## Reply to Aron P. Kater *et al.*

We do wish to thank Kater *et al.* for their interest in our article about *BIRC3* mutations in fludarabine, cyclophosphamide and rituximab (FCR) treated chronic lymphocytic leukemia (CLL) patients and for expanding the knowledge on the clinical implications of *BIRC3* mutations in the context of novel biological drugs.[1]

We conducted a retrospective multicenter real life study on 287 CLL patients treated with first line FCR and observed that *BIRC3* mutated patients experienced a poor outcome, superimposable to that of patients with *TP53* disruption, that represents the strongest marker of chemorefractoriness.[2] Our initial results, corroborated also by other prospective trials and complemented with *in vitro* evidence, validated *BIRC3* as a prognostic biomarker after chemoimmunotherapy in CLL.[1-4]

A prognostic biomarker is a biological feature of the tumor that provides information about the disease natural history independent of the treatment received. However, in order to gain solid clinical relevance, a biomarker should also be provided with a predictive value that informs about the likely benefit from a specific treatment.[5,6] Currently, *TP53* abnormalities and immunoglobulin variable heavy chain gene (*IGHV*) mutational status fulfill the criteria of predictive biomarkers whose usage is recommended by guidelines for the clinical management and treatment choice of CLL patients.[7]

Molecular studies of phase 3 randomized clinical trials are essential to transform a prognostic biomarker into a predictive biomarker by showing the interaction between the biomarker and treatment. In that sense, *BIRC3* mutations are a validated prognostic biomarker since they associate with shorter progression free survival when patients are treated with chemoimmunotherapy, but not when treated with fixed duration venetoclax in combination with anti-CD20 monoclonal antibody. In this issue of the journal, Kater *et al.* report the initial results of the molecular analysis of the MURANO trial dedicated to relapsed/refractory CLL, and show that *BIRC3* mutated patients treated with bendamustine rituximab experienced a worse outcome compared to wild-type patients. Conversely, the combination of venetoclax with rituximab was able to overcome the negative impact of *BIRC3* mutations (Table 1).[1] Similarly, the companion biomarker study of the CLL14 trial indicated that, also in the first line setting, obinutuzumab-venetoclax, but not obinutuzumab-chlorambucil is an effective therapeutic option for *BIRC3* mutated patients (Table 1).[5]

Whereas the efficacy of venetoclax in overcoming *BIRC3* disruption is validated in two trials, the role of ibrutinib in this context is still unexplored. Mantle cell lymphomas carrying *BIRC3* mutations appear to be resistant to ibrutinib *in vitro*, but *in vivo* studies are needed to confirm this pre-clinical information.[8] Although several phase 3 clinical trials have demonstrated the superiority of ibrutinib *versus* chemoimmunotherapy in CLL, the predictive value of *BIRC3* mutations has not been tested to date in this context.[9-11]

The introduction of Bruton tyrosine kinase inhibitors and of venetoclax have changed the natural history of CLL. Despite these advantages, molecular predictors, namely *IGHV* mutational status and *TP53* disruption, are still essential in treatment choices. In this context, *BIRC3* is emerging as a novel predictive biomarker that might enter the routine clinical practice allowing a better treatment algorithm for every individual CLL patient.

*Riccardo Moia,[1] Gianluca Gaidano[1] and Davide Rossi[2]*

*[1]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy and [2]Institute of Oncology Research and Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

*Correspondence: DAVIDE ROSSI - davide.rossi@eoc.ch*

*doi:10.3324/haematol.2020.255596*

*Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.*

## References

1. Kater AP, Jiang Y, Chyla B, et al. Response in patients with BIRC3-mutated relapsed/refractory chronic lymphocytic leukemia treated with fixed-duration venetoclax and rituximab. Haematologica. 2020;105(7):382-383.
2. Diop F, Moia R, Favini C, et al. Biological and clinical implications of BIRC3 mutations in chronic lymphocytic leukemia. Haematologica. 2020;105(2):448-456.
3. Estenfelder S, Tausch E, Robrecht S, et al. Gene mutations and treatment outcome in the context of chlorambucil (Clb) without or with the addition of rituximab (R) or obinutuzumab (GA-101, G) - results of an extensive analysis of the Phase III Study CLL11 of the German CLL Study Group. Blood. 2016;128(22):3227.
4. Tausch E, Schneider C, Robrecht S, et al. Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. Blood. 2020 Mar 23. [Epub ahead of print].
5. Rossi D, Gerber B, Stüssi G. Predictive and prognostic biomarkers in the era of new targeted therapies for chronic lymphocytic leukemia. Leuk Lymphoma. 2017;58(7):1548-1560.
6. Ballman KV. Biomarker: predictive or prognostic? J Clin Oncol. 2015; 33(33):3968-3971.
7. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-2760.
8. Rahal R, Frick M, Romero R, et al. Pharmacological and genomic profiling identifies NF-κB-targeted treatment strategies for mantle cell lymphoma. Nat Med. 2014;20(1):87-92.
9. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381(5):432-443.
10. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379(26):2517-2528.
11. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.

**Table 1.** Clinical impact of *BIRC3* mutations in the MURANO and in the CLL14 trial.

| Trial | Phase | Setting | Interventions | *BIRC3* mutations |
|---|---|---|---|---|
| MURANO trial[1] | 3 | Relapsed/refractory CLL patients | Venetoclax + Rituximab | HR 1.50 (95% CI: 0.50–4.30) *P*=0.44 |
| | | | Bendamustine + Rituximab | HR 2.20 (95% CI: 0.92–5.10) *P*=0.077 |
| CLL14 trial[4] | 3 | Untreated CLL patients | Venetoclax + Obinutuzumab | HR 1.10 (95% CI: 0.15–8.13) *P*=0.92 |
| | | | Chlorambucil + Obinutuzumab | HR 4.03 (95% CI: 1.73–9.37) *P*<0.01 |

CLL: chronic lymphocytic leukemia; HR: hazard ratio; CI: confidence interval; *P*: *P*-value.