

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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ABT-199 for Chronic Lymphocytic Leukemia



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H&O What is ABT-199?

JS ABT-199 is a small-molecule, highly specific inhibitor of intracellular interactions with the B-cell lymphoma 2 (Bcl-2) protein. Bcl-2 is a molecule involved in the physiologic process of modulating the life span of cells through inhibition of apoptosis. Many types of cancer, including chronic lymphocytic leukemia (CLL), exploit cellular pathways involving Bcl-2; overexpression and deregulation have been identified in several studies. In CLL, Bcl-2 regulates apoptosis and also appears to be involved in both the selection and maintenance of B cells, enabling them to accumulate.

ABT-263 (navitoclax) is an earlier version of a Bcl-2–targeting molecule that inhibited Bcl-2 but also other members of the same protein family, including Bcl-xL. Because Bcl-xL is involved in platelet life span, ABT-263 was associated with dose-limiting thrombocytopenia. ABT-199 is the result of efforts to create a Bcl-2 inhibitor that does not also inhibit Bcl-xL. As a result of inhibiting Bcl-2 alone, ABT-199 does not cause dose-related thrombocytopenia.

H&O How did the Bcl-2 pathway become a focus for research and drug development?

JS The role of Bcl-2 in cancer was first identified in other malignancies. The *BCL2* gene is involved in a translocation between chromosomes 14 and 18, an abnormality that is present in about 80% to 90% of follicular lymphomas and some subtypes of diffuse large B-cell lymphoma. The translocation leads to overexpression of Bcl-2. It was

the discovery of the involvement of *BCL2* in this translocation that led to the first cloning of this gene.

Although the translocation occurs in just these 2 cancer types, deregulation and overexpression of Bcl-2 occurs in a wide range of solid tumors and hematologic malignancies, including CLL, acute myeloid leukemia, mantle cell lymphoma, Waldenström macroglobulinemia, breast cancer, prostate cancer, small cell lung cancer, and others. Currently the research on ABT-199 is restricted to hematologic malignancies, but because Bcl-2 is involved in so many cancer types, this agent may turn out to be active, either alone or in combination, against other malignancies.

H&O How did CLL become a focus for ABT-199 studies?

JS In preclinical studies, CLL samples were found to be among the most sensitive to killing by ABT-199. Lymphoma, breast cancer, acute myeloid leukemia, and lung cancer cell lines were also variably sensitive, but clinical trial development is moving forward most rapidly with CLL.

H&O Could you discuss the results of preclinical and early clinical studies of ABT-199?

JS As mentioned earlier, Bcl-2 was most strongly validated as a potential therapeutic target through studies of navitoclax. In a phase 1 study of this agent for CLL, which was published in the *Journal of Clinical Oncology* in 2012, 35% of patients (9 out of 26) achieved a partial response, with stable disease lasting more than 6 months in 7 patients and a median progression-free survival of 25 months. Although

dose-limiting thrombocytopenia was a problem, the study validated Bcl-2 as an active target for treatment in CLL.

A substantial and elegant body of protein chemistry and medicinal chemistry research conducted by scientists at AbbVie in collaboration with researchers at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, led to the creation of ABT-199 as a sensitive and specific inhibitor of Bcl-2. A study published last year in *Nature Medicine* with Dr Andrew Souers as the first author demonstrated that ABT-199 maintained a high affinity for Bcl-2 but did not inhibit Bcl-xL or Bcl-W, other members of the Bcl family. Preclinical animal studies have shown no effect on platelet count.

The first 3 human patients treated with ABT-199 experienced tumor lysis with the first 24 hours of administration but did not manifest drug-related thrombocytopenia.

H&O What are the current outcomes for CLL with today's standard treatments?

JS Up to one-third of patients diagnosed with CLL have indolent and clinically acquiescent disease that will never require treatment. The majority of patients who require treatment have favorable outcomes with currently available chemotherapy regimens. The standard of care—for patients who can tolerate it—is a 3-drug combination with fludarabine, cyclophosphamide, and rituximab.

For CLL, there are 3 main areas of unmet need: elderly patients or those with comorbidities that leave them unable to tolerate standard therapy; patients with disease that is refractory to the current standard of care; and patients with a deletion of chromosome 17, who tend to have very poor outcomes with currently available therapies.

H&O What other novel approaches to the treatment of CLL are approved or being investigated?

JS There are 3 other approaches that have received FDA approval for CLL. These drugs include obinutuzumab (Gazyva, Genentech) and ofatumumab (Arzerra, GlaxoSmithKline), which are second-generation anti-CD20 monoclonal antibodies; idelalisib (Zydelig, Gilead Sciences), which is a phosphatidylinositol 3-kinase (PI3K) δ inhibitor indicated for relapsed disease; and ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech), which is indicated for the first-line treatment of CLL patients with a 17p deletion. A study published earlier this year in the *New England Journal of Medicine* with Dr Richard Furman as the first author found that idelalisib plus rituximab led to significantly improved progression-free survival, response rate, and overall survival compared with rituximab alone among patients with relapsed disease.

