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.

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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.