Response in patients with *BIRC3*-mutated relapsed/refractory chronic lymphocytic leukemia treated with fixed-duration venetoclax and rituximab

BIRC3 is a negative regulator of the non-canonical NF-kB signaling pathway.[1] *BIRC3* gene mutation occurs in ~3–5% of patients with chronic lymphocytic leukemia (CLL) and is considered one of the disease-driver events.[2-5] In a recent issue of *Haematologica*, Diop *et al.* reported that *BIRC3*-mutated primary CLL cells exhibited active non-canonical NF-kB signaling and resistance to fludarabine *in vitro*.[6] Furthermore, this study also demonstrated that *BIRC3* mutation increased the risk of clinical progression after treatment with fludarabine-based chemoimmunotherapy. However, the impact of *BIRC3* mutation on the clinical outcome of patients treated with novel targeted therapies is largely unknown. Recently, Tausch *et al.* reported that *BIRC3* mutation was not associated with shorter progression-free survival (PFS) in front-line CLL patients treated with venetoclax, a highly selective BCL2 inhibitor, in combination with obinutuzumab.[4] In this letter, we report minimal residual disease (MRD) and clinical responses and PFS in patients with relapsed/refractory (R/R) CLL with *BIRC3* mutations who were treated with fixed-duration venetoclax plus rituximab (VenR).

The combination of VenR is approved for the treatment of patients with R/R CLL based on results of the MURANO Phase III study (NCT02005471), which demonstrated improved PFS and overall survival (OS) with fixed-duration VenR (2 years of 400 mg venetoclax once daily, plus monthly rituximab for the first six months) *versus* bendamustine plus rituximab (BR).[7] MURANO also showed early and durable undetectable MRD (uMRD) status with VenR, which is associated with improved survival in CLL.[8]

In MURANO, non-silent, deleterious *BIRC3* mutations were found in 8 of 160 (5.0%) patients in the BR arm and 9 of 153 (5.9%) in the VenR arm by whole-exome sequencing with DNA specimens from CD19-enriched baseline samples (313 of 389 enrolled patients). The prevalence of *BIRC3* mutation in the MURANO study is therefore comparable to what was reported in the front-line setting. All patients with *BIRC3* mutations and a known immunoglobulin variable heavy chain gene (*IGVH*) mutation status (n=15) were unmutated for *IGVH*. Forty-seven per cent of patients with *BIRC3* mutations had concomitant *TP53* disruption by deletion of chromosome 17p (del[17p]) and/or mutations in the *TP53* gene: 3 of 8 in the BR arm and 5 of 9 in the VenR arm.

In MURANO, PFS was based on investigator assessment, and Kaplan-Meier estimates were used to analyze time-to-event data. With a median follow-up of 48 months, within the BR arm, PFS was shorter in patients with *BIRC3* mutations (Hazard ratio [HR] 2.2, 95% confidence interval [CI]: 0.92–5.1, *P*=0.077, adjusted for *TP53*, del(17p) and *IGVH* status; Figure 1A). Whereas, in the VenR arm, there was no statistically significant impact on PFS seen with *BIRC3* mutations (HR 1.5, 95% CI: 0.5–4.3, *P*=0.44, same adjustments as BR; Figure 1B). While noting the small number of cases involved, for those with *BIRC3*-mutated disease, PFS was superior with VenR compared with BR (HR 0.15, 95% CI: 0.04–0.63, *P*=0.0089).

Previously, we reported that a higher rate of peripheral blood (PB) uMRD (uMRD defined as <1 CLL cell/10,000 leukocytes [$<10^{-4}$], assessed centrally by either allele-specific oligonucleotide PCR or multi-color flow cytometry according to the European Research Initiative on CLL guidance) was achieved at the end of combination treatment (EOCT) in the VenR arm (62.4%) *versus* the BR arm (13.3%).[8] Furthermore, achieving uMRD status at EOCT is associated with prolonged PFS regardless of the clinical response status.[8] Looking specifically into

