-risk, 247 as intermediate-risk, and 80 as high-risk. Calculating point scores according to BALL score, 372 patients (68.8%) were classified as low-risk, 132 (24.4%) as intermediate-risk, and 37 (6.8%) as high risk, with low-risk patients having 2-year OS probability of 89.2% intermediate-risk patients of 79.9% and high-risk patients of 48.2%. This result suggested that SRSI is more accurate in predicting survival, especially in the setting of the real world.

Subsequently, the accuracy of this score in predicting prognosis has been evaluated in a cohort of R/R CLL patients treated with R-Idela [90]. Univariate and multiple Cox regression analyses showed an association between the three parameters (β2M, LDH, and hemoglobin level) and OS. OS was dramatically different among the three groups of risk, with a 2-year OS probability of nearly 89% in the low-risk category to 54% in the high-risk one. These data confirmed the prognostic power of this score also in the setting of R/R patients treated with R-Idela.

Table 2. Score systems in CLL.

Ref	Score System	CLL therapy	N° of pts	Status of disease	Variables	Categories (points)	OS category
86	CLL-IPI	Idela-based regimens	897	R/R	• age >65 • Rai I-IV or Binet B/C • β2M >3.5mg/L	• Low (0-1) • Int (2-3)	1y-OS 93.3% 88.3%

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					• IGHV unmutated • del(17p) and/or TP53M	• High (4-6) • Very high (7-10)	69.8% 52.5%
87	BALL score	Ibr	727	R/R	• β2M (≥5mg/L) • LDH > ULN • Hb (<110 g/L for women or <120 g/L for men) • time to initiation of last therapy (<24 months)	• low (0-1) • int (2-3) • high (4)	89.7% 79.5% 55.8%
		Idela	897			• low (0-1) • int (2-3) • high (4)	82.6% 61.8% 49.5%
		Ven	389			• low (0-1) • int (2-3) • high (4)	95.1% 84.6% 82.2%
88	SRS_i	Ibr	541	R/R	• Hb (<110 g/L for women or <120 g/L for men) • β2M (≥5mg/L) • LDH > ULN	• Low (0) • Int (1-3) • High (4-5)	2y-OS 95.3% 81% 60.6%
89	SRS_i	R-idela	142	R/R	• Hb (<110 g/L for women or <120 g/L for men) • β2M (≥5mg/L) • LDH > ULN	• Low (0) • Int (1-3) • High (4-5)	2y-OS 88.6% 69.6% 54.3%
90	4-factor prognostic model	Ibr	720	R/R	• TP53 aberration • prior treatment • β2M >5 mg/L • LDH >250 U/L	• Low (0-1) • Int (2) • High (3-4)	3y-OS 93% 83% 63%
91	4-factor prognostic model	Ibr	586	R/R	• TP53 aberration • prior treatment • β2M >5 mg/L • LDH >250 U/L	• Low (0-1) • Int (2) • High (3-4)	3y-OS 89.7% 77.8% 60.3%
93	CLL-3 model	Ibr	338	R/R	• LDH values >UNL • Rai stage III/IV • early POD	• Low (0) • Int (1) • High (2-3)	3-y OS 91% 84% 65%

A milestone in scoring systems in the era of small molecules is represented by the 4-factor prognostic model [91]. Seven-hundred-twenty patients, treated with Ibr within phase II and III trials, were included in the data set. Patients were subdivided into a training and an internal validation cohort. Most cases were R/R and 44% harbored *TP53* mutations. Eleven factors, associated with the worst outcome in terms of OS and PFS, were individualized in the univariate analysis. In particular, complex karyotype was shown to impact negatively on the two survival parameters, and unmutated IGHV was associated with an inferior PFS but not OS. Multivariable analysis and machine-learning algorithms identified four parameters model that was validated in internal and external cohorts. Those four factors, represented by TP53 aberration, prior treatment, β2M >5 mg/L, and LDH >250 U/L, were demonstrated to be independently associated with an inferior PFS and OS. Given one point for each parameter, it was possible to delineate three categories of risk: low (0-1), intermediate (2), and high (3-4). The 3-year PFS rates were 87%, 74%, and 47%, respectively, while the 3-year OS rates were 93%, 83%, and 63%, respectively. Although the relapse of disease contributed one point to the prognostic index, the model maintained statistical significance for PFS and OS also in the treatment

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naïve cohort. Moreover, authors investigated rates of BTK and/or PLCγ2 mutations, which classically confer resistance to Ibr therapy, and they found that cumulative incidence of those mutations is increased in the high-risk group compared to intermediate and low-risk (50% vs. 40% and 17%, respectively). In addition, the high-risk group had a major probability to develop Richter's transformation.

