Paper:
Final analysis of the CLL2-GIVe trial: obinutuzumab, ibrutinib, and venetoclax for untreated CLL with del(17p)/TP53mut.
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In the last issue of *Blood*, Huber and colleagues present a three-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 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 MRD ($<10^{-4}$) rate of 67% following 14 cycles,[2] while 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 (i.e. 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. 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% respectively in the peripheral blood (PB) and bone marrow (BM) at 15 months, and a notable 95% 2-year progression-free (PFS) and overall survival (OS).[5]

Herein, the investigators presented 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, while median PFS and OS were not reached.[1] 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 respectively 100% and 52% at a median follow-up of 35 months, and 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 for 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 pre-pandemic era, and although cytopenia was common, there were few reported treatment-limiting toxicities.[1] However, attention needs to be paid to ascertain whether or not 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] Similarly, in older individuals 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 versus obinutuzumab-venetoclax will be eagerly awaited.

Although exploratory by nature due 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 to those with a sole *TP53* mutation (see figure).[1] Biallelic *TP53* loss arising from deletion of one 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, while the latter in a shorter MRD doubling time upon stopping treatment.

This raises two 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, *TP53*-null clones is 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 (e.g. clonoSEQ; 10^{-6}) may assist in guiding treatment duration and preempting the need for re-treatment.

Finally, with covalent BTK inhibitors 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!

References

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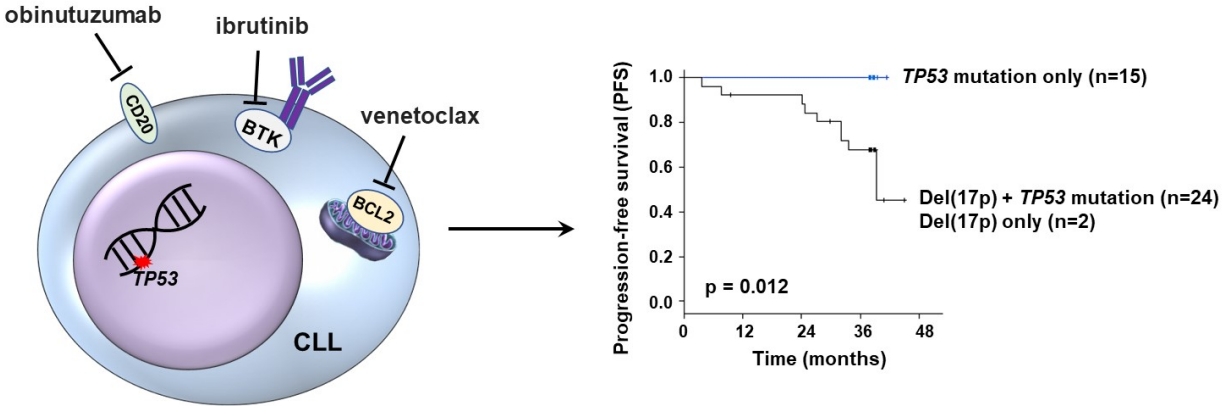

3-year PFS data from the CLL2-GIVe trial stratified by *TP53* status. Patients with *TP53* mutation only (n=15, blue curve) displayed superior PFS with the triplet combination of obinutuzumab, ibrutinib and venetoclax compared to patients with both del(17p) and *TP53* mutation (biallelic *TP53* loss,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