with a cytokine-mediated mechanism of action. Hence, it will be interesting to determine if miR-146a is a determinant of initial leukemic transformation in conjunction with driver mutations that have been well documented.[8]

This interesting work also raises additional questions. Is there a difference in hematopoietic miR-146a expression between AML patients and age-matched controls? Studies in autoimmune disease have demonstrated polymorphisms in the promoter of miR-146a, which reduce its expression.[9] It will be interesting to determine if this is the key to reduced miR146a expression during aging and in the setting of AML. Another open question is whether the difference in prognosis in AML is related to the direct sensitivity of AML blasts to inflammaging signaling or whether non-AML "inflammaged" HSCs are less able to recover within the bone marrow following therapy. Furthermore, the reduction in HSC function appears to be the result of both cell-intrinsic and cell-extrinsic mechanisms. The extent to which each mechanism contributes to HSC dysfunction is an exciting area for future investigation. Answers to these questions should guide future therapeutic strategies, including replenishing miR-146a, which initial evidence suggests is possible.[10]

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LYMPHOID NEOPLASIA

Comment on Lin et al, page 2266

Inverting the BTK-BCL2 order

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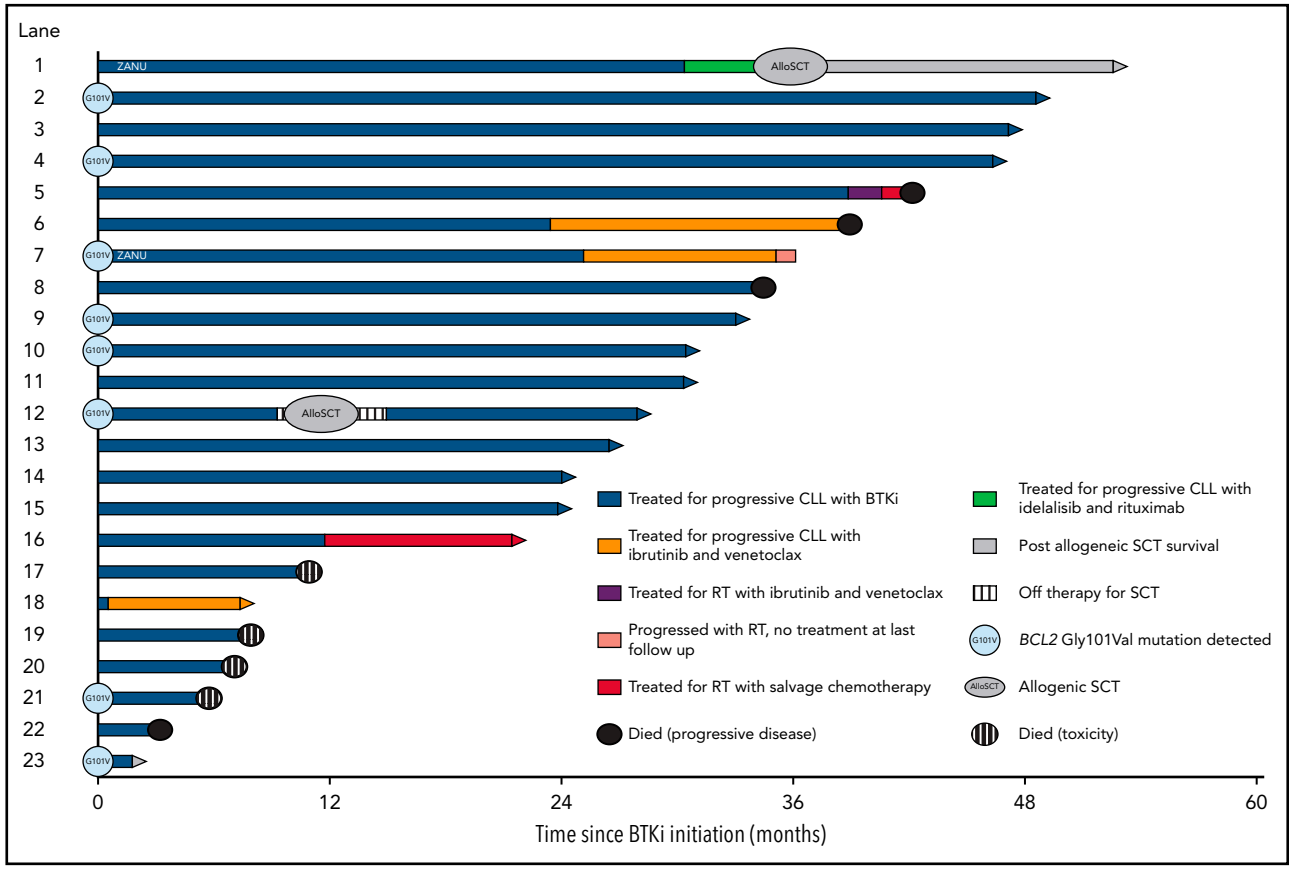
In this issue of *Blood*, Lin et al report the first long-term follow-up data showing that Bruton tyrosine kinase inhibitors (BTKi's) are effective in chronic lymphocytic leukemia (CLL) after previous progression on venetoclax.[1]

