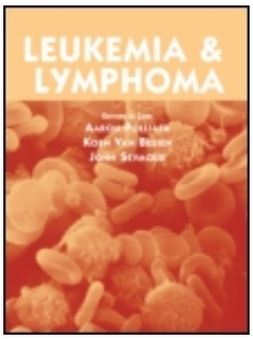

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COMMENTARY

ABT-199 partners with azacitidine to contest myeloid malignancies

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The challenge to clinicians when faced with older patients with acute myeloid leukemia (AML) is formidable. For patients over the age of 65, which constitutes two-thirds of the AML population, 5-year survival rates remain less than 10%, despite decades of clinical research. In stark contrast, researchers have made stunning progress in defining the genetic architecture of AML, cataloging a rich tapestry of mutations affecting transcription, tumor suppressor, methylation, kinase, chromatin modifier, cohesin and spliceosome function [1]. The discovery revolution, however, has also made the task of rational targeted therapy for this disease even more daunting. There are now numerous therapeutic targets identifiable in each case of AML, segregated into layers of initiating, pre-leukemic, leukemic and evolving sub-clones. How then will researchers successfully target a disease that is so fundamentally complex and characterized by chameleon-like qualities?

Part of the solution may lie in taking advantage of the inherent genomic complexity of AML, which appears to increase with age [2]. The cell protects itself from the accumulation of excessive and potentially dangerous genomic errors through activation of an endogenous cell suicide program, orchestrated by a family of pro-apoptotic BH3-only proteins which engage a number of pro-survival Bcl-2 related proteins, whose interactions have been deduced [3]. In order to tolerate increased genomic stress, transformed cells must acquire a counterbalanced survival advantage. Leukemic cells display seemingly invincible strength in the face of toxicity incurred by induction chemotherapy and stem cell transplant conditioning. In stark contrast, the feeble capacity of leukemic cells to survive *ex vivo* highlights a precarious sensitivity to apoptosis once removed from the protective bone marrow microenvironment. Therefore, identifying which survival factor the leukemia is most addicted to, and "surgically" neutralizing Bcl-2, Bcl-x, Bcl-w, Mcl-1 or A1, provides a strategy for targeting AML, thus avoiding the complexity linked to targeting the specific functions of multiple genomic drivers.

A major clinical breakthrough was heralded by the development of clinical-grade BH3-mimetics, with impressive responses observed in chronic lymphocytic leukemia (CLL) by drugs targeting Bcl-2, Bcl-x and Bcl-w (ABT-737/ABT-263) or Bcl-2 selectively (ABT-199). ABT-199 avoids on-target platelet toxicity related to Bcl-x, which limited the development of ABT-263 in AML [4,5]. Preclinical research supports the effectiveness of targeting Bcl-2 in AML [6], although other research suggests that Mcl-1 may also play an important role [7]. Building on recent work demonstrating the anti-leukemic potential of ABT-737 in AML in combination with azacitidine [8], Bogenberger and colleagues from the Mayo Clinic now show preliminary data in this issue [9] that the selective Bcl-2 inhibitor ABT-199 may also combine synergistically with azacitidine to induce leukemic cell death. ABT-199 has recently commenced clinical trial evaluation in human AML (NCT01994837). Once this is completed, a logical next step will likely involve demonstration of enhanced survival outcomes in combination with azacitidine, especially in elderly populations with oligoblastic AML considered unfit for intensive chemotherapy [10].

In favor of such an approach is the prior demonstration that ABT-737 in combination with azacitidine may induce leukemic death independently of p53, as does ABT-199 in 17p defective CLL [11,12]. This may be advantageous in adverse karyotype AML, which frequently harbors defective p53 [13]. Azacitidine has also been shown to suppress the expression of pro-survival Mcl-1, although sustained exposure to high-dose azacitidine for 48–72 h was necessary [11]. It remains unknown whether standard azacitidine schedules used in the clinic will be sufficient to suppress Mcl-1 in AML cells *in vivo*. It is also unknown whether ABT-199 will be as effective against newly diagnosed AML, compared to AML failing prior chemotherapy, as relapsed AML has been linked to higher expression of Mcl-1 [14]. It will be imperative for clinical trial investigators to focus attention on identifying molecular response signatures, which may enhance the likelihood of success in future registration studies. For example, preliminary results from a synthetic lethal screen of IDH1 mutant AML identified pro-survival dependence on Bcl-2 and 10-fold greater sensitivity of IDH1 mutant AML to ABT-199, compared to IDH wild-type AML

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[15]. This finding has particular relevance with recent identification of the importance of pre-leukemic IDH mutant AML clones with hematopoietic potential and a precursor for AML relapse despite intensive chemotherapy [16].

It must be highlighted that the findings in this issue by Bogenberger *et al*. regarding the role of ABT-199 in combination with azacitidine in AML, myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) are very preliminary. Only five cases in total were examined. The safety of this combination regarding hematopoietic stem cell function remains to be determined, along with the rationale for targeting Bcl-2 in MDS, with one publication suggesting that pro-survival Bcl-2 actually prevents leukemic transformation in MDS, although this mouse model finding may not relate to the setting of human MDS [17]. A barren and long neglected therapeutic landscape awaits, with expectant hope of the arrival of the BH3-mimetic class of drugs to the clinical AML stage. ABT-199 has already shown much early promise in potently targeting Bcl-2 in human cancer. In the coming months, the long-running controversy regarding whether pro-survival Bcl-2 is important for sustaining the viability of AML blast and leukemic stem cell function *in vivo* will finally be answered. We can only hope that this represents the beginning, rather than the end of yet another drug seeking to achieve "breakthrough" status in AML, a feat that has so far eluded prior contenders.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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