frontiers | Frontiers in Oncology

TYPE Opinion
PUBLISHED 09 February 2023
DOI 10.3389/fonc.2023.1106579

OPEN ACCESS

EDITED BY
Tadeusz Robak,
Medical University of Lodz, Poland

REVIEWED BY
Marco Montillo,
Niguarda Ca 'Granda Hospital, Italy
Anna Fink,
University Hospital of Cologne, Germany

*CORRESPONDENCE
Jennifer Edelmann
j.edelmann@posteo.de

SPECIALTY SECTION
This article was submitted to Hematologic Malignancies, a section of the journal Frontiers in Oncology

RECEIVED 23 November 2022
ACCEPTED 23 January 2023
PUBLISHED 09 February 2023

CITATION
Edelmann J, Malcikova J and Riches JC (2023) Opinion: What defines high-risk CLL in the post-chemoimmunotherapy era? *Front. Oncol.* 13:1106579. doi: 10.3389/fonc.2023.1106579

Opinion: What defines high-risk CLL in the post-chemoimmunotherapy era?

Jennifer Edelmann[1]*, Jitka Malcikova[2,3] and John C. Riches[4,5]

[1]ClinSciNet - The Clinician Scientist Network, Münsingen, Germany, [2]Department of Internal Medicine – Hematology and Oncology, University Hospital Brno, Masaryk University, Brno, Czechia, [3]Center of Molecular Medicine, Central European Institute of Technology, Masaryk University, Brno, Czechia, [4]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom, [5]Department of Haemato-Oncology, Barts Health NHS Trust, St. Bartholomew's Hospital, London, United Kingdom

KEYWORDS

chronic lymphocytic leukemia (CLL), high-risk, TP53, definition, BTK - Bruton's tyrosine kinase, BCL2 (B-cell lymphoma 2), COVID - 19, risk factor

The definition of high-risk chronic lymphocytic leukemia (CLL) was relatively simple in the chemoimmunotherapy era, as it was defined by only one genomic marker, *TP53* alteration, along with poor responses to purine-analogue based treatment (1). While other biomarkers such as unmutated IGHV, del(11q), high ZAP70 expression and high CD38 expression were associated with inferior prognosis, *TP53* deficiency by mutation and/or del (17p) remained the only biomarker that clearly guided treatment decisions (2).

The emergence of targeted compounds has rendered chemoimmunotherapy virtually obsolete for CLL treatment, with it remaining an option only for patients with a mutated IGHV, normal *TP53* and a non-complex karyotype (3). Instead, non-chemotherapeutic targeted treatment has now become the standard of care. Approved treatment options in first- and second-line include continuous treatment with a covalent BTK inhibitor (e.g. ibrutinib, acalabrutinib) plus/minus anti-CD20 monoclonal antibody (4–9), fixed duration therapy with the BCL2 inhibitor venetoclax plus anti-CD20 monoclonal antibody (10, 11), fixed duration therapy with venetoclax plus ibrutinib (12, 13), and for *TP53* altered cases, continuous monotherapy with venetoclax (14). Moreover, clinical trials are currently evaluating triple drug regimens that combine BTK and BCL2 inhibitors with anti-CD20 treatment (15–18). Looking forward, non-covalent BTK inhibitors (e.g. pirtobrutinib and nemtabrutinib) (19, 20), BTK degraders (e.g. NX-2127) (21), and second-generation BCL2 inhibitors (e.g. Lisaftoclax) (22) are promising alternatives in clinical development, along with immunotherapeutic approaches such as CAR T-cells and bispecific antibodies.

The paradigm shift from chemoimmunotherapy to targeted therapy and the ever-increasing number of treatment options has meant that defining high-risk CLL is less straight-forward. This is mainly because BTK and BCL2 inhibitors have been demonstrated to markedly improve progression-free and overall survival (PFS and OS) in *TP53*-deficient and IGHV unmutated CLL patients (4, 5, 7, 9, 10, 14, 23–25). Limited data from clinical trials evaluating ibrutinib first-line and acalabrutinib have even raised the possibility that BTK-inhibition may overcome the adverse effects of *TP53* deficiency (5, 6, 9, 26). Although results

