the BTK inhibitor ibrutinib (PCI-32765). It is unclear if this is a direct effect or mediated by kinase inhibition. Sphingolipids are also known as mediators of mitochondrial apoptosis. Consistent with the antiapoptotic effect of glucosylceramide, BCR stimulation reduced the effect of the mitochondria-targeting drug ABT-737. Concomitant treatment with low doses of the kinase (and apparently UGCG) inhibitors GS-1101 and ibrutinib restored the activity of ABT-737 leading to CLL cell death. Thus, the 2 drugs may also be regarded as sensitizers for ABT-737, opening up the possibility for novel drug combinations.

The discovery adds novel aspects to our understanding of BCR function as well as the potential implications for drug therapy. It will help to explain changes in (sphingo-) lipid metabolism as well as BCR-triggered gene regulation in CLL. This opens up a whole new approach for treatment options, the mechanism of action and functional downstream effects of novel kinase inhibitors as well as many other drugs that act on the BCR or one of its signaling pathway components. CLL therapy continues to be a success story.

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

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6. Steininger C, Widhopf GF 2nd, Ghia EM, et al. Resistance to imatinib respond to second-generation TKIs.8-10 With these drugs being used more frequently as initial therapy, that we use the agent of choice to its full potential and avoid quick transition from one drug to another for questionable indications.

A frequent question now is whether results such as the ones reported here mean that all patients should be treated with a second-generation TKI. Taken at face value, we should always aim in cancer treatment to use our best agent first to have the best chance of rendering our patient free of disease for the longest time, and cured if possible. Our first shot is always our best shot. Nonetheless, one cannot disregard some important facts: (1) most patients do well with imatinib, (2) most patients with resistance to imatinib are still in chronic phase and in generally good condition, and (3) many patients with resistance to imatinib respond to second-generation TKIs. If one adjusts for the sequential use of effective therapy, the current event-free survival is 88% at 7 years compared with the unadjusted rate of 81%. 7 However, only 40% to 50% of patients with resistance to imatinib achieve a complete cytogenetic response with second-generation TKIs.8-10 With growing awareness of the relevance of early

responses, an argument can be made for using imatinib first and switch patients who are lagging behind early on. This is an attractive approach, but one without data that confirms that patients who fall behind on their response can catch up (in long-term outcome) after such intervention. Then there is the argument of what we would use if we start with a second-generation TKI and the patient develops resistance to it. This argument reminds me of a family anecdote when my father wanted to buy all the balloons from a balloon vendor for my infant brother many years ago. The balloon vendor would not sell them to my father because he would not have anything else to sell if he did. In cancer, using our best therapy first gives us the best long-term outcome, even if the patients who do not have an adequate response might be more difficult to treat. Despite all these arguments for and against, we have to be realistic that circumstances will exist that will mandate the use of one agent or the other, because of our medical expertise and interpretation of the data, or because of peripheral factors such as economics. Based on results such as the ones presented by Radich et al, second-generation TKI might give us the best outcome overall and would be preferred whenever possible. For patients for whom these options are not available or preferred, proper monitoring, suitable management of adverse events, and adequate dose optimization are of increasing relevance to offer each patient the opportunity for the best long-term outcome. With optimal management, our goal today ought to be that no patient should die of CML. And we should aim higher, to cure all patients with CML. If we are to accomplish this, continued research is needed and all patients should be included in clinical trials that help us understand the biology and optimal management of CML.

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Comment on Xu-Monette et al, page 3986

TP53 mutations and rituximab-CHOP

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In this issue of Blood, Xu-Monette and colleagues report the results of TP53 mutational profiles in a cohort of 506 de novo diffuse large B-cell lymphoma patients treated with rituximab-CHOP, and they concluded that TP53 mutation was an independent adverse factor for survival.1 Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma and is characterized by an aggressive clinical course. However, DLBCL exhibits considerable heterogeneity in terms of clinical, morphologic, molecular, and cytogenetic features. Gene expression profiling (GEP) studies have identified 2 primary molecular subgroups of DLBCL: germininal center B (GCB) cells and activated B cells (ABCs).2 The GCB subgroup shows better survival than the ABC subgroup, independent of the international prognostic index (IPI). In the past decade, the introduction of the humanized monoclonal anti-CD20 antibody rituximab (R) to the combination chemotherapy of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) has clearly improved the outcome of DLBCL.3 The improvement is mostly observed in patients with a low or intermediate risk based on the IPI and in the GCB subtype.4 The search for new biologic markers in neoplastic diseases is of major interest because they can provide a better understanding of the biology of the disease. They can also suggest the probability of treatment failure. In relapsed DLBCL patients, among those with early relapse and prior treatment with rituximab, the response rate of salvage therapy is only 46%, with a 25% 3-year progression-free survival (PFS).5 It is clear that a biomarker could be affected by new treatment,6 but conducting studies for designing more targeted treatment is essential. However, such a marker needs to be validated in a large cohort of patients. It should also be an independent parameter from clinical data and be much easier and less expensive to collect.

The choice for this study was the TP53 tumor suppressor gene, which plays an important role in the regulation of the cell cycle, cell proliferation, apoptosis, and genomic integrity. The p53 protein mediates cell-cycle arrest when cells experience stressful challenges, such as DNA damage, hypoxia, or oncogene activation, whereas mutant p53 protein results in cell-cycle dysregulation, genomic instability, and the uncontrolled proliferation of damaged cells (see figure). The presence of TP53 mutations has been associated with drug resistance, poor response to treatment, and short survival in several cancers, including DLBCL.7

In DLBCL patients treated with CHOP, the same group described that TP53 mutations were an adverse prognostic factor for survival but was restricted to patients with GCB-DLBCL.8 The focus of this new study

●●● LYMPHOID NEOPLASIA
CML: the good, the better, and the difficult choices

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