Response to Comment by Jonathan Weiss *et al.*

We are very grateful to Weiss *et al.* for their confirmatory finding of acquired *BCL2* mutations in patients with chronic lymphocytic leukemia (CLL) who became resistant to venetoclax treatment.[1]

We had identified mutations in *BCL2* as a resistance mechanism characterizing patients with slowly outgrowing, refractory CLL after at least 3 years of continuous therapy with venetoclax.[2] Correspondingly, Blomberry *et al.* had previously identified *BCL2* variants up to 25 months before progressive disease in patients with CLL on long-term treatment with venetoclax.[3]

In contrast, the patient cohort studied by Herling *et al.* progressed after 4-22 months with CLL characterized by genomic features of Richter transformation.[4] Indeed, half of their patients had histologically confirmed Richter syndrome and it was not reported if diagnostic attempts were made to exclude this in the remaining cases. The resistance mechanism of this aggressive phenotype may be different and the genomic characterization showed mainly variants known from aggressive lymphoma (e.g. tetraploidy, *CDKN2A/B* deletion, 8q gain). Such aggressive clones may outperform and abolish the slow outgrowth of *BCL2* variants, which at this early time point remain subclonal (*see Figure*). We can confirm the absence of *BCL2* mutations in cases with accelerated CLL and Richter syndrome after venetoclax treatment from analyses at our center, but these events should be the exception and not the rule deduced from current clinical trials with venetoclax in earlier treatment lines.

Moreover, the pattern of resistance with late occurring, specific mutations in CLL progression but not in early progression with transformed disease is analogous to what was observed in the context of ibrutinib treatment in CLL.[5,6] Also in this scenario, early progressions were mostly Richter transformations devoid of *BTK/PLCg2* mutations while late CLL progressions are characterized by such mutations in the vast majority of cases.

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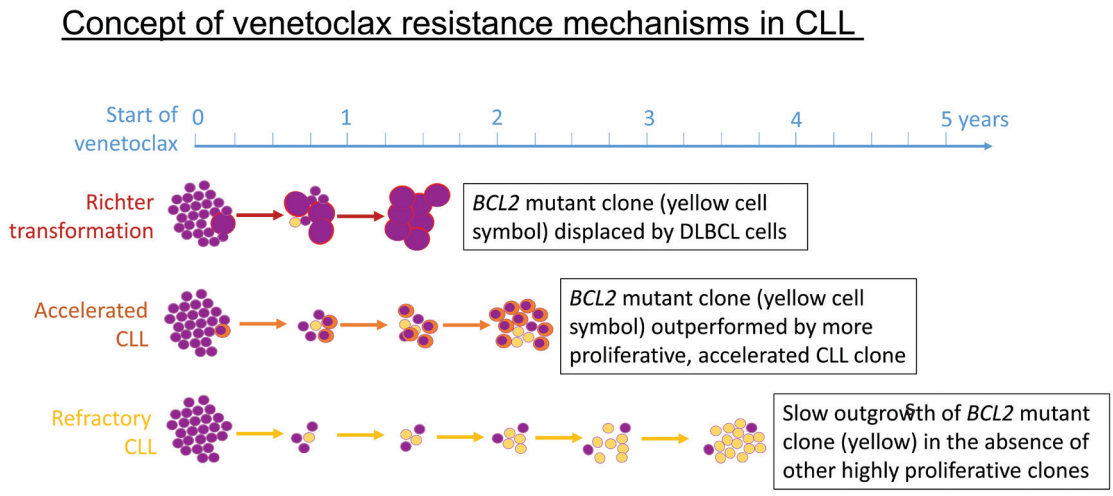

Figure 1. Concept of venetoclax resistance mechanisms in CLL.