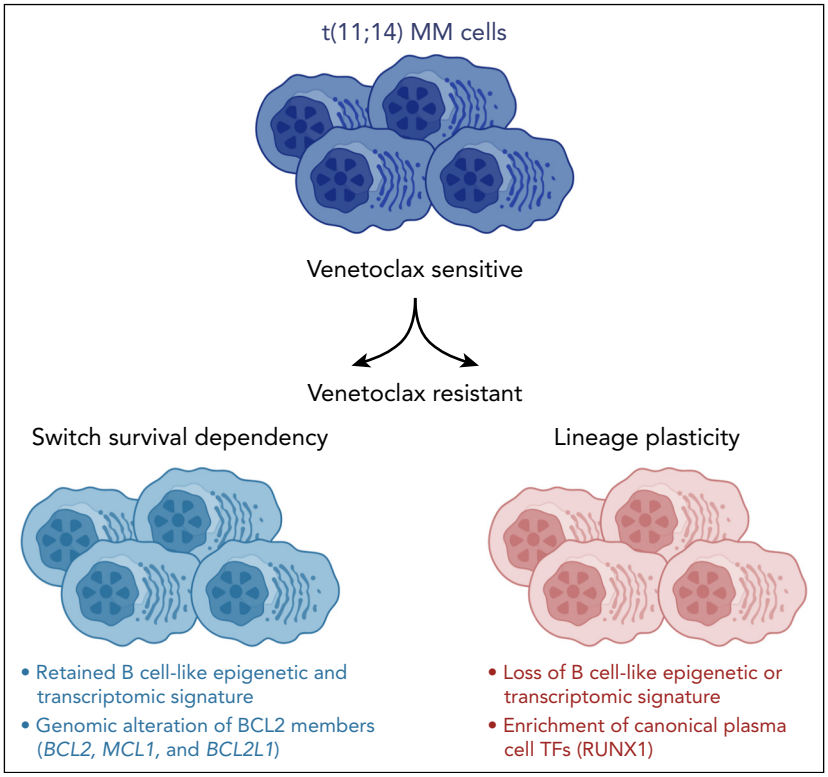

In patients with t(11;14) myeloma, a loss of a "B-cell–like" epigenetic and transcriptomic signature with a gain of canonical plasma cell transcription factors (TFs) is observed at the time of resistance to venetoclax. *MCL1* and *BCL2L1* copy number gains and structural rearrangements are also linked to venetoclax resistance. See the visual abstract in the online version of the article by Leblay et al that begins on page 42.

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LYMPHOID NEOPLASIA

Comment on Papazoglou et al, page 57

Ibrutinib reversal of immune exhaustion in CLL

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PD-1$^+$ "exhausted" T cells accumulate in chronic lymphocytic leukemia (CLL) and, in this issue of *Blood*, Papazoglou et al show that these correlate with good clinical outcome after ibrutinib treatment, potentially revealing a role in immune surveillance.[1] The findings provide a fascinating range of novel insights that should drive future studies in this neglected topic.

