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CLINICAL TRIALS AND OBSERVATIONS

*Comment on Cramer et al, page 1805*

# Improving the outlook for TP53-aberrant CLL

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**In this issue of *Blood*, Cramer et al[1] present a pooled analysis of 3 prospective phase 2 trials in which 51 patients with chronic lymphocytic leukemia (CLL) with TP53 mutations or del(17p) were treated with an anti-CD20 antibody plus either ibrutinib or venetoclax. Despite the adverse prognosis, most patients had deep and durable responses, including some who remained in remission after stopping treatment with undetectable minimal residual disease (MRD). This reinforces the role of targeted therapies and the potential use of MRD to tailor the duration of treatment of patients, even with high-risk CLL.**

A truism in oncology is that prognosis is not only affected by the growth rate of the cancer cells but also based on the effectiveness of treatment. To paraphrase one of my mentors, patients with bad disease just need better therapies.

This has certainly been true for patients with CLL with deletion of the TP53 locus on chromosome 17 or TP53 gene mutations. Such aberrations are found in approximately 7% of cases in the frontline setting and predict resistance to chemoimmunotherapy.[2] TP53 aberrations are more common in relapsed or refractory cases, up to 40% in some datasets, consistent with an expansion of mutant subclones under the selective pressure of therapy.[3]

The outlook for patients with TP53-aberrant CLL has improved greatly with the development of the inhibitors of Bruton's tyrosine kinase (BTK) and B-cell lymphoma 2, which have TP53-independent mechanisms of action. Ibrutinib results in durable remissions, especially in the frontline setting; the progression-free survival (PFS) in a phase 2 year exceeds 6 years (and still counting).[4] The pivotal study of single-agent venetoclax for relapsed/refractory CLL with del(17p) showed a high response rate as well, but with a median PFS of approximately 2 years, albeit in a more heavily previously treated population.[5] In the frontline setting, venetoclax plus obinutuzumab is effective as a fixed duration regimen; however, cases with aberrant TP53 appear to have a shorter treatment-free remission, although the total number of relapses is low to date.[6]

Despite this progress, there are several questions regarding the optimal management of patients with TP53-aberrant CLL. Should we aim to maximize the depth of response with a fixed-duration regimen that leads to a time off treatment? Is MRD an appropriate end point to use to stop treatment? Is it preferrable to continue a maintenance therapy that maximizes PFS because of a risk of early relapse with TP53-aberrant CLL?

By pooling the patients with TP53 aberrations across similarly structured clinical trials, this report provides some helpful information. Each of the German CLL Study Group CLL2-BXX trials evaluated bendamustine debulking (optional, based on high tumor burden), followed by an anti-CD20 antibody plus ibrutinib or venetoclax.[7] Patients with undetectable MRD stopped treatment. The overall hope is that such sequential combination approaches may eradicate disease below detectable levels and enable meaningful treatment-free remissions.[8]

Across the trials, the patients with TP53-aberrant CLL had generally excellent outcomes. Nearly all responded. Thirty-three percent had undetectable MRD, mostly from the venetoclax plus obinutuzumab trial. The durability of responses was notable. Previously untreated patients had an estimated 89% 36-month PFS rate. The patients who stopped treatment with undetectable MRD did not have immediate relapses. Ten of the 17 patients who stopped treatment remain in remission to date. These patients have been followed off treatment between 9 and 43 months.

Do these results change our standard of care for TP53-aberrant CLL? Probably not. The role of bendamustine debulking was not a central aspect of this report. Although most patients responded, it may have less "bang for the buck" in cases with TP53 mutations based on its mechanism of action. The demonstrated efficacy of the targeted therapies makes this debulking step less critical. It is also still not clear if patients on a BTK inhibitor benefit from the addition of an anti-CD20 antibody, at least in terms of PFS.

Rather, the significance of this report is the demonstration that some patients who have deep remissions may have long treatment-free remissions, even with TP53 aberrancies. This may not be important for all patients. Certainly, it will be difficult in the near term to demonstrate that any regimen results in a quantitative improvement over single-agent ibrutinib, at least in terms of PFS. However, some patients may prioritize qualitative aspects of being off treatment altogether, and this may still be a reasonable goal of therapy for such patients, despite TP53 mutations or del(17p).