Clinical development of the BTKi ibrutinib preceded that of the BCL2 inhibitor venetoclax, with approval for use in relapsed CLL in February 2014. The initial approval of venetoclax came in April 2016 for the limited group of previously treated CLL patients with 17p deletion. Given this timing, a prospective clinical trial was rapidly performed that established the effectiveness of venetoclax in patients with disease progression during or after ibrutinib.[2] Since then, approval has been extended for venetoclax, in combination with rituximab for any CLL patient who has had at least 1 previous therapy,[3] and in combination with obinutuzumab for previously untreated CLL patients.[4] These venetoclax regimens have certain advantages: they have a defined duration, are well-tolerated, and achieve deep remissions with undetectable minimal residual disease (MRD). The inevitable question then arises: will BTKi's work well after venetoclax, that is, can the order of therapy be inverted, using venetoclax as a first targeted agent? The hesitation comes from the unknown efficacy of BTKi's after treatment with venetoclax has failed.

The article by Lin et al seeks to fill this knowledge gap. They present the outcomes of BTKi therapy in 23 patients previously treated on 1 of 4 early venetoclax trials and whose CLL progressed during ongoing venetoclax therapy. The patients were all heavily pretreated, with a median of 4 previous regimens that included fludarabine-cyclophosphamide-rituximab in almost all cases, and no previous BCRi exposure. *TP53* abnormalities were present in 76% of patients and complex karyotype was present in 68% of patients. The patients had a median duration of response on previous venetoclax therapy of 29 months, mostly partial responses. Twenty-one patients went on to receive ibrutinib, and 2 patients went on to receive zanubrutinib, with an overall response rate (ORR) of 91%. Their median progression-free survival (PFS) was 34 months when being treated with a BTKi; 11 patients with a median follow-up of 33 months were still receiving therapy, and 12 discontinued therapy (8 for progression and 4 for toxicity) (see figure). Median overall survival was 42 months.

Although the Lin et al study is a retrospective single-institution study with a limited sample size, overall, these data are reassuring because the ibrutinib results seem largely comparable to those reported in the most similar patient population previously studied: the phase 1b/2 study of ibrutinib.[5] That study



Modified version of Figure 1A from Lin et al showing individual patient outcomes with BTKi treatment after progression while receiving venetoclax. Median PFS was 34 months. See Figure 1A in the article by Lin et al that begins on page 2266.

enrolled 101 patients with a median of 4 previous treatment regimens, of whom 37% had complex karyotype and 34% had a 17p deletion; thus, they had a similar number of previous therapies but lower-risk disease characteristics, and they were naïve to targeted therapy. Median PFS overall was 52 months, but it was 39 months in patients with 4 or more previous therapies, 26 months in patients with a 17p deletion, and 31 months in patients with complex karyotype, all subgroups comparable to the patients studied by Lin et al, who had similar PFS.

Other emerging data on the efficacy of ibrutinib after venetoclax support the findings of Lin et al. Recent follow-up data from the MURANO clinical trial included 12 patients who progressed after venetoclax who are now being treated with ibrutinib, with 10 patients responding (ORR, 83%).[3] The largest series to date has been presented in abstract form and comes from a retrospective real-world study that included 326 patients who discontinued venetoclax.[6] A subcohort of 44 patients were BTKi naïve before treatment with venetoclax, and the ORR with subsequent BTKi therapy among these patients was 83.9%, with a median PFS of 32 months. These data are strikingly consistent with the findings of Lin et al.

