

# Highlights From the 2014 Congress of the European Hematology Association

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## NHL Responds to ABT-199 in Phase 1 Trial

The investigational agent ABT-199 has antitumor activity in several subtypes of non-Hodgkin lymphoma (NHL), according to results from a phase 1 trial. ABT-199 is a selective, orally bioavailable, small-molecule inhibitor of the antiapoptotic protein BCL2.

The study, which was presented by Dr Matthew S. Davids from Dana-Farber Cancer Institute in Boston, Massachusetts, included 44 patients. Of these, 15 had mantle cell lymphoma (MCL), 11 had follicular lymphoma (FL), 10 had diffuse large B-cell lymphoma (DLBCL), 4 had Waldenström macroglobulinemia (WM), 2 had marginal zone lymphoma (MZL), 1 had primary mediastinal B-cell lymphoma (PMBCL), and 1 had multiple myeloma (MM). Patients received continuous, once-daily dosing of ABT-199 until progressive disease or unacceptable toxicity. The final doses ranged from 200 to 900 mg.

The overall response rate in 40 patients evaluable for efficacy was 48%, with a median time on study of 3.9 months. This included 9 of the 12 MCL patients (1 complete response, 3 of the 11 FL patients, 3 of the 9 DLBCL patients (1 complete response), 3 of the 4 WM patients, 1 of the 2 MZL patients, and the 1 patient with PMBCL. Neither the patient with PMBCL nor the one with MM responded to treatment. All of the responses in patients with DLBCL and FL occurred at doses of at least 400 mg.

The most common adverse events, affecting at least 20% of the patients, were nausea, upper respiratory tract infection, diarrhea, and fatigue. Anemia, neutropenia, and thrombocytopenia all occurred in more than 3 patients. Two patients experienced a dose-limiting toxicity at the target dose of 600 mg (neutropenia and febrile neutropenia), and grade 3 laboratory tumor lysis syndrome occurred after the initial dose in 1 patient with bulky MCL and 1 patient with DLBCL.

The researchers concluded that ABT-199 monotherapy showed antitumor activity across the range of ABT-199 doses in several subtypes of NHL, especially MCL and WM. Higher doses of ABT-199 also produced responses in DLBCL and FL.

Dose escalation is continuing to determine the maximum tolerated dose and the recommended phase 2 dose.

Davids MS, Seymour JF, Gerecitano JF, et al. Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory non-Hodgkin lymphoma: responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses [EHA abstract S1348]. *Haematologica*. 2014;99(suppl 1).

## CLL Responds to ABT-199 in Phase 1 Studies

ABT-199 has a high response rate in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), according to two phase 1 studies undertaken to determine the maximum tolerated dose and the recommended phase 2 dose.

For the first study, researchers including Dr John F. Seymour of the Peter MacCallum Cancer Centre in Melbourne, Australia, administered ABT-199 monotherapy to patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL). Patients received the agent until disease progression, intolerance, or withdrawal. After cases of tumor lysis syndrome occurred early in the trial, the researchers lowered the starting dose to 20 mg per day and altered the dose escalation schedule to reflect weekly dose increases to the target cohort dose of 150 to 1200 mg per day.

A total of 93 patients were enrolled as of January 2014, with a median follow-up of 6.1 months. Of these patients, 24% had del(17p) and 59% had fludarabine-refractory CLL. Of the 42 patients with *IGHV* status available, 32 had unmutated *IGHV*. The median number of prior therapies was 4.

Seventy-six percent of the patients responded to treatment; 20% had a complete response and 56% had a partial response. The median duration of response was 20.5 months, and 91% of the patients with a complete response and 67% of those with a partial response remained free of disease after 12 months. The high rate of complete response or partial response extended to patients who had unmutated *IGHV* (17% and 57%, respectively), chromosome 17p deletions (14% and 57%), or fludarabine-refractory CLL (15% and 59%).

The most common adverse events were neutropenia, diarrhea, nausea, upper respiratory tract infection, and fatigue. Grade 3 and 4 adverse events included neutropenia, anemia, tumor lysis syndrome, thrombocytopenia, hyperglycemia, and febrile neutropenia and hypokalemia.

For the second study, researchers including Dr Andrew W. Roberts of the Royal Melbourne Hospital and the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, administered increasing amounts of ABT-199 in combination with rituximab (Rituxan, Genentech/Biogen Idec) until disease progression. The final cohort dose of ABT-199 was 200 to 600 mg per day.

A total of 37 patients were enrolled as of January 2014, with a median follow-up of 4.8 months. Of these patients, 9 had del(17p), 9 had fludarabine-refractory CLL, and 9 had rituximab-refractory CLL. Of the 42 patients with *IGHV* status available, 32 had unmutated

*IGHV*. The median number of prior therapies was 2. A total of 6 patients discontinued treatment.

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A total of 18 patients completed treatment or discontinued prior to completion. Of these, 39% achieved a complete remission and 39% achieved a partial remission.

The most common adverse events in both studies included neutropenia, diarrhea, and nausea. Grade 3 and 4 adverse events included neutropenia, anemia, and thrombocytopenia. One fatal episode of tumor lysis syndrome occurred in the second study.

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).

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).

**Commentary:** In 1960, Dr William Dameshek published his belief that diseases such as CLL were not lymphoproliferative disorders, but rather lympho-accumulative disorders: the cells were not rapidly growing, but were unable to die. This process of programmed cell death subsequently became known as apoptosis, from the Greek for "falling off." The identification of the *BCL2* gene and its associated protein led to a better understanding of the mechanisms by which malignant B cells outlived their predetermined lifespan and became resistant to standard treatments. *BCL2* has been an elusive target for therapy until recently.

The most effective agent to date for lymphomas and CLL is ABT-199. While much of the recent attention has focused on the BTK and PI3-kinase pathways, data have been accumulating for ABT-199. These 2 abstracts confirmed the results of earlier trials that demonstrated impressive activity with an acceptable safety profile. The complete response rate in CLL was higher than that reported for either ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotch) or idelalisib (Zydelig, Gilead Sciences). However, as with these drugs, combination strategies need to be developed to bring this drug to its true potential in the management of patients with lymphomas and CLL.

## NHL Responds to Polatuzumab Vedotin and Pinatuzumab Vedotin in Phase 2 Trial

The antibody-drug conjugates polatuzumab vedotin (PoV) and pinatuzumab vedotin (PiV) showed efficacy against relapsed or refractory NHL when used in combination with rituximab, according to a