from a direct PFS comparison between *TP53* deficient and non-deficient cases are not available yet, data from the SEQUOIA and ALPINE trials testing the second-generation covalent BTK inhibitor zanubrutinib in first-line and in relapsed/refractory CLL further support this hypothesis (27, 28). In contrast, *TP53* alterations remained prognostic for shorter PFS in studies on ibrutinib treatment of relapsed/refractory CLL (29–31). This difference may be explained by a high prior treatment load in the relapsed/refractory population leading to a selection of adverse risk factors associated with *TP53* deficiency such as high karyotype complexity (32–34). Genomic characterization of sequential samples taken pre-ibrutinib treatment and at disease progression demonstrated that *TP53*-deficient subclones were not necessarily responsible for ibrutinib failure. For instance, several studies on the clonal dynamics of *BTK* mutation as a frequent resistance mechanism towards covalent BTK inhibitors have shown that at relapse, *BTK* mutation can evolve within a *TP53* wild-type subclone while the *TP53*-deficient subclone is eliminated or remains effectively controlled (35–37).

With regards to BCL2 inhibition, clinical trial data revealed that fixed-duration first-line treatment with venetoclax in combination with obinutuzumab could not completely overcome the adverse effects of *TP53* deficiency (10), with corresponding results after combination with ibrutinib pending. As data on continuous venetoclax first-line treatment and on venetoclax re-exposure is also currently lacking, it remains unclear as to what extent the impact of *TP53* deficiency relates to the mode of action and what relates to the treatment duration (time-limited versus continuous).

Results from PFS comparisons between CLL cases with mutated and unmutated IGHV status suggested that continuous ibrutinib and acalabrutinib monotherapy was able to abrogate the negative prognostic impact of unmutated IGHV in treatment-naïve and in relapsed/refractory CLL (4, 5, 26, 30). In treatment arms combining ibrutinib with rituximab or obinutuzumab, the PFS seems to be shorter in the IGHV unmutated than mutated subgroup, but direct comparisons are missing and results on the combination of acalabrutinib and obinutuzumab did not suggest a prognostic impact of the IGHV status (5–7, 9). With regards to venetoclax-based fixed-duration therapy, unmutated IGHV status retained prognostic significance and one can speculate that as IGHV unmutated patients achieved high response rates and MRD negativity, shorter PFS may reflect the more proliferative nature of IGHV unmutated CLL cells potentially leading to a faster re-growth of the CLL clone after end of treatment (10, 38–40).

Given the long PFS in IGHV unmutated (7-year PFS 58% in the RESONATE-2 trial) (4) and in *TP53* altered CLL cases (6-year PFS 61% in a phase II clinical trial) (23) that can already be achieved by continuous BTK inhibition in first-line, these characteristics should no longer be seen as high-risk features for treatment failure *per se*. They should rather be seen as factors associated with an increased risk for early disease progression in certain therapeutic regimens. To fully evaluate the impact of *TP53* alteration and IGHV status, longer follow-up data and more direct PFS comparisons of *TP53* altered versus non-altered and IGHV mutated versus unmutated cases are clearly required for all targeted treatment approaches. Likewise, disease and patient characteristics beyond *TP53* and IGHV must be validated or newly defined, and potentially integrated in new prognostic models, since risk scores like the CLL International Prognostic Index (CLL-IPI) and the Continuous Individualized Risk Index (CIRI)) were developed using data from patients treated by chemoimmunotherapy with re-evaluation in the context of novel agents pending (41, 42). For patients treated with ibrutinib, a four-factor scoring system involving *TP53* alterations, prior treatment, serum β2-microglobulin concentration, and lactate dehydrogenase level was developed to identify patients at increased risk of ibrutinib failure by the time of treatment initiation and relapse (43). This prognostic score is independently evaluated (44, 45), but remains to be evaluated in clinical trials testing second-generation covalent BTK inhibitors.

The absence of fully validated prospective biomarkers and generally valid risk scores stratifying treatment outcome has led to a return to a clinical definition of high-risk CLL: as being described by dual resistance towards BTK and BCL2 inhibition (46). While this approach can help to select patients for more perilous treatment strategies such as allogeneic stem cell transplantation, the obvious limitation is that this "post-hoc" definition comes too late for the patients. Hence, there remains a requirement to define biomarkers that identify high-risk disease at the time of diagnosis or first relapse.

