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Comment on Scarfò et al, page 2348

A balancing act between toxicity and deep response

Carlos Chiattone[1,2] and Alvaro J. Alencar[3] | [1]Santa Casa Medical School; [2]Hospital Samaritano—Higienópolis; and [3]University of Miami Sylvester Comprehensive Cancer Center

In this issue of *Blood*, Scarfò et al on behalf of the Italian Strategic Research Program on CLL present the results of the phase-II study IMPROVE, that evaluates a measurable residual disease (MRD)-driven model to individualize the treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) with discontinuation of single-agent venetoclax if displaying undetectable MRD4 (uMRD4; $<10^{-4}$) or treatment intensification with addition of ibrutinib and later discontinuation of both upon uMRD4.[1] The strategy was successful in 33 of 38 evaluable patients (87%) with combination therapy required in only half (16 of 33). While the combination of Bruton's tyrosine kinase (BTK) and BCL2 inhibitors is synergistic and highly effective by respectively addressing two critical survival mechanisms of CLL—inhibition of the proliferation signal from the B-cell receptor, and induction of apoptosis[2-4]—deep responses can be achieved with monotherapy minimizing the risk of added toxicity. IMPROVE thoughtfully addressed the challenge of identifying patients to avoid under- or overtreatment.

A total of 38 patients (median age 64) with R/R CLL after at least one line of therapy that did not include a BTK or BCL2 inhibitor who required therapy according to International Workshop on CLL (iwCLL) criteria were started on single-agent venetoclax at standard doses for a total of twelve 28-day cycles (see figure). This adequately reflects our current R/R CLL population, who may now be relapsing after having received chemoimmunotherapy as first line. Although BTKi's are more commonly seen as a go-to option for monotherapy, the choice of venetoclax was based on its previously documented higher uMRD rate of up to 16% in the bone marrow (BM) in this setting,[5] which is rarely achieved with ibrutinib alone.[6]

Assessment of MRD after 12 cycles of venetoclax was done with a six-color flow cytometry panel from peripheral blood (PB). Undetectable MRD4 was achieved in 19 patients and confirmed in BM in 17 (45% of intent-to-treat population). This uMRD rate is higher than previously described and may reflect a median of one previous treatment line or simply a small study sample. It is nevertheless an important finding, considering the population reflects current clinical scenarios and the high-risk features include 27/34 unmutated IGHV (79%), 7/33 del(17p) (21%), and 9/31 mutated *TP53* (29%).

Ibrutinib at standard 420 mg PO daily dose was added to venetoclax on cycle 13 for the 19 patients who had not achieved uMRD4 by cycle 12 (see figure). All patients benefitted from the addition of ibrutinib. Sixteen successfully achieved PB/BM uMRD4 and were able to discontinue therapy after a median of 7 months (range 3–10). In the MURANO study (evaluating fixed venetoclax and rituximab in R/R CLL for 24 months),[7] PB uMRD4 was achieved in 62% of patients during the first year without deepening of response on the second year. Curves of MRD assessment over time on IMPROVE demonstrate stable, or even rising, MRD levels in patients who did not achieve uMRD4 with venetoclax alone and clear improvement once ibrutinib was added. The authors appear to have identified a reasonable timepoint for intervention with added effect from ibrutinib in patients with suboptimal response to venetoclax.

Although iwCLL responses were evaluated with 63% of intent-to-treat patients (24 of 38) achieving uMRD4 CR with the MRD-tailored strategy, the strategy nevertheless considered only MRD-by-flow for treatment decisions. The rate of concordance between PB and BM MRD was around 90%, suggesting feasibility in standard practice where BM biopsies for CLL are rare.

After a median follow-up of 36.5 months, 10 patients had progressed for median progression free-survival not reached, and an estimated 36-month progression free-survival of 74.5%. MRD was detectable in 78% after a median of 7 months since treatment discontinuation. However, median time from MRD relapse to clinical progression was not reached, with no difference whether uMRD4 was achieved with venetoclax or combination. These are highly comparable with similar strategies that use fixed-duration combination therapies that include BTK and/or BCL2 inhibitors.

Most adverse events (AEs) were grade 1–2 with only grade 3–4 neutropenia and bronchitis occurring in more than one patient (n = 17, 43.6% and n = 2, 5%, respectively) and no discontinuation from treatment-related AE. AEs of interest for ibrutinib such as atrial fibrillation, bleeding, and hypertension all occurred in grades 1 or 2 in less than 15% of patients. It is obviously difficult to compare studies; however, these are comforting when other combination strategies of fixed-duration venetoclax–ibrutinib report similar rates of neutropenia, a frequent venetoclax complication, but higher rates of ibrutinib-related AEs, likely reflecting a longer exposure.[2,8] No tumor lysis syndrome was identified despite the initial venetoclax monotherapy, and most patients with at least medium risk of tumor lysis syndrome emphasized the safety of the current venetoclax ramp-up protocol.

