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CLINICAL TRIALS AND OBSERVATIONS

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CLL patients: GIVe me three!

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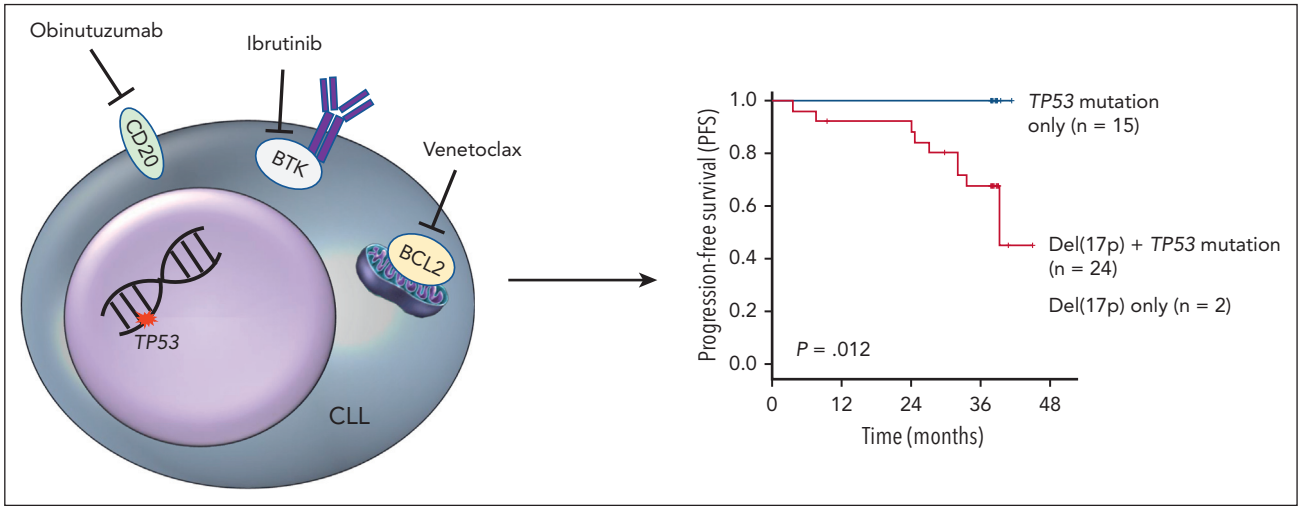
In this issue of *Blood*, Huber et al present a 3-year follow-up analysis of the phase 2 CLL2-GIVe trial, demonstrating continued robust clinical activity of the triplet combination of obinutuzumab, ibrutinib, and venetoclax in previously untreated patients with del(17p) and/or *TP53*-mutated chronic lymphocytic leukemia (CLL).[1]

Triplet therapy for CLL involving the combined use of B-cell receptor (BCR) signaling inhibitor, BCL2 inhibitor, and CD20-targeting monoclonal antibodies represents an emerging therapeutic innovation. Simultaneously targeting multiple CLL dependencies could theoretically limit the selection of therapy-resistant subclones, which could translate into deeper remissions that permit safe treatment discontinuation. In genetically unselected treatment-naïve patients, the triplet combination comprising ibrutinib, venetoclax, and obinutuzumab (IVO, also known as GIVe) previously demonstrated an undetectable measurable residual disease (MRD) ($<10^{-4}$) rate of 67% following 14 cycles,[2] whereas acalabrutinib, venetoclax, and obinutuzumab (AVO) produced MRD negativity ($<10^{-4}$) in 86% of patients after 15 cycles in an earlier phase 2 study.[3]

TP53 alterations confer genomic instability and are associated with inferior long-term outcomes even with targeted therapy.[4] Accordingly, the rationale for the use of triplet therapeutic combination is arguably stronger in the setting of high-risk CLL harboring *TP53* deletion (ie, del[17p]) and/or mutation, and therefore warrants investigation specifically within this genetic subgroup. In this regard, the CLL2-GIVe trial, which enrolled 41 previously untreated patients with *TP53*-deleted/mutated CLL on a single-arm IVO regimen, provides instructive insight into the clinical activity of this triplet regimen for such a patient population. Specifically, patients enrolled in this study were treated with 6 cycles of IVO induction followed by 6 cycles of ibrutinib and venetoclax as consolidation and thereafter with 3 further cycles of ibrutinib. The subsequent duration of maintenance therapy was intended to be MRD-guided with ibrutinib monotherapy continued until the attainment of an MRD-negative complete response (CR/CRi). An interim report last year provided early evidence of its efficacy with MRD-negative ($<10^{-4}$) rates of 78% and 66% in the peripheral blood (PB) and bone marrow (BM), respectively, at 15 months and a notable 95% 2-year progression-free survival (PFS) and overall survival (OS).[5]