Analyses of CLL cells resistant towards BTK or BCL2 inhibitors have identified biomarkers that predict for non-durable response to targeted treatments (33, 34, 47). Genomic instability is one example, possibly due to it facilitating the evolution of clones resistant to the selective pressure of therapy (33, 34). High levels of pro-proliferative stimuli driven by *MYC* gain, constitutive BCR-signaling and loss of cell-cycle control (e.g. by *CDKN2A*/*CDKN2B* deletion) may have similar effects on clonal evolution and drive CLL cells towards transformation (48–50). Furthermore, the immune microenvironment has been shown to play a crucial role in CLL, but it is not clear how to integrate these factors into risk stratification models (51).

Besides these non-treatment-specific risk factors, the acquisition of resistance mutations in *BTK*, *PCL2G* or *BCL2* represents an alternative mechanism of resisting the relevant inhibitor (52–56). While it is tempting to speculate that patients with these risk factors may benefit from treatment intensification with multi-agent combinations, prospective validation of this assumption is challenging as resistance mutations cannot be anticipated at the time of treatment initiation.

Therefore, the "brave new world of personalized CLL medicine" (51) remains a distant goal, with isolated analyses of putative biomarkers in individual clinical trial cohorts struggling to bring it closer. Biomarkers should be seen within the context of pathobiology and grouped for the definition of molecular CLL subtypes that will derive the most benefit from specific drug classes or treatment combinations (57). To reach that goal, collaborative initiatives as the CLL HARMONY Alliance are vital to compile patient registries that incorporate clinical trial as well as real-world data. This requires the application of complex "big data" analytical techniques including artificial intelligence and machine learning to identify the best biomarkers, to clearly define patient subgroups and to develop tailored therapeutic approaches.

Apart from this focus on the CLL cells and their biological heterogeneity, we feel that the definition of "high-risk CLL" should be broadened by including factors such as individual patient characteristics, treatment design, and the situational context of a patient's care (see Figure 1). Some of these factors were already encapsulated within former CLL treatment algorithms such as the

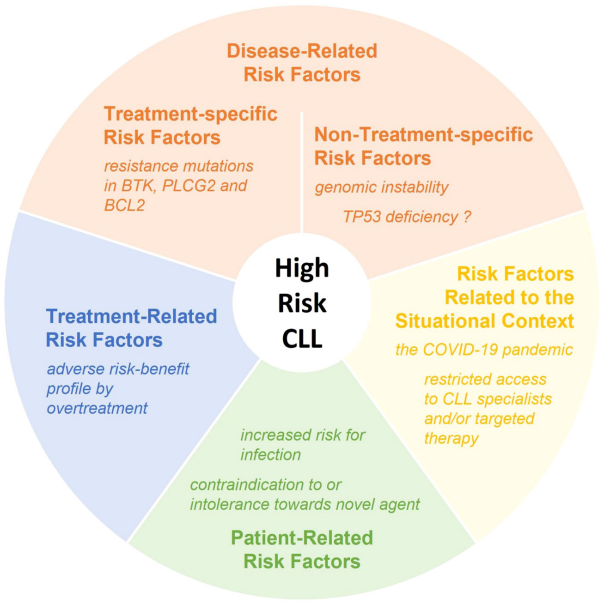

FIGURE 1
Factors increasing the risk for early CLL-related death. Examples are provided for each category of risk factors.

"go-go", "slow-go" and "no-go" three-tier "traffic light" approach developed during the chemotherapy era (58). The enhanced tolerability of targeted therapies has led to this approach becoming less important since a wider range of patients can now benefit from highly effective treatments, but on the other hand, targeted therapies have brought a new set of considerations that impact outcome.

