Validation of a survival-risk score (SRS) in relapsed/refractory CLL patients treated with idelalisib–rituximab

Massimo Gentile1,2, Enrica Antonia Martino1, Andrea Visentin3, Marta Coscia4, Gianluigi Reda5, Paolo Sportoletti6, Francesca Romana Mauro7, Luca Laurenti8, Marzia Varettoni9, Roberta Murru10, Annalisa Chiarenza11, Ernesto Vigna1,2, Francesco Mendicino1, Eugenio Lucia1, Sabrina Bossio2, Anna Grazia Recchia2, Riccardo Moia12, Daniela Pietrasanta13, Giacomo Loseto14, Ugo Consoli15, Ilaria Scortechni16, Francesca Maria Rossi17, Antonella Zucchetto17, Hamdi Al-Janazreh18, Candida Vitali19, Giovanni Tripepi19, Grazziella D’Arrigo9, Ilaria Angeletti20, Riccardo Bomben17, Antonino Neri21, Giovanna Cutrona21, Gilberto Fronza22, Francesco Di Raimondo11, Gianluca Gaidano12, Antonio Cuneo23, Robin Foà2, Manlio Ferrari24, Livio Trentin23, Valter Gattei7,2 and Fortunato Morabito17,21

Dear Editor,

The identification of prognostic models for overall survival (OS) of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) treated with novel target drugs, such as B-cell receptor (BCR) and BCL-2 inhibitors, represents an unmet clinical need. Recently, our group proposed a survival-risk score for real-life R/R CLL patients treated with Ibrutinib (SRSI). This SRSI is based on three laboratory parameters, β2 microglobulin (β2 M, 1 point for cases with β2 M > 5 mg/L), lactic dehydrogenase values (LDH, 2 points for cases with LDH > upper limit of normal), and hemoglobin level (2 points for men with hemoglobin < 11 g/L and 2 points for women with hemoglobin < 12 g/L) (Supplementary Table 1), and represents a powerful and easily applicable prognostic tool for the prediction of OS. Indeed, unique information originated from a real-life retrospective study with a huge number of R/R CLL patients treated either with chemotherapy or with new drugs, and proposed a comprehensive risk score for the OS prediction. On the other hand, the randomized trial comparing Idela-R versus R showed the greater performance of the Idela-R in all experimental settings [i.e., IGHV-unmutated cases, del (17p) cases] (2). Moreover, the final results of the same randomized trial (3) reported that the presence of del (17p) or TP53 mutations did not negatively affect clinical outcomes among patients treated with Idela/R. The present retrospective, multicenter study was undertaken with the aim of testing whether SRSI was also useful for R/R CLL patients treated with idelalisib–rituximab (Idela-R), thus further refining the role of some prognostic factors in predicting OS in a setting homogeneously treated for patients.

Overall, 142 CLL patients present in the CLL databases from 15 Italian centers (see Supplementary Appendix for details), could be included in this analysis. The majority of patients were Binet stages B and C (94.6%). The median age was 75.1 years (range: 37.1–91) and 98 cases (69%) were male. The median number of previous therapies was 3 (range: 1–9). Fifty-six patients discontinued Idela-R due to toxicity, 20 for CLL progression, and 6 for Richter transformation; 2 responding cases underwent an allogeneic stem cell transplantation. The baseline patients’ features are listed in Supplementary Table 2. After a median follow-up of 1.6 years, 45 patients had died.

The relationship between the SRSI parameters and OS was assessed. All three SRSI parameters were associated with OS in univariate analysis and in a multiple Cox regression analysis (Table 1). Thirty-six patients were classified at low risk, 76 at intermediate risk and 30 at high risk according to the SRSI. The OS of the three patient groups

© The Author(s) 2020

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.
Table 1 Univariate and multivariate analyses.

| Features                        | Univariate analysis | Multivariate analysis (SRSI model) | Multivariate analysis (BALL model) | Multivariate analysis (SRSI + biological parameter model) |
|--------------------------------|---------------------|------------------------------------|-----------------------------------|----------------------------------------------------------|
|                                | HR (95% CI)         | P                                 | HR (95% CI)                       | P                                                        | HR (95% CI)                           | P                                                        |
| Hemoglobin <110 g/L for women  | 3.63 (1.87–7.05)    | <0.0001                           | 2.36 (1.15–4.84)                  | 0.02                                                    | 2.19 (1.05–4.58)                     | 0.036                                                   | 2.37 (1.15–4.89)                           | 0.019                                                   |
| <120 g/L for men               |                     |                                   |                                  |                                                         |                                         |                                                         |                                         |                                                         |
| β2 M ≥ 5 mg/L                  | 3.98 (2.15–7.36)    | <0.0001                           | 2.25 (1.13–4.48)                  | 0.021                                                   | 2.23 (1.12–4.46)                     | 0.023                                                   | 2.23 (1.12–4.46)                           | 0.022                                                   |
| LDH > ULN                      | 3.18 (1.73–5.87)    | <0.0001                           | 2.29 (1.21–4.33)                  | 0.011                                                   | 2.21 (1.16–4.19)                     | 0.016                                                   | 2.03 (1.05–3.94)                           | 0.035                                                   |
| Time from the last therapy <24 months | 2.37 (1.01–5.6)         | 0.049                             |                                   |                                                         |                                         |                                                         |                                         |                                                         |
| Age >65 years                  | 0.66 (0.32–1.38)    | 0.274                             | –                                 | –                                                       | –                                         | –                                                       | –                                         | –                                                       |
| I7p deletion positive          | 2.07 (1.14–3.78)    | 0.017                             | –                                 | –                                                       | –                                         | –                                                       | –                                         | –                                                       |
| IGHV unmutated                 | 1.3 (0.93–1.74)     | 0.13                              | –                                 | –                                                       | –                                         | –                                                       | –                                         | –                                                       |

HR hazard ratio, 95% CI 95% confidence interval, β2 M β2 microglobulin, ULN upper limit of normal.