Herein, the investigators present an updated analysis of this important trial. With a median follow-up of 38 months, the outcome data remain highly encouraging. At final restaging at cycle 15, the overall response (OR) rate was 100%, and the CR/CRi rate was 59%, with a PB MRD-negative rate of 44% at 36 months. The 36-month PFS and OS were 80% and 93%, respectively, and median PFS and OS were not reached. In comparison, within the expansion cohort of the AVO trial that likewise enrolled exclusively treatment-naïve patients with *TP53*-aberrant CLL, the OR and CR rates in the 29 evaluable patients were 100% and 52%, respectively, at a median follow-up of 35 months, with 86% of patients achieving undetectable MRD ($<10^{-4}$) in PB and BM at 15 months.[6] Triplet combinations involving Bruton tyrosine kinase inhibitors (BTKi), venetoclax, and obinutuzumab thus appear highly active in the setting of previously untreated *TP53*-aberrant CLL.

Currently, triplet combination therapies for CLL remain investigational rather than the standard of care. Important questions to be addressed include their efficacy and toxicity relative to single or dual targeted agents and whether such therapeutic combinations are desirable for all patients or only a select group of young and fit individuals. The COVID-19 pandemic has disproportionately affected patients with hematologic malignancies including CLL and brings to light the importance of considering potential infectious complications of CLL treatment. The current study was initiated in the prepandemic era, and although cytopenia was common, there were few reported treatment-limiting toxicities. However, attention needs to be paid to ascertain whether triplet therapies are more toxic than dual therapy or monotherapy in the post-pandemic setting. In terms of comparative efficacy among previously untreated patients without *TP53* alterations, IVO demonstrated superiority over venetoclax-rituximab or chemoimmunotherapy in the GAIA-CLL13 trial, but clear difference in MRD-negative rates between IVO and venetoclax-obinutuzumab was not apparent.[7]



Three-year PFS data from the CLL2-GIVe trial stratified by *TP53* status. Patients with *TP53* mutation only (n = 15, blue curve) displayed superior PFS with the triplet combination of obinutuzumab, ibrutinib, and venetoclax compared with patients with both del(17p) and *TP53* mutation (biallelic *TP53* loss, n = 24) or del(17p) alone (n = 2).

Similarly, in older patients with treatment-naïve CLL, the Alliance A041702 trial thus far failed to demonstrate superiority of IVO over ibrutinib-obinutuzumab.[8] Within the specific context of *TP53*-deleted/mutated CLL, results from the ongoing phase 3 CLL16 trial comparing AVO vs obinutuzumab-venetoclax will be eagerly awaited.

Although exploratory by nature owing to the limited sample size, correlative work in the current study revealed significantly inferior PFS in patients harboring both *TP53* mutation and del(17p) compared with those with a sole *TP53* mutation (see figure). Biallelic *TP53* loss arising from deletion of 1 copy of the *TP53* gene and inactivating mutation in the other results in the complete loss of p53-mediated cell cycle control and apoptosis in response to cellular stress and oncogenic activity.[9] This could render CLL subpopulations harboring biallelic *TP53* loss more genetically unstable with heightened risk of acquiring additional resistance mutations during treatment, as well as increased clonal repopulation propensity due to higher CLL proliferation rate upon subsequent treatment discontinuation.[10] The former may manifest in a slower rate of CLL depletion during treatment and ultimately shallower remissions, whereas the latter may manifest in a shorter MRD doubling time upon stopping treatment.

This raises 2 important implications. First, maintenance therapy may be needed for patients with both *TP53* mutation and del(17p), and in this respect, maintenance with ibrutinib monotherapy following completion of the triplet regimen appeared effective in suppressing subclonal outgrowth, with relapses being witnessed exclusively among patients without maintenance therapy. On the other hand, sole *TP53*-mutated CLL with mutated *IGHV* showed no progression events, and hence time-limited therapy could suffice. Second, if *TP53*-null clones are indeed associated with accelerated regrowth kinetics, this would suggest that remissions deeper than the conventional 10^{-4} MRD threshold may be necessary for treatment cessation to achieve durable response. More sensitive methods for MRD monitoring (eg, clonoSEQ; 10^{-6}) may assist in guiding treatment duration and preempting the need for re-treatment.