For example, the situational context of a patient can become a risk factor when access to CLL specialists is restricted or when the health care system of a country does not permit the prescription of more expensive targeted therapies. Moreover, patients who have a contraindication to or are intolerant towards one of the novel agents lack an important treatment option, which may become critical over the course of the disease. A patient with mechanical heart valve requiring anticoagulation could hence be regarded as high-risk due to BTK inhibition contraindication, even if high-risk biological factors are lacking. Another good example is the risk from infection, which has been brought into sharp focus in the context of the COVID-19 pandemic. Infection is a major cause of morbidity and mortality for CLL patients, including those with early-stage disease (59–61). This risk can be aggravated by treatment, as for instance, both anti-CD20 monoclonal antibodies and BTK inhibitors are associated with reduced ability to respond to anti-COVID-19 vaccination (62–64). Therefore, the pandemic has shown very clearly how the situational context can change a patient's individual risk of harm from a certain treatment approach and that it remains important to balance the benefit and risks from treatment to avoid overtreatment. As an example, the benefit from addition of anti-CD20 therapy to targeted therapy must be critically evaluated particularly for BTK inhibitors, as the addition of rituximab to ibrutinib was shown to provide no clinical benefit (5, 31). Furthermore, the choice between a monotherapy, a dual therapy or a triple drug regimen must be adjusted to the patient's individual risk profile to avoid situations where the risks of serious or even fatal adverse events from treatment exceed the risks from the disease itself.

Taken together, we believe that a more holistic definition of "high-risk CLL" would be to define it simply as any patient who has an increased risk of early CLL-related death. This could be from treatment, from infection, or many other factors on top of risks from the disease itself. With this definition in mind, risk assessment would be based on a combination of "prospective" biomarkers, such as *TP53* alterations, IGHV mutation status and karyotype complexity and "retrospective" factors, such as the duration of response to, and side effects from, a particular therapy. It would hence require regular updates over the disease course as suggested by the CIRI score (42). Such perspective would encourage investigators conducting future clinical trials to focus on the elements influencing overall survival, with greater consideration of a patient's journey through multiple lines of treatment rather than just a single intervention. This would be stark contrast to the current situation where, for example, patients with a contraindication to one drug class are excluded from the relevant clinical trial. While a prospective approach would be the ideal, this will be close to impossible due to the timescales and rapid evolution of therapies. Alternatively, large-scale retrospective analyses could be employed to determine the best sequencing of drugs across multiple treatment lines for molecularly and/or risk stratified patient subgroups. Future research should therefore aim to incorporate all of the elements described above to tailor treatment towards the specific circumstances of individual patients.

Author contributions

All authors listed above have made a substantial, direct and intellectual contribution to the work, wrote the article and approved it for publication.

Funding

JM was supported by the project Conceptual development of research organization (FNBr 6526975) provided by the Ministry of Health of the Czech Republic and by the National Institute for Cancer Research (Programme EXCELES, ID Project No. LX22NPO5102) funded by the European Union – Next Generation EU.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. *Hematol Am Soc Hematol Educ Program* (2010) 2010:481–8. doi: 10.1182/asheducation-2010.1.481

2. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* (2018) 131:2745–60. doi: 10.1182/blood-2017-09-806398

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2021) 32:23–33. doi: 10.1016/j.annonc.2020.09.019

4. Barr PM, Owen C, Robak T, Tedeschi A, Bairey O, Burger JA, et al. Up to 8-year follow-up from RESONATE-2: First-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv* (2022) 6:3440–50. doi: 10.1182/bloodadvances.2021006434

5. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med* (2018) 379:2517–28. doi: 10.1056/NEJMoa1812836

6. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: Final analysis of the randomized, phase III iLLUMINATE trial. *Haematologica* (2022) 107:2108–20. doi: 10.3324/haematol.2021.279012

7. Shanafelt TD, Wang XV, Hanson CA, Paietta EM, O'Brien S, Barrientos J, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: Updated results of the E1912 trial. *Blood* (2022) 140:112–20. doi: 10.1182/blood.2021014960

8. Hillmen P, Bloor A, Broom A, Young M, Kennedy B, Walewska R, et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: Results of the phase III NCRI FLAIR trial. *Blood* (2021) 138:642. doi: 10.1182/blood-2021-152319

9. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. *Leukemia* (2022) 36:1171–5. doi: 10.1038/s41375-021-01485-x

10. Al-Sawaf O, Zhang C, Lu T, Liao MZ, Panchal A, Robrecht S, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. *J Clin Oncol* (2021) 39:4049–60. doi: 10.1200/JCO.21.01181

11. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* (2018) 378:1107–20. doi: 10.1056/NEJMoa1713976