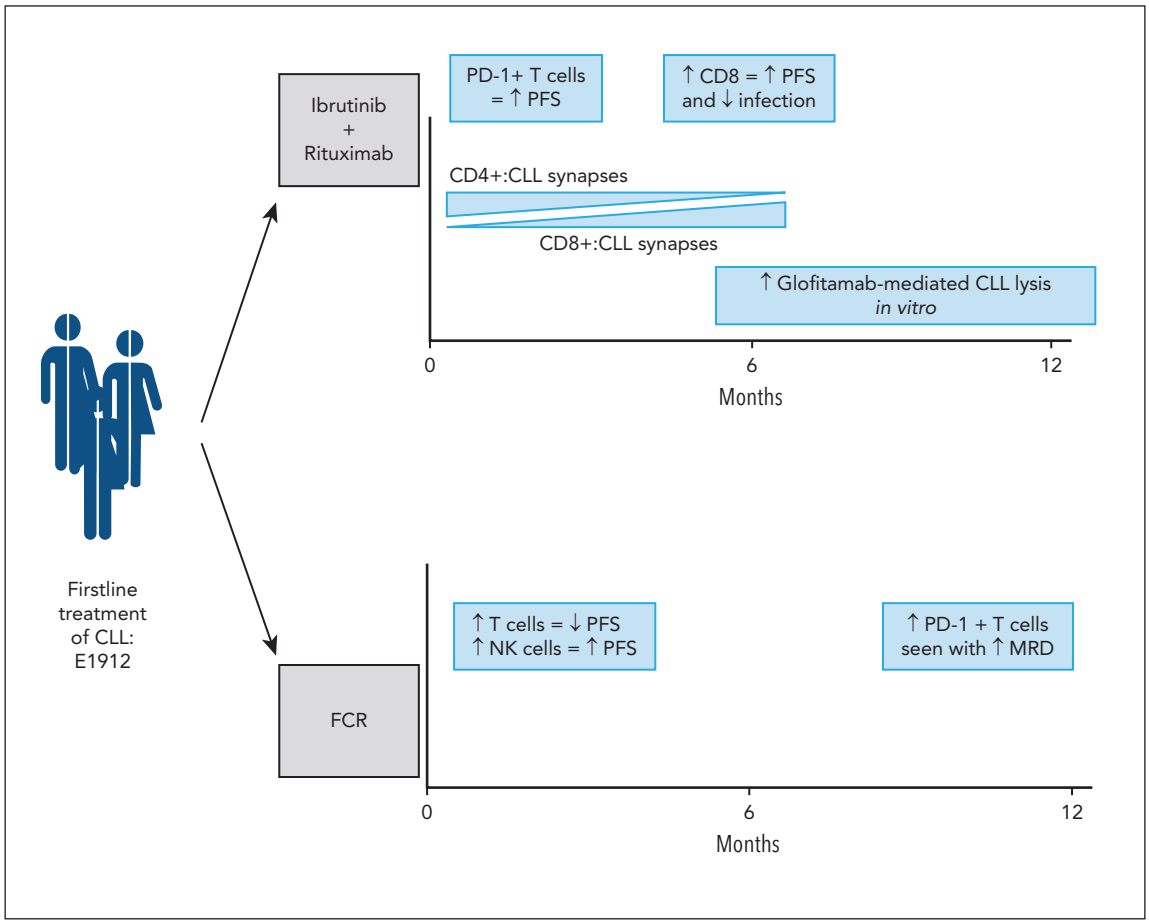
A remarkable characteristic of the CLL tumor cell is its immune suppressive phenotype.[2,3] Indeed, this might be considered as "smoking gun" evidence for obligate tumoral evasion from immune surveillance. Potential demonstration of a CLL-specific immune response may perhaps be seen in the failure of most $CD5^+$ B-cell clonal proliferations to progress to CLL[4] and occasional, albeit rare, spontaneous remission.[5] Furthermore, in addition to T-cell control of tumor growth, the COVID-19 pandemic brutally exposed the depth of immune suppression in patients with CLL[6], and optimization of global T-cell immune function is a critical area for future study. Despite these challenges, few studies have assessed the correlative importance of T-cell phenotype and function in patients with CLL recruited into large phase 3 clinical trials. The report by Papazoglou et al uses samples from the E1912 clinical study to do just that.

The E1912 trial was the first frontline phase 3 study comparing ibrutinib and rituximab (I+R) against fludarabine-cyclophosphamide-rituximab (FCR) chemotherapy.[7] Clinical outcomes strongly favored I+R, with a hazard ratio of 0.37 for progression-free survival and 0.47 for overall survival after 5.8 years. A major strength of E1912 was the curation of biobanked samples, and Papazoglou and colleagues used these to determine immune phenotype at baseline and 6 and 12 months from 89 patients on I+R and 62 allocated to FCR.