The Italian multicentre working group on CLL ("Campus CLL dataset") investigated the validity in terms of survival parameters (PFS and OS) and the reproducibility of the 4-factor score, in a cohort of 586 patients treated with Ibr outside clinical studies as first-line and salvage therapy [92]. In this cohort *TP53* aberration, R/R-CLL, high LDH, and high β2-M, both in univariate and in multivariate analysis were significantly associated with prognosis. The 3-year OS was 89.7% for low-risk, 77.8% for intermediate-risk, and 60.3% for high-risk, according to those observed in the original study. The comparison between CLL-IPI and the 4-factor score within this cohort confirmed the lower power of prediction of the first in the setting of patients treated with small molecules.

Molica et al recently compared the modified CLL-IPI, 4-factor model, and BALL score within a cohort of 111 R/R CLL patients treated with Ibr. Both the modified CLL-IPI and 4-factor model did not seem to provide prognostic power in the setting of R/R cases, while the BALL score prognostically segregated two groups (low- and intermediate-high risk) of patients. Low-risk patients showed a 3-year OS of 85% versus 50% for those at intermediate-high risk. In this cohort, patients with del(17p) and/or *TP53* were well distributed among low and intermediate-high risk groups. Therefore, a sub-classification was performed based on the BALL score and del(17p). Median OS was not reached in the BALL low-risk patients without del(17p), while it was drastically lower (28 months) in those categorized as BALL intermediate-high risk harboring del(17p). Thus, these data showed as the BALL score may be refined by biological markers as TP53 status [93].

Finally, Molica et al. [94] analyzed 338 CLL patients to assess the reliability of CLL-IPI, Barcelona, and Brno (B-B) scores, BALL, and 4-factor scores. B-B score is a prognostic model comprising only two biomarkers (IGHV mutational status and FISH cytogenetics) which allows of segregates CLL patients with different outcomes [95]. In this cohort, the 3-year PFS and OS were 70.7% and 78.1%, respectively. The 4-factor and BALL scores were applied to the examined cohort and predicted successfully PFS and OS, while CLL-IPI and B-B, created in the era of chemo-immunotherapy, succeeded only in predicting PFS. In the multivariate analyses of fourteen baseline parameters, only three factors were strongly negatively associated with PFS and OS: LDH>UNL, Rai stage III/IV, and early POD (progression of the disease). Therefore, three risk groups were delineated: low-risk (0 factors), intermediate-risk (1 factor), and high-risk (2-3 factors). A concordance analysis showed a substantial agreement between the 3-factor score, proposed by the authors, and the 4-factor model. Both scoring systems allowed for capturing a similar rate of high-risk cases. A comparative analysis between the 3-factor and 4-factor models and the BALL score showed as the 4-factor model works better in terms of both PFS and OS than the other two systems. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

4. Future directions: conclusions

Novel drugs has profoundly changed the outcomes in CLL patients and traditional prognostic/predictive factors need to be verified in the contest of these new targeted therapies. A better definition of prognostic predictive factors will help to identify the most appropriate and efficacious treatment in the different biological and clinical settings particularly when fixed duration or continuous treatments are available and novel treatment combinations with drugs with different but synergic mechanisms of action are being tested in prospective clinical trials [96]. MRD could represent an interesting surrogate clinical endpoint for outcome evaluation and to guide individualized treatment decision although a its clinical utility in the different biological settings require further research and a standardization and reproducibility of the methodologies [97]. Finally, sustainability of therapies with novel agents represents a further issue to be considered to enable a widespread accessibility to these treatment [98].

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