Acquisition of the recurrent Gly101Val mutation in *BCL2* confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia (*Comment to Tausch et al.*)

In a recent issue of Haematologica Tausch *et al.*[1] described a novel resistance mechanism against the Bcl2 antagonist venetoclax in chronic lymphocytic leukemia (CLL) cells, by describing a *BCL2* mutation, *BCL2*-G101V.

In our previous work on clonal evolution and resistance in 9 CLL patients under venetoclax monotherapy using whole exome sequencing (WES), we were initially unable to identify the reported *BCL2*-G101V mutation.[2] Therefore, we re-investigated this phenomenon within our cohort using the assay described by Blombery *et al.*[3] We tested 19 DNA samples from nine CLL patients. Eight samples were collected prior to venetoclax treatment and eleven at the time of the clinically manifested resistance. In these samples, we detected the *BCL2*-G101V mutation in three out of nine patients post-treatment, confirming the findings of Tausch and colleagues. However, the allele frequency of the *BCL2*-G101V mutation in our cohort was below 1% in two cases and ~1.4% in one case post-treatment. In addition, we tested material from three sites post-treatment at the time of resistance in one of our patients (peripheral blood, bone marrow (BM), lymph node (LN)). Interestingly, the mutation could only be detected in two (BM and LN) of the three sites. Where available, we additionally investigated matched samples collected prior to venetoclax treatment. For this purpose, we tested an average of ~36000 DNA molecules (reaching a theoretical lower limit of detection of 0.002%). In concordance with our colleagues we could not detect any G101V mutated *BCL2* DNA in the pre-treatment samples. Therefore, the question of a *de novo* acquisition *versus* previously existing, venetoclax-resistant subclones could be answered definitively. Taken together, our results explain why we initially failed to identify the *BCL2*-G101V mutation in our study, as the resolution of our methodology was insufficient to identify such low frequency events.

More importantly, our data, with a very low allele frequency of the *BCL2*-G101V mutation which we observed only in a minority of CLL subclones in our cohort, challenge the hypothesis that the resistance to venetoclax can be explained by the *BCL2*-G101V mutation alone. While Blombery and colleagues have shown that the mutation alone can render CLL cells resistant to venetoclax *in vitro*, it remains unclear how such an infrequent sub-clone (~1%) is capable to render the whole CLL population venetoclax-resistant *in vivo*. Instead, we propose that the *BCL2*-G101V mutation is a rather late, subclonal event that may mediate some resistance against CLL cells, but the mechanism of resistance to venetoclax remains far from being understood. For example, one would have to examine whether mutant Bcl2 protein (or RNA) can be transported from one CLL cell to another to mediate resistance. More likely, different mutations may create stronger mechanisms of resistance for the bulk of leukemic cells. In any case, more work is needed before one can draw conclusions about the mechanisms of resistance against venetoclax in CLL.

Jonathan Weiss,[1] Martin Peifer,[2,3] Carmen D. Herling,[1] Lukas P. Frenzel[1] and Michael Hallek[1]

[1]University of Cologne, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf; [2]Department of Translational Genomics, Center of Integrated Oncology Cologne-Bonn, Medical Faculty, University of Cologne; [3]Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany

Correspondence: JONATHAN WEISS
jonathan.weiss@uk-koeln.de
doi:10.3324/haematol.2019.232835

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. Tausch E, Close W1, Dolnik A, et al. Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. Haematologica. 2019 April 26 [epub ahead of print]
2. Blombery P, Anderson MA, Gong JN, et al. Acquisition of the Recurrent Gly101Val Mutation in BCL2 Confers Resistance to Venetoclax in Patients with Progressive Chronic Lymphocytic Leukemia. Cancer Discov. 2019;9(3):342-353.
3. Herling CD, Abedpour N, Weiss J, et al. Clonal dynamics towards the development of venetoclax resistance in chronic lymphocytic leukemia. Nat Commun. 2018;9(1):727.