Patients may not only appreciate the abbreviated treatment exposure with less clinical toxicity but also lower financial toxicity. Cost-effectiveness models demonstrate the lower costs of fixed-duration therapies compared with indefinite therapies.[9] In addition, the convenience of a fully oral regimen and avoidance of an anti-CD20 antibody is relevant considering its SARS-CoV-2–related complications.[10]

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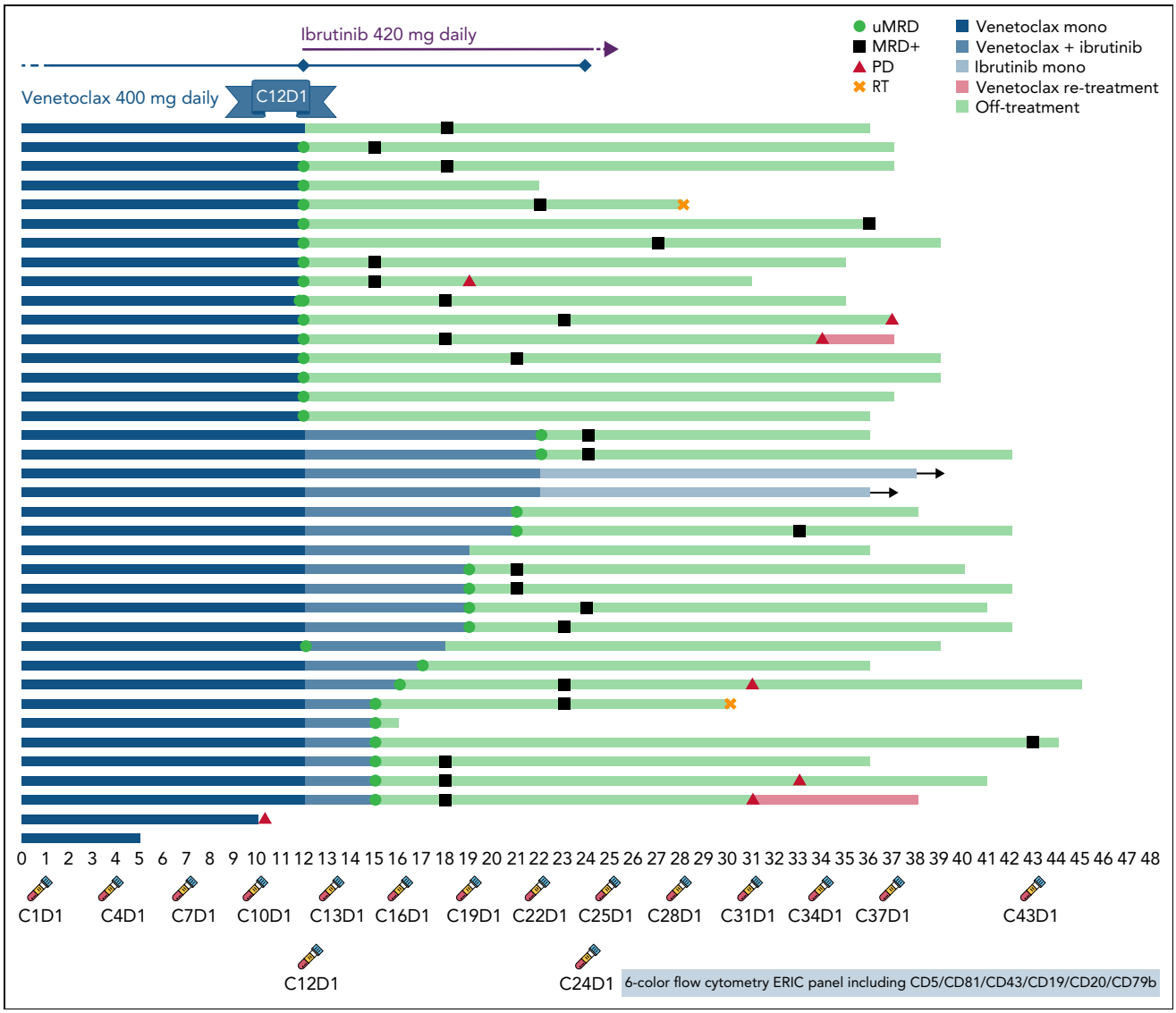

Strategy and outcomes. Treatment schema with initial venetoclax monotherapy followed by potential combination with ibrutinib according to MRD analysis performed every 3 months (timepoints at bottom) and swimmer's plot with outcomes of all 38 evaluable patients.

The question is where do we go from here? A large proportion of patients were able to successfully achieve deep response and interrupt therapy within approximately a year of therapy with median time to uMRD4 of 14 months (range 11–22). Can we get by with less? Median time to PB uMRD4 was 5 months (range 5–10). While median to PB/BM uMRD4 was 10 months (range 10–11), concordance between PB and MRD was around 90%. Those who required ibrutinib had in many instances passed their best MRD response from venetoclax. Earlier ibrutinib introduction may spare some months of suboptimal therapy and further shorten length without impact on disease control.