What comes next? It will be critical to learn how patients respond to retreatment when they relapse after stopping treatment. I am hopeful that progression off

treatment is less likely to be caused by new resistant subclones and that the overall time from initial treatment to retreatment failure may be comparable to that seen with continuous therapies. Direct comparison of ibrutinib vs venetoclax plus obinutuzumab is ongoing as part of the German CLL17 trial (NCT04608318). Finally, there are other combinations to consider, including BTK inhibitors plus venetoclax, as we continue to optimize treatment of patients with TP-aberrant CLL.[9]

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*Comment on Jetani et al, page 1830*

# Siglec-6 CAR T: magic bullet for a moving target

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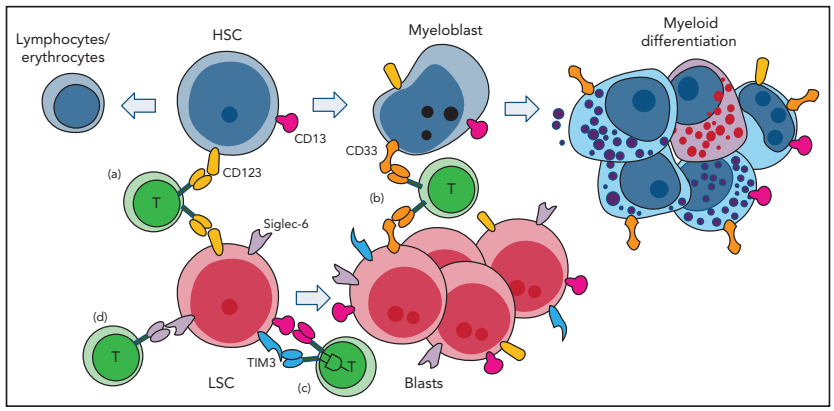
**In this issue of *Blood*, Jetani et al[1] explore models of CAR T-cell targeting of Sialic acid-binding Ig-like lectin-6 (Siglec-6) in acute myeloid leukemia (AML). Whereas CAR T cells are a useful new treatment for patients with refractory B-cell acute lymphoblastic leukemia (B-ALL), developing CAR T-cell therapies for AML has been hampered by a lack of suitable targets. Most obvious CAR targets for AML are also expressed on hematopoietic stem cells (HSCs) or myeloid cells. Given the propensity for CAR T cells to persist, prolonged myeloid aplasia would be expected if myeloid cells or HSCs were recognized. Importantly, Siglec-6 has no significant expression on HSCs or myeloid cells; consequently, Siglec-6 CAR T cells should spare normal hematopoiesis.**

Targeting AML with CAR T cells poses additional challenges. AML is a heterogenous disorder arising from dysregulation at diverse points in myeloid differentiation. CAR T-cell targets should be broadly expressed on all AML subtypes and should target leukemia stem cells (LSCs), a cell population held responsible for relapse. However, LSCs may be phenotypically distinct from the bulk population and may differ among patients. Different LSC subpopulations may even be present in a single patient (see figure). Finally, potential AML targets should not be expressed on other critical nonmyeloid or nonhematopoietic cells.

The best explored AML target antigens are CD33[2] and CD123.[3] These targets are not ideal, as they are expressed by normal myeloid cells and HSCs, respectively. With targets that do not spare normal hematopoiesis, 1 pragmatic strategy is to use CAR T cells to act as a "bridge" to allogeneic HSC transplant (allo-HSCT). In that case, conditioning chemotherapy should eradicate the CAR T cells and rescue the patient from aplasia. However, this strategy involves a lengthy period of myelosuppression and may be poorly tolerated. There are limited, early clinical data on CAR T-cell therapy in AML using such




CAR T-cell therapy for AML ideally targets LSCs and AML blasts, but spares HSCs and myelopoiesis. Early approaches such as targeting of CD123 (a) and CD33 (b) did not spare HSCs or myelopoiesis, resulting in aplasia. (c) More complex targeting approaches where CAR T activation is triggered only by the presence of 2 antigens can allow increased specificity. In this example, CD13 is expressed by LSC and blasts, but it is also expressed by HSCs and myeloid cells. Although TIM3 is expressed outside the hematopoietic system, it is expressed on AML cells but not on normal HSCs. (d) Finally, some antigens such as Siglec-6, which are expressed on AML cells but not on normal hematopoietic cells may allow simple and selective targeting of AML.