Initial studies defined the phenotypic profile of immune cells in relation to tumor control and infection rate. A curious feature of CLL is that T-cell numbers are paradoxically elevated prior to treatment and, whilst this was also seen within E1912, the association of baseline T-cell number with clinical outcome varied greatly according to treatment arm. For patients on I+R, higher levels of effector T cells at baseline and at 6 months were favorable and were associated with longer progression-free survival (see figure). Furthermore, this was most notable for T cells that expressed PD-1, the dominant marker of T-cell "exhaustion." Ibrutinib can reverse T-cell exhaustion,[8] and these findings indicate that this may contribute to the clinical efficacy of I+R. Following treatment initiation, higher levels of effector $CD8^+$ T cells after 6 months remained linked to improved progression-free survival, suggesting a direct role for cytotoxic $CD8^+$ populations, although a failure to normalize the elevated PD-1 expression on $CD8^+$ cells was associated with persistent minimal residual disease (mrd).

Correlative associations with infectious episodes in the I+R arm were also noteworthy. A low CD4:CD8 ratio, an established marker of replicative senescence,[9] was associated with elevated infection risk, but high numbers of T and natural killer (NK) cells after 6 months were highly protective against infection.

Very different observations were seen in patients who were allocated to chemotherapy. In those patients, T-cell numbers were profoundly suppressed by



Clinical correlates of T-cell immune profile at 0, 6, and 12 months for patients in the E1912 study randomized to I+R or FCR treatment. PFS, progression-free survival. Created using Biorender.com.

6 months, with reconstitution recovering only after a year. Furthermore, a high level of PD-1$^+$ T cells at baseline was associated with impaired disease control, in direct contrast to the profile observed with I+R.

Given these correlative associations in relation to treatment allocation, the team next looked at potential underlying mechanisms of cellular function, utilizing their proven excellence in study of synapse formation between T cells and tumor cells. In the I+R arm, high levels of CD4$^+$ T cell:tumor synapse formation at baseline was associated with shorter progression-free survival and higher levels of severe infection, which likely reflects the capacity of CD4$^+$ T cells to support tumor cell survival. However, a switch to superior CD8$^+$ T cell:tumor synapse formation was noted at 6 and 12 months. Moreover, this was associated with improved disease control, and no comparable transition was seen in the chemotherapy treatment group.

Antibody-mediated PD1 checkpoint blockade has been disappointing in the management of CLL, and *in vitro* analysis here also demonstrated little efficacy. As such, the authors assessed the capacity of the bispecific antibody glofitamab, which crosslinks CD20 with CD3, to induce tumor cell lysis using immune effector cells taken from biobanked study samples. Remarkably, although this elicited high levels of CLL killing using samples taken after at least 6 months of I+R, no response was seen using samples from patients on chemotherapy.

These important findings extend interest in efforts to understand and empower T-cell immune surveillance of CLL and yet, quite typically of translational research, raise many questions. Bruton tyrosine kinase inhibitor (BTKi) therapy is not typically associated with high rates of mrd-negative status, suggesting an apparent failure of any T-cell reengagement to completely eradicate tumor cells. The mechanism of potential reversal of T-cell exhaustion is also unclear and may partially reflect massive reduction in tumor cell antigen load following ibrutinib. Furthermore, immunological mechanisms underlying the proven utility of chemotherapy should be considered. A 6-month course of FCR can achieve long-term remission in patients with immunoglobulin heavy chain variable region gene (IGVH)-mutated CLL,[10] and it is difficult to believe that this efficacy does not have an important immune component. The positive prognostic impact of NK cell number at FCR treatment baseline is intriguing in this regard.

The findings provide potential evidence for established, but exhausted, T-cell control of CLL, which can be reactivated following BTKi therapy. The importance of rituximab in this regard remains uncertain. Current CLL therapies are not completely tumor specific but are highly effective, and most patients do not succumb to their disease. Their potential displacement with targeted immunotherapy will require greater understanding of the molecular basis of cellular recognition and mechanisms by which surveillance is lost during disease progression. This valuable translational study should reenergize interest in this fascinating question and overcome any nascent exhaustion of academic ambition to develop immunotherapies for this challenging disorder.

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

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PLATELETS AND THROMBOPOIESIS

Comment on Buka et al, page 64

JA(c)K-in-the-platelet and M(i)PL fetch PF4

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In this issue of *Blood*, Buka et al have identified myeloproliferative leukemia oncogene (MPL)-mediated Janus kinase (JAK) 2 activation as a signaling mechanism through which platelet factor 4 (PF4) triggers platelet aggregation.[1]