signaling pathways provide drug resistance in cross-talk between the CLL cells and their milieu, not only in lymph nodes, but also in other tissue sites, such as the marrow. ABT-737 (as ABT-263) is under clinical investigation,12 and its cytoreductive effects in the marrow versus lymph nodes will be of major interest. This study also emphasizes the challenge to identify, target, and validate the key pathways of microenvironment-CLL interactions. While ABT-737 targets Bcl-2 and Bcl-xL with high potency, a panantagonist of Bcl-2 family antiapoptotic proteins is a desirable molecule. Gossypol analogs act as pan–Bcl-2 antagonists, but they have not reached the desired potency. Alternatively, CXCR4 antagonists13 and spleen tyrosine kinase (Syk) inhibitors14 therapeutically target and disrupt the leukemia microenvironment cross-talk in CLL and now are entering the clinical stage. These targets were developed and tested in the above-mentioned models,13,14 emphasizing the importance and validity of in vitro models for dissecting the tumor microenvironment in leukemia and beyond.

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Response

Microenvironment-dependent resistance to ABT-737 in chronic lymphocytic leukemia

We appreciate the comments of Burger and Gandhi on our article describing the resistance of chronic lymphocytic leukemia (CLL) cells to apoptosis induced by ABT-737, a specific BCL2 antagonist, after coculture with CD154-expressing fibroblasts in the presence of interleukin-4 (IL-4).1 The major question they raised is which signaling pathways provide drug resistance in cross-talk between the CLL cells and their milieu, not only in lymph nodes, but also in other tissue sites, such as the marrow. ABT-737 (as ABT-263) is under clinical investigation, and its cytoreductive effects in the marrow versus lymph nodes will be of major interest.

This study also emphasizes the challenge to identify, target, and validate the key pathways of microenvironment-CLL interactions. While ABT-737 targets Bcl-2 and Bcl-xL with high potency, a panantagonist of Bcl-2 family antiapoptotic proteins is a desirable molecule. Gossypol analogs act as pan–Bcl-2 antagonists, but they have not reached the desired potency. Alternatively, CXCR4 antagonists and spleen tyrosine kinase (Syk) inhibitors therapeutically target and disrupt the leukemia microenvironment cross-talk in CLL and now are entering the clinical stage. These targets were developed and tested in the above-mentioned models, emphasizing the importance and validity of in vitro models for dissecting the tumor microenvironment in leukemia and beyond.

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Greater understanding of the microenvironment-CLL interactions should enable improved targeted therapy of CLL and circumvent potential resistance problems to novel therapeutic agents, such as ABT-263, the orally active form of ABT-737, that is entering clinical trials in CLL. As ABT-737 and ABT-263 inhibit only BCL2, BCL-XL, and BCL-w, but do not inhibit MCL1 and BCL2A1, it may possibly be preferable to use a pan-antiapoptotic BCL2 family antagonist, although toxicities might be expected to be more severe with such antagonists. Several pan-BCL2 family antagonists have been proposed, including Obatoclax, gossypol, apogossypol, and chelerythrine. However, none of these compounds are BCL2 family–specific, and they appear to kill cells in a nonspecific manner.8–10 As Burger and Gandhi indicate, concurrent interference with microenvironment-CLL interactions by antagonizing interactions of CXCR4-CXCL12 and/or CD40-CD154 or use of inhibitors of BAFF, APRIL, or spleen tyrosine kinase may all be promising avenues to improve therapy of CLL either alone or in combination.1,9,11,12 However, all will require careful preclinical validation under situations that most closely mimic those in vivo to maximize clinical benefit and minimize possible toxicities.

Contribution: M.B. and M.V. performed the experiments; and all authors wrote the response.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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