The authors provide strong proof of principle that an MRD-driven strategy is feasible in the R/R setting and there is no obvious reason why it could not be attempted in first line. Larger studies and longer follow-up should certainly follow, potentially with second generation BTK inhibitors that could further improve on the low AE rates. The time for indefinite therapy is coming to an end.

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MYELOID NEOPLASIA

Comment on Poplineau et al, page 2358

APL: Nemo finds its sea anemone

Qian-Fei Wang[1,2] and Hong-Hu Zhu[3] | [1]Beijing Institute of Genomics; [2]China National Center for Bioinformation; and [3]Beijing Chaoyang Hospital

In this issue of *Blood*, Poplineau et al[1] identified a retinoic acid (RA) resistance network involving the E2F-EZH2 axis by utilizing a PLZF-RARA transgenic acute promyelocytic leukemia (APL) mouse model probed with multiomics and elegant functional assays. They also showed that nonenzymatic activity of EZH2 is critically involved in RA resistance. Targeting pan-EZH2 activity significantly improved survival in mice reconstituted by RA-resistant PLZF-RARA leukemia cells.

During the last 3 decades, the field witnessed miraculous improvements in the treatment of classical PML-RARA APL, through the usage of RA and arsenic trioxide (ATO), targeting the RARA and PML moiety of the PML-RARA fusion protein, respectively.[2] Mouse models of APL have provided unexpected insights into the mechanism of action for these 2 drugs. RA binding activates PML-RARA target gene transcription and initiates degradation of the fusion protein, and arsenic binding to PML-RARA triggers its conjugation by SUMO, ultimately resulting in full degradation of PML-RARA.[3] Now, more than 90% of APL patients can be cured by the RA + ATO combination in a chemo-free treatment model.[4]

However, this miracle has not been replicated in the treatment of variant APL, which accounts for ~5% of all APL cases and is characterized by chromosomal translocations involving RARA and 18 different non-PML partner genes. As ATO does not work on non-PML partner proteins,[3] new treatment strategies are needed to overcome primary drug resistance in variant APL. PLZF-RARA, the most common APL variant, was first described in 1993 by Chen and colleagues.[5] Although RA treatment in a PLZF-RARA mouse model triggers cellular differentiation, it does not clear leukemia-initiating cells or induce disease remission.[6] Mechanistically, PLZF-RARA, but not PML-RARA, forms a stable complex with transcriptional corepressor SMRT. Transcriptional silencing plays a major role in RA insensitivity.[7] However, it remains unknown whether cellular heterogeneity exists in PLZF-RARA leukemia cells and how to target RA resistance in a treatment-related setting. The current study by Poplineau et al provides novel insights into these important questions by pinpointing a unique subset of PLZF-RARA-driven leukemia cells. These cells are RA resistant and dependent on a fine-tuned E2F-EZH2 network. Targeting pan-EZH2 activity, in combination with RA administration, leads to PLZF-RARA degradation and prolonged survival of APL mice given RA-resistant PLZF-RARA leukemia cells.

Drug resistance is often mediated by a small subset of cells with potent tumor-initiating capacity within a mixture of functionally heterogeneous tumor cells. It is a challenge to pinpoint the critical molecular circuit(s) in the drug-resistant cells that can drive disease progression. Using single-cell transcriptome sequencing, Poplineau et al first mapped out multiple leukemia cell subpopulations that were present before and after RA treatment in a PLZF-RARA APL mouse model. Development trajectory analysis and drug sensitivity assessment further identified an RA-resistant progenitor cell cluster (ReP), which maintained PLZF-RARA expression. To characterize molecular features associated with RA resistance, the authors combined single-cell transcriptome and chromatin accessibility profiling to dissect regulon activity. Activation of the E2F-EZH2 network was found to be most prominent in the ReP cells and was maintained after RA treatment.

The functions of EZH2, as an enzymatic catalytic subunit of Polycomb repressive complex 2 (PRC2), include post-translational methylation of histone and nonhistone protein substrates. Recent studies also reveal a noncatalytic function of EZH2 in solid tumors via transcriptional activation rather than H3K27me3-related repression.[8] Interestingly, this current study discovered a functional and physical interdependency between EZH2 and PLZF-RARA proteins (see figure). The PLZF-RARA fusion stabilized the interaction of 2 PRC2 components, EZH2 and SUZ12, and depletion of EZH2 resulted in degradation of this fusion protein. Functionally, EZH2 was essential for initiation and maintenance of PLZF-RARA oncogenic activity ex vivo and in vivo. Targeting the pan activity of EZH2 with a commercial EZH2 degrader along with RA repressed the resistance-related biological processes such as cell proliferation and DNA replication and significantly prevented disease progression in mice transplanted with RA-treated PLZF-RARA leukemia cells. In contrast, inhibition of EZH2 methyltransferase activity did not reverse RA resistance or leukemia progression

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