Finally, with noncovalent BTKi and novel BCL2 inhibitors adding to the panoply of CLL treatments, the GIVe regimen of Huber et al may be the first therapeutic triplet for *TP53*-aberrant CLL but will certainly not be the last. For patients, cautious optimism is the order of the day. Watch this space!

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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LYMPHOID NEOPLASIA

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Chemoresistance pathways in DLBCL

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In this issue of *Blood*, Zhou et al reveal the role of KLHL6 inactivation in chemoresistance in diffuse large B-cell lymphoma (DLBCL).[1] KLH6 is a cullin-ring ubiquitin type 3 ligase and a central player in the ubiquitin proteasome system, a cellular system that targets proteins for subsequent degradation, thereby limiting their half-life and activity. Type 3 ligases, such as KLHL6, attach the ubiquitin chain to the target protein.

KLHL6 mutations have been described in many cancers, including DLBCL, in which mutations have been reported in 7% to 15% of patients. These genetic variants are usually loss of function, supporting a tumor-suppressor role for the enzyme.[2] A link between loss of activity of KLHL6 and DLBCL generation was previously made by the same investigators, who showed that loss of enzyme activity resulted in NF-κB signaling through a molecular circuit involving roquin2, an RNA-binding protein that promotes RNA decay.[3] Now, by using elegant genetic and biochemical approaches, the authors show that KLHL6 ubiquitinates NOTCH2, resulting in its degradation and terminating signaling. Thus, inactivating mutations in *KLHL6* result in the lack of NOTCH2 ubiquitination and prolonged signaling. Likewise, NOTCH2 mutations evade KLHL6-mediated ubiquitination, with the same overall result of overactivation of NOTCH2-regulated RAS-dependent oncogenic pathways (see figure).

NOTCH2 codes for a ligand-activated receptor-activated transcription factor that is recurrently mutated in DLBCL. According to 2 seminal articles that recently reclassified DLBCL based on their molecular lesions, *NOTCH2* mutations are present in more than 20% of all cases, defining specific disease subsets.[4,5] From the clinical standpoint, a subsequent large study performed on 928 unselected patients determined that *NOTCH2*-mutated DLBCLs are a mixture of activated B-cell, germinal center B-cell, and unclassified lymphomas, with an intermediate prognosis.[6] Conversely, *KLHL6* mutations are typical of the subset of DLBCLs enriched in SGK1/TET2 mutations, which in some, but not all, studies are associated with a favorable prognosis. As they impact the same oncogenic pathways, *NOTCH2* and *KLHL6* mutations do not overlap. Although it is interesting that the molecular subgroups with *NOTCH2* and *KLHL6* mutations present with similarities to splenic marginal zone lymphomas (SMZL) in which *NOTCH2* mutations are among the most common genetic event, their biology and behavior are highly different, and no DLBCL occurs in a preexisting SMZL.

A link between activation of NOTCH2-regulated pathways and chemoresistance was previously made in other experimental models, including breast cancer[7] and neural stem cells,[8] but never in DLBCL. The link to chemoresistance is important. Despite recent advances in our understanding of the molecular architecture of DLBCL, initial therapy for routine clinical care is not based on the molecular architecture. The mainstay of therapy remains a combination of chemotherapeutic agents, steroids, and anti-CD20 monoclonal antibodies (R-CHOP). A significant proportion of patients acquire resistance to this regimen. Currently, there are 146 clinical trials actively recruiting patients with DLBCL (https://clinicaltrials.gov/), most of them investigating therapy of relapsed/refractory disease.

By elegantly joining their molecular data to patient data set analyses, the authors determined a connection between the presence of *KLHL6* mutations, resistance to R-CHOP, and poor overall survival. These observations provide the rationale for overcoming resistance using nirogacestat, which inhibits NOTCH2 and the RAS pathway, which is directly affected by *NOTCH2* mutations. Nirogacestat is a novel and highly promising γ secretase inhibitor, which very recently showed significant benefits in adult patients with progressing desmoid tumors. In that study, in which the drug was used as a single agent, side effects of treatment, although frequent, were usually well tolerated.[9] Clinical exploration in DLBCL is still far off as the drug needs to be studied in other models, such as patient-derived xenografts, before being considered for moving to the clinic.

Many questions remain open, such as defining the exact role of the NOTCH2 pathway in DLBLC. In the current report, the authors concentrate on early cellular consequence of NOTCH2 mutations in DLBCL, showing that R-CHOP–resistant *NOTCH2*-mutated cells have an overactivation of the AKT/ERK pathway. Thus, there are complex genetic effects that still need to be identified and studied. Identifying the specific molecular intermediates will be essential to tailor therapy to the causative molecular lesion in patients who are chemoresistant.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■