12. Kater AP, Owen C, Moreno C, Follows G, Munir T, Levin MD, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. *NEJM Evid* (2022) 1. doi: 10.1056/EVIDoa2200006

13. Tam CS, Allan JN, Siddiqi T, Kipps TJ, Jacobs R, Opat S, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: Primary analysis of the CAPTIVATE FD cohort. *Blood* (2022) 139:3278–89. doi: 10.1182/blood.2021014488

14. Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: Results from the full population of a phase II pivotal trial. *J Clin Oncol* (2018) 36:1973–80. doi: 10.1200/JCO.2017.76.6840

15. Rogers KA, Huang Y, Ruppert AS, Abruzzo LV, Andersen BL, Awan FT, et al. Phase II study of combination obinutuzumab, ibrutinib, and venetoclax in treatment-naive and relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* (2020) 38:3626–37. doi: 10.1200/JCO.20.00491

16. Huber H, Edenhofer S, von Tresckow J, Robrecht S, Zhang C, Tausch E, et al. Obinutuzumab (GA-101), ibrutinib, and venetoclax (GIVe) frontline treatment for high-risk chronic lymphocytic leukemia. *Blood* (2022) 139:1318–29. doi: 10.1182/blood.2021013208

17. Davids MS, Lampson BL, Tyekucheva S, Wang Z, Lowney JC, Pazienza S, et al. Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: A single-arm, open-label, phase 2 study. *Lancet Oncol* (2021) 22:1391–402. doi: 10.1016/S1470-2045(21)00455-1

18. Soumerai JD, Mato AR, Dogan A, Seshan VE, Joffe E, Flaherty K, et al. Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: A multicentre, single-arm, phase 2 trial. *Lancet Haematol* (2021) 8:e879–e90. doi: 10.1016/S2352-3026(21)00307-0

19. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, et al. Pirtobrutinib in relapsed or refractory b-cell malignancies (BRUIN): A phase 1/2 study. *Lancet* (2021) 397:892–901. doi: 10.1016/S0140-6736(21)00224-5

20. Muhowski EM, Ravikrishnan J, Gordon B, Yu L, Misra S, Walker B, et al. Preclinical evaluation of combination nemtabrutinib and venetoclax in chronic lymphocytic leukemia. *J Hematol Oncol* (2022) 15:166. doi: 10.1186/s13045-022-01386-1

21. Zhang D, Harris HM, Chen J, Judy JT, James G, Kelly A, et al. NRX-0492 degrades wildtype and C481 mutant BTK and demonstrates *in vivo* activity in CLL patient derived xenografts. *Blood* (2022). doi: 10.1182/blood.2022016934

22. Deng J, Paulus A, Fang DD, Manna A, Wang G, Wang H, et al. Lisaftoclax (APG-2575) is a novel BCL-2 inhibitor with robust antitumor activity in preclinical models of hematologic malignancy. *Clin Cancer Res* (2022) 28:5455–68. doi: 10.1158/1078-0432.CCR-21-4037

23. Ahn IE, Tian X, Wiestner A. Ibrutinib for chronic lymphocytic leukemia with TP53 alterations. *N Engl J Med* (2020) 383:498–500. doi: 10.1056/NEJMc2005943

24. Allan JN, Shanafelt T, Wiestner A, Moreno C, O'Brien SM, Li J, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with TP53 aberrations: A pooled analysis from four clinical trials. *Br J Haematol* (2022) 196:947–53. doi: 10.1111/bjh.17984

25. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med* (2019) 380:2225–36. doi: 10.1056/NEJMoa1815281

26. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* (2020) 38:2849–61. doi: 10.1200/JCO.19.03355

27. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. *Haematologica* (2020) 106:2354–63. doi: 10.3324/haematol.2020.259432

28. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kazmierczak M, Lamanna N, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med* (2022). doi: 10.1056/NEJMoa2211582

29. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum K, et al. Ibrutinib treatment for first-line and Relapsed/Refractory chronic lymphocytic leukemia: Final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res* (2020) 26:3918–27. doi: 10.1158/1078-0432.CCR-19-2856

30. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol* (2019) 94:1353–63. doi: 10.1002/ajh.25638

31. Burger JA, Sivina M, Jain N, Kim E, Kadia T, Estrov Z, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood* (2019) 133:1011–9. doi: 10.1182/blood-2018-10-879429

