The Use of the BH3 Inhibitor, PI3K, To Overcome Stroma-Mediated Resistance.
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Although CLL cells can initially be killed by chemotherapy, the disease remains incurable. Sanctuary sites like lymph nodes and bone marrow may particularly protect CLL cells from the effects of otherwise effective therapies. Our laboratory developed a technique known as BH3 profiling, which assesses how close malignant cells are to undergoing apoptosis, and identifies the anti-apoptotic proteins necessary for malignant cell survival. We have preliminary data using BH3 profiling on primary CLL cells showing that stroma markedly decreases the likelihood of CLL cell apoptosis and that this effect can be partially reversed through PI3K inhibition. Moving forward, we seek to evaluate whether stroma-mediated treatment resistance in CLL patients can be overcome through a clinical trial of the pan-PI3K inhibitor XL-147. We will conduct a phase I/Ib trial of XL-147 in patients with relapsed/refractory CLL. Our primary objective in phase I is to determine the MTD of the drug in this patient population, and our primary objective in phase lb is to characterize toxicity at the MTD. Our secondary objectives will be to evaluate overall response to XL-147 and to determine whether BH3 profiling can serve as a predictive biomarker for response. Through this study, we hope to identify a new treatment option for patients with CLL and to determine which patients will benefit most from this novel agent.