~2500 R/R CLL patients treated either with chemoimmunotherapy or with new drugs (Ibrutinib, Idelalisib, or Venetoclax), and proposed a comprehensive risk score for the OS prediction, based on four widely accessible parameters: β2 M, anemia, LDH, and time from last therapy, a.k.a. BALL score (Supplementary Table 2). According to the BALL score, 46 patients of the present study were classified at low risk, 77 at intermediate risk and 19 at high risk. Although significant differences in OS were found between low-risk versus intermediate-risk patients (P<0.001), this stratification failed to detect significant differences between intermediate-risk versus high-risk cases (P = 0.057) (Supplementary Fig. 1). Since the BALL score differs from SRSI for the presence of the time from last therapy (≥24 versus <24 months) variable, the prognostic power of this parameter was also evaluated in our cohort. At univariate analysis, time from last therapy was significantly associated with OS (HR = 2.27; 95% CI: 1.01–5.6; P = 0.049) (Table 1), but it lost its prognostic significance when forced into a multivariate model, together with the three parameters of the SRSI score, which remained independently associated with OS (Table 1).

The above differences were somewhat expected, given that the BALL score was designed for R/R CLL patients undergoing salvage treatment, using either biological agents or chemoimmunotherapy, whereas the SRSI score was specifically adapted for R/R patients undergoing BCR-inhibitor treatment. Probably, the use of new drugs as salvage therapy in this setting of patients can overcome the negative prognostic impact of a short time from last therapy (<24 months), as previously reported by our group in the ibrutinib setting.1

![Fig. 1 Overall survival of the entire population of 142 CLL patients according to SRSI](image-url)
Finally, we evaluated the prognostic significance of two biological parameters (i.e., IGHV mutational status and 17p deletion) in our series. At univariate analysis, 17p deletion (HR: 2.07; 95% CI: 1.14–3.78; P = 0.017) and not the IGHV status (HR: 1.3; 95% CI: 0.93–1.74; P = 0.13) remained significantly associated with survival (Table 1). Nonetheless, 17p deletion failed to maintain its independent prognostic power when added to LDH, β2-M values, and hemoglobin levels in a multivariate model, while all three SRS\textsubscript{II} parameters remained independently associated with survival (Table 1).

These data are in line with the exploratory analysis performed in the Study 116 trial,\textsuperscript{3,4} indicating that the presence of 17p deletion does not negatively affect the survival of R/R CLL patients who are generally ineligible for standard chemotherapy, but can be treated with Idela-R.\textsuperscript{3,4} At univariate analysis, age (HR 0.66; 95% CI: 0.32–1.38; P = 0.274) did not remain significantly associated with survival (Table 1).

Overall, the present data indicate that parameters related to tumor burden (i.e., LDH and β2-M values) and to bone marrow reserve (i.e., hemoglobin level) represent the most important prognostic markers of survival in R/R CLL patients receiving Idela-R. This is similar to what we found for Ibrutinib, and suggests that these criteria may be universally valuable for BCR inhibitors [survival risk score for real-life R/R CLL patients treated with Ibrutinib or with Idela-R (SRS\textsubscript{II})]. Furthermore, SRS\textsubscript{II} is a simple and parsimonious prognostic score, which is unlikely to be affected by missing genetic data, when employed in clinical practice. Nevertheless, in the absence of ad hoc phase III randomized studies, the final choice of the most appropriate BCR-inhibitor therapy is frequently dictated by the presence of comorbidities or by the expected toxicity drug profiles. In this context, the proposed SRS\textsubscript{II} may represent an additional and easily applicable tool for the prediction of OS in R/R CLL patients treated with BCR inhibitors. However, in the current era of CLL treatments that have relegated therapy with Idela-R to the third or potentially fourth line of treatment, patients with high-risk SRS score should be considered for a combination of new drugs, aimed at attaining undetectable minimal residual disease and treatment-free remissions.

Author contributions
MG, EAM, F.R.M., F.D.R., MF., RF., ACu., GG., LT., VG., and FM designed the study, analyzed and interpreted data, and wrote the paper, MG., GT., GD.A, and FM performed statistical analysis; AGR, SB., F.M.R., AZ., RB., AN, GC., GF., and MF performed central laboratory tests; A.V., M.C., G.R., P.S., L.L., M.V., R.M., and F.M. performed statistical analysis; A.G.R., S.B., F.M.R., A.Z., R.B., A.N., G.C., and I.A. provided the patients and collected clinical data; all authors gave final approval for the paper.

Conflict of interest
The authors declare that they have no conflict of interest.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41375-020-0833-x). (2020) [Epub ahead of print].

Received: 24 June 2020 Revised: 28 July 2020 Accepted: 30 July 2020
Published online: 16 September 2020

References
1. Gentile M, et al. Survival-risk score for real-life relapsed/refractory chronic lymphocytic leukemia patients receiving brutinib. A Campus CLL study. Leukemia https://doi.org/10.1038/s41375-020-0833-x. (2020) [Epub ahead of print].
2. Soumerai, J. D. et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukemia treated with targeted therapies or checkpoint inhibitors: a retrospective, pooled cohort study with external validations. Lancet Haematol 6, e366–e374 (2019).
3. Furman, R. R. et al. Idenalisib and rituximab in relapsed chronic lymphocytic leukemia. N. Engl. J. Med. 370, 997–1007 (2014).
4. Sharaman, J. P. et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J. Clin. Oncol. 37, 1391–1402 (2019).