In contrast to the newer defined-duration venetoclax regimens, the patients evaluated by Lin et al progressed during continuous venetoclax therapy and might be at higher risk of developing venetoclax-specific resistance mutations. In fact, the BCL2 Gly101Val mutation is a resistance mutation that develops late during continuous therapy.[7] The Lin et al study included 8 patients with this mutation, and their median PFS with subsequent ibrutinib therapy has not been reached; so far, they have an estimated PFS rate of 69% at 24 months, which provides reassuring evidence that patients with this mutation can respond well to ibrutinib. Future studies will be needed to assess BTKi response in patients with other proposed mechanisms of venetoclax resistance, including overexpression of other BCL2 family members,[7,8] metabolic reprogramming,[8] deletions of *CDKN2A/B*,[9] or mutations in *BTG1*.[9]

The primary predictors of ibrutinib outcome in the Lin et al study were a long venetoclax remission duration of 24+ months, or attaining a deep remission during venetoclax therapy (CR and/or undetectable MRD). All of the patients in the latter group were also in the former group, and both groups correlated with prolonged PFS with ibrutinib treatment. Interestingly, these findings are reminiscent of predictors of outcome after chemoimmunotherapy (CIT). In fact, although the use of venetoclax as a time-limited therapy may reduce the incidence of late-developing *BCL2* mutations, nonetheless recurrent disease after very deep remissions may be enriched in higher-risk clones as with CIT. Even though the data in the Lin et al study are limited, 6 relapsing patients had adverse features not previously documented: 2 with *TP53* abnormalities and 4 with complex karyotype. Much work will be needed to understand relapse and clonal evolution after treatment with venetoclax.

In that context, it is noteworthy that 5 patients in their cohort who had Richter transformation during venetoclax therapy still achieved durable disease control with chemotherapy with or without autologous stem cell transplantation. This suggests that patients receiving venetoclax who develop diffuse large B-cell lymphoma-type Richter transformation can sometimes be salvaged with standard therapy, in contrast to patients who are receiving ibrutinib, who have a uniformly poor prognosis.[10]

Finally, Lin et al report 2 patients with previous progression when receiving ibrutinib and venetoclax as single agents, who nonetheless derived clinical benefit from being treated with both drugs simultaneously, with remissions of about 1 year. This study adds to the increasing anecdotal experience of successful combination therapy in patients who have progressed on either or both single agents. Systematic studies in this patient population are warranted, particularly as the CLL field begins to grapple with the role of BTKi-venetoclax combination therapy: Does initial combination therapy lead to better outcomes than therapy with sequential single agents? While we await these data, this first report of long-term successful BTKi therapy in CLL patients after venetoclax progression can provide clinicians some comfort in choosing time-limited venetoclax therapy for their patients before treating with a BTKi.

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PLATELETS AND THROMBOPOIESIS

Comment on Morodomi et al, page 2292

The never-ending enigma of immune thrombocytopenia

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In this issue of *Blood*, Morodomi et al advance our understanding of the mechanisms involved in antibody-mediated immune thrombocytopenia (ITP).[1]

ITP is an autoimmune disease characterized by isolated thrombocytopenia with platelet counts <100 000 per cubic millimeter where other causes of thrombocytopenia have been excluded. ITP is idiopathic in 80% of cases.[2] In 20% of cases, ITP is secondary to other illnesses, most commonly acute infections and chronic inflammatory processes, such as autoimmune and rheumatologic conditions; 1% to 5% of patients with chronic lymphocytic leukemia also develop ITP.[2,3] The incidence of ITP in adults ranges from 2 to 4 cases per 100 000 per year, with 2 peaks in age: first between 20 and 30 years of age, with a slight female predominance, and a larger peak after 60 years of age affecting men and women equally.[2,3] At presentation, patients with ITP may be asymptomatic, have mild mucocutaneous bleeding, or, in ~5%, have life-threatening bleeding, such as intracranial hemorrhage.[3] However, patients with ITP often report other symptoms, such as fatigue, and have reduced health-related quality of life.[3] Paradoxically, the risk of venous thromboembolism is higher in ITP patients compared with the general population, complicating the management of venous thromboembolism, given the associated bleeding risk.[3]

The pathophysiology of ITP is complex and incompletely understood. The conventional explanation is that platelets with autoantibodies bound to their surface are prematurely destroyed in the spleen, liver, or both through interaction with Fcγ receptors.[4] Autoantibodies can also induce complement-mediated[5] or desialylation-induced destruction of platelets,[6,7] as well as inhibit megakaryocyte function. Aged desialylated platelets are cleared via the hepatic Ashwell-Morell receptor (AMR).[8] Recent findings support the notion that opsonization of platelets with anti-GPIbα antibodies activates the platelets, resulting in the translocation of neuraminidase-1 to the surface, where it desialylates the platelets, thereby leading to Fc-independent hepatic clearance via the hepatic AMR.[6] Despite these elegant