32. Baliakas P, Jeromin S, Iskas M, Puiggros A, Plevova K, Nguyen-Khac F, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. *Blood* (2019) 133:1205–16. doi: 10.1182/blood-2018-09-873083

33. Thompson PA, O'Brien SM, Wierda WG, Ferrajoli A, Stingo F, Smith SC, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. *Cancer* (2015) 121:3612–21. doi: 10.1002/cncr.29566

34. Kittai AS, Miller C, Goldstein D, Huang Y, Abruzzo LV, Beckwith K, et al. The impact of increasing karyotypic complexity and evolution on survival in patients with CLL treated with ibrutinib. *Blood* (2021) 138:2372–82. doi: 10.1182/blood.2020010536

35. Malcikova J, Pavlova S, Kunt Vonkova B, Radova L, Plevova K, Kotaskova J, et al. Low-burden TP53 mutations in CLL: Clinical impact and clonal evolution within the context of different treatment options. *Blood* (2021) 138:2670–85. doi: 10.1182/blood.2020009530

36. Gango A, Alpar D, Galik B, Marosvari D, Kiss R, Fesus V, et al. Dissection of subclonal evolution by temporal mutation profiling in chronic lymphocytic leukemia patients treated with ibrutinib. *Int J Cancer* (2020) 146:85–93. doi: 10.1002/ijc.32502

37. Kadri S, Lee J, Fitzpatrick C, Galanina N, Sukhanova M, Venkataraman G, et al. Clonal evolution underlying leukemia progression and Richter transformation in patients with ibrutinib-relapsed CLL. *Blood Adv* (2017) 1:715–27. doi: 10.1182/bloodadvances.2016003632

38. Tausch E, Furstenau M, Robrecht S, Yosifov DY, Mertens D, Gregor M, et al. Genetic markers and front line FCR/BR vs. rve, gve and give treatment - outcome results from the CLL13/GAIA trial. *Blood* (2022) 140:839–41. doi: 10.1182/blood-2022-163775

39. Niemann CU, Moreno C, Owen C, Follows GA, Benjamini O, Janssens A, et al. Residual disease kinetics among patients with high-risk factors treated with first-line fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O): The glow study. *Blood* (2022) 140:228–30. doi: 10.1182/blood-2022-156070

40. Munir T, Bloor A, Pettitt A, Patten PEM, Forconi F, Schuh A, et al. Combination of ibrutinib plus venetoclax with MRD-driven duration of treatment results in a higher rate of MRD negativity in IGHV unmutated than mutated CLL: Updated interim analysis of FLAIR study. *Blood* (2022) 140:231–33. doi: 10.1182/blood-2022-170463

41. International CLLIPIwg. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): A meta-analysis of individual patient data. *Lancet Oncol* (2016) 17:779–90. doi: 10.1016/S1470-2045(16)30029-8

42. Kurtz DM, Esfahani MS, Scherer F, Soo J, Jin MC, Liu CL, et al. Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction. *Cell* (2019) 178:699–713 e19. doi: 10.1016/j.cell.2019.06.011

43. Ahn IE, Tian X, Ipe D, Cheng M, Albitar M, Tsao LC, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: Development and

validation of a four-factor prognostic model. *J Clin Oncol* (2021) 39:576–85. doi: 10.1200/JCO.20.00979

44. Morabito F, Tripepi G, Del Poeta G, Mauro FR, Reda G, Sportoletti P, et al. Assessment of the 4-factor score: Retrospective analysis of 586 CLL patients receiving ibrutinib. a campus CLL study. *Am J Hematol* (2021) 96:E168–E71. doi: 10.1002/ajh.26127

45. Molica S, Baumann T, Giannarelli D. Prognostic models in chronic lymphocytic leukemia patients receiving ibrutinib therapy: Results of a comparative performance analysis. *Eur J Haematol* (2021) 106:425–7. doi: 10.1111/ejh.13548

46. Dreger P, Ghia P, Schetelig J, van Gelder M, Kimby E, Michallet M, et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: Integrating molecular and cellular therapies. *Blood* (2018) 132:892–902. doi: 10.1182/blood-2018-01-826008