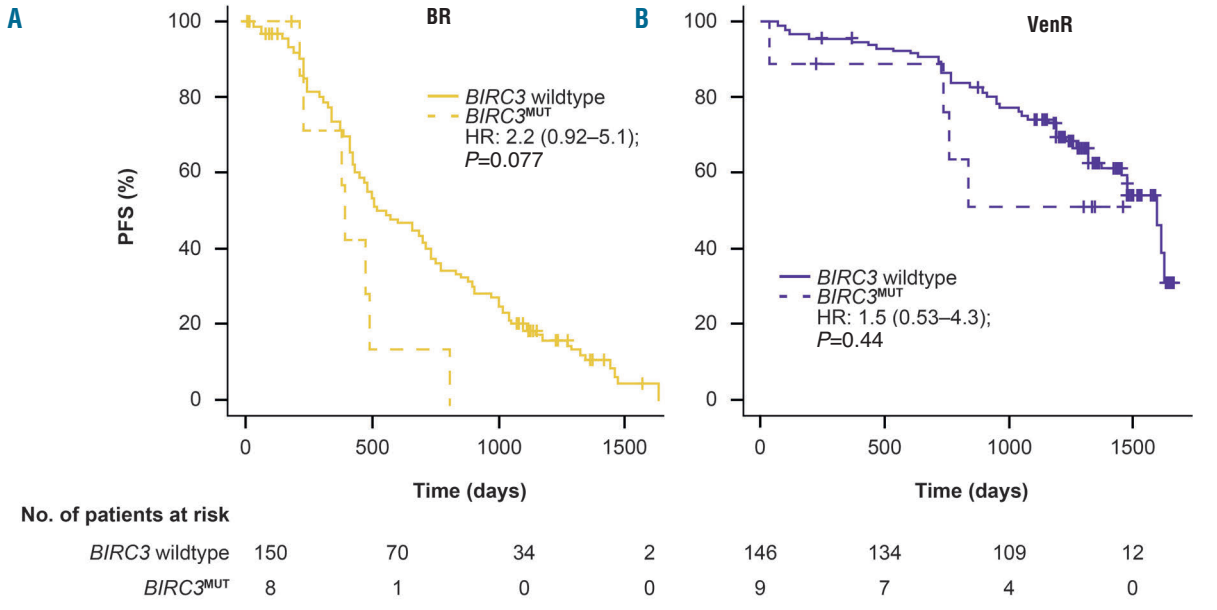

Figure 1. Progression-free survival in the MURANO study according to *BIRC3* mutation status. PFS: progression-free survival; BR: bendamustine plus rituximab; VenR: venetoclax plus rituximab; HR: hazard ratio; MUT: mutated.

the *BIRC3*-mutated subgroup, two patients failed to reach EOCT (one treatment-unrelated death in the VenR arm, one disease progression [PD] in the BR arm). Of the remaining patients, at EOCT, in the BR arm (n=7), three patients with *BIRC3* mutations had partial response (PR), one stable disease (SD), one PD, and two had no available response status due to missing computerized tomography scan or physical examination. Only one patient with *BIRC3* mutation in the BR arm achieved uMRD with treatment but became MRD-positive three months after treatment cessation. At EOCT, in the VenR arm (n=8), three patients with *BIRC3* mutations achieved PR and uMRD in PB at EOCT; three had PR and low-MRD$^+$ ($\geq 10^{-4}$–$<10^{-2}$) status, one of whom subsequently attained uMRD during venetoclax monotherapy; one had SD with high-MRD$^+$ ($\geq 10^{-2}$) status, one was withdrawn for non-compliance and had no clinical response assessment at this visit but was low-MRD$^+$. Notably, all four patients with *BIRC3* mutations who achieved uMRD in the VenR arm maintained their uMRD status after cessation of the treatment and remain progression free at this follow-up (43–50 months); among these, one had concomitant *TP53* disruption.

These data from the MURANO study suggest that, similar to the setting of fludarabine, cyclophosphamide and rituximab (FCR), PFS was reduced in patients with *BIRC3*-mutated relapsed/refractory CLL treated with BR, indicating *BIRC3* mutation is an independent adverse risk factor with a range of chemoimmunotherapy. Within the limitations of the small numbers of patients involved, there was no significant PFS reduction observed in patients with *BIRC3* mutations treated with VenR overall with the current follow-up; nearly half of these patients were able to achieve and maintain uMRD, supporting the use of time-limited, chemotherapy-free VenR in R/R CLL patients with *BIRC3* mutations.

Arnon P. Kater,[1] Yanwen Jiang,[2] Brenda Chyla[3] and John F. Seymour[4]

[1]Department of Hematology, Amsterdam University Medical Centers, Location AMC, Amsterdam, on behalf of Hovon CLL Working Group, Amsterdam, the Netherlands; [2]Genentech, Inc., South San Francisco, CA, USA; [3]AbbVie, North Chicago, IL, USA and [4]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia

Correspondence: ARNON P. KATER - a.p.kater@amc.uva.nl

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