ABT-199 is showing substantial promise, and so are these other agents with novel mechanisms. These clinical developments raise the exciting possibility of new combinations and chemotherapy-free treatment regimens that may be extremely well tolerated in both the short- and long-term.

H&O What are the most recent data reported for ABT-199?

JS In 2014, I presented results from studies of ABT-199 for CLL at the annual meetings of both the American Society for Clinical Oncology (ASCO) and the European Hematology Association (EHA).

The study presented at ASCO was a phase 1, single-agent, dose-escalation trial with 105 patients enrolled at the time of the presentation. The median age of the patients was 66 years, and the patients had received a median of 4 prior therapies. We used a stepwise dose-escalation schema in order to mitigate the risk of tumor lysis syndrome that had been observed with ABT-199 in earlier phases of development. Dosing began at 20 mg per day, with the compound given orally, and escalated to a maximum dose of 1200 mg. There was no dose-limiting toxicity, but pharmacokinetic and pharmacodynamic modeling suggested that the optimal efficacy was reached at 400 to 600 mg.

A total of 63 patients were evaluable for efficacy. The study demonstrated marked efficacy, with an objective response rate of 79% and a median duration of response of 20.5 months. Computed tomography scans showed that 84% of patients had at least a partial remission in lymph node masses, with patients reaching a 50% reduction by a median of 6 weeks. Among the 23 patients with 17p deletion, the objective response rate was 78%.

Eight patients discontinued the study owing to adverse events. The most common side effects were moderate and manageable, and included diarrhea (37% of patients), nausea (36%), neutropenia (35%), upper respiratory tract infection (29%), and fatigue (27%). Infectious complications were less common, and 6% of patients experienced grade 3 or 4 neutropenia.

One of the most encouraging findings from this study regarded bone marrow clearance. Ninety percent of patients in this study had at least a 50% clearance of their bone marrow infiltrate.

H&O Why is this finding important?

JS The degree of bone marrow clearance is a reflection of the potency of the compound and the degree of leukemic cell eradication. The high percentage of bone marrow clearance seen in this phase 1 study raises the possibility of exploring a treatment paradigm with time-limited drug exposure followed by a period of drug withdrawal.

A treatment resulting in a more limited response, with significant detectable disease remaining, means that ongoing treatment is more likely to be needed.

H&O How do the results of this phase 1 study compare with those of current standard treatments for CLL?

JS This assessment is difficult to make, in part because the regimens have not been directly compared in a large, randomized clinical trial, and also because the patients in this study were not anticipated to benefit from standard treatment. They had received a median of 4 prior therapies, with some having received up to 11 prior treatments. Eighty-five percent had previously received fludarabine, the most potent of the currently available standard chemotherapy agents, and 60% of patients had disease refractory to fludarabine, a factor that is typically predictive of a low likelihood of response to other treatments.

H&O What are the next steps for ABT-199?

JS A randomized phase 3 study comparing ABT-199 plus rituximab with bendamustine plus rituximab in relapsed/refractory CLL is now underway. This approach follows a phase 1 study of ABT-199 (400 mg) plus rituximab that Dr Andrew Roberts presented at this year's EHA meeting. The EHA study showed a complete remission rate of 36% within a very short follow-up. Although not a direct comparison, the remission rates achieved with this combination were higher than those seen with ABT-199 as a single agent.

In addition, a phase 2 study investigating ABT-199 for patients with CLL and a 17p deletion has completed

enrollment. Again, the selected dose level for ABT-199 is 400 mg, based on results from the phase 1 study.

Based on the observation in the phase 1 studies that a significant proportion of patients achieved complete remission and had no detectable disease by high-sensitivity flow cytometry, the potency and efficacy of ABT-199 appear extremely promising. In the preclinical setting, ABT-199 showed synergy with several compounds, including anti-CD20 antibodies, chemotherapy drugs, and the PI3K δ inhibitor. The potential promise of these combinations is very exciting.

Disclosure

Dr Seymour is a member of the advisory boards of and has received honoraria from AbbVie, Genentech, and Roche.

Suggested Reading

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2014;370(11):997-1007.

Roberts AW, Ma S, Kipps S, et al. ABT-199 (GDC-0199) combined with rituximab (R) in patients with relapsed / refractory (R/R) chronic lymphocytic leukemia (CLL): interim results of a phase 1B study [EHA abstract S703]. *Haematologica.* 2014;99(suppl 1).

Roberts AW, Seymour JF, Brown JR, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase 1 study of navitoclax in patients with relapsed or refractory disease. *J Clin Oncol.* 2012;30(5):488-496.

Seymour JF, Davids MS, Pagel JM, et al. ABT-199 (GDC-0199) in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic leukemia: high complete response rate and durable disease control [ASCO abstract 7015]. *J Clin Oncol.* 2014;32(5)(suppl).

Seymour JF, Davids MS, Pagel JM, et al. ABT-199 (GDC-0199) in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: high response rates among patients with high risk disease features including unmutated IGHV [EHA abstract S702]. *Haematologica.* 2014;99(suppl 1).

Souers AJ, Levenson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med.* 2013;19(2):202-208.