47. Herling CD, Abedpour N, Weiss J, Schmitt A, Jachimowicz RD, Merkel O, et al. Clonal dynamics towards the development of venetoclax resistance in chronic lymphocytic leukemia. *Nat Commun* (2018) 9:727. doi: 10.1038/s41467-018-03170-7

48. Chigrinova E, Rinaldi A, Kwee I, Rossi D, Rancoita PM, Strefford JC, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood* (2013) 122:2673–82. doi: 10.1182/blood-2013-03-489518

49. Fabbri G, Khiabanian H, Holmes AB, Wang J, Messina M, Mullighan CG, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med* (2013) 210:2273–88. doi: 10.1084/jem.20131448

50. Agathangelidis A, Darzentas N, Hadzidimitriou A, Brochet X, Murray F, Yan XJ, et al. Stereotyped b-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. *Blood* (2012) 119:4467–75. doi: 10.1182/blood-2011-11-393694

51. Kwok M, Wu CJ. Clonal evolution of high-risk chronic lymphocytic leukemia: A contemporary perspective. *Front Oncol* (2021) 11:790004. doi: 10.3389/fonc.2021.790004

52. Woyach JA, Furman RR, Liu TM, Ozer HG, Zapatka M, Ruppert AS, et al. Resistance mechanisms for the bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med* (2014) 370:2286–94. doi: 10.1056/NEJMoa1400029

53. Maddocks KJ, Ruppert AS, Lozanski G, Heerema NA, Zhao W, Abruzzo L, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol* (2015) 1:80–7. doi: 10.1001/jamaoncol.2014.218

54. Woyach JA, Ruppert AS, Guinn D, Lehman A, Blachly JS, Lozanski A, et al. BTK (C481S)-mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol* (2017) 35:1437–43. doi: 10.1200/JCO.2016.70.2282

55. Blombery P, Anderson MA, Gong JN, Thijssen R, Birkinshaw RW, Thompson ER, et al. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. *Cancer Discovery* (2019) 9:342–53. doi: 10.1158/2159-8290.CD-18-1119

56. Tausch E, Close W, Dolnik A, Bloehdorn J, Chyla B, Bullinger L, et al. Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. *Haematologica* (2019) 104:e434–e7. doi: 10.3324/haematol.2019.222588

57. Knisbacher BA, Lin Z, Hahn CK, Nadeu F, Duran-Ferrer M, Stevenson KE, et al. Molecular map of chronic lymphocytic leukemia and its impact on outcome. *Nat Genet* (2022) 54:1664–74. doi: 10.1038/s41588-022-01140-w

58. Hallek M, Pflug N. Chronic lymphocytic leukemia. *Ann Oncol* (2010) 21(Suppl 7): vii154–64. doi: 10.1093/annonc/mdq373

59. Molica S. Infections in chronic lymphocytic leukemia: risk factors, and impact on survival, and treatment. *Leuk Lymphoma* (1994) 13:203–14. doi: 10.3109/10428199409056283

60. Hilal T, Gea-Banacloche JC, Leis JF. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: Linking mechanisms with infections. *Blood Rev* (2018) 32:387–99. doi: 10.1016/j.blre.2018.03.004

61. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP. Infection and immunity in chronic lymphocytic leukemia. *Mayo Clin Proc* (2000) 75:1039–54. doi: 10.4065/75.10.1039

62. Roeker LE, Knorr DA, Thompson MC, Nivar M, Lebowitz S, Peters N, et al. COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia. *Leukemia* (2021) 35:2703–5. doi: 10.1038/s41375-021-01270-w

63. Shen Y, Freeman JA, Holland J, Solterbeck A, Naidu K, Soosapilla A, et al. COVID-19 vaccine failure in chronic lymphocytic leukaemia and monoclonal b-lymphocytosis; humoural and cellular immunity. *Br J Haematol* (2022) 197:41–51. doi: 10.1111/bjh.18014

64. Herishanu Y, Rahav G, Levi S, Braester A, Itchaki G, Bairey O, et al. Efficacy of a third BNT162b2 mRNA COVID-19 vaccine dose in patients with CLL who failed standard 2-dose vaccination. *Blood* (2022) 139:678–85. doi: 10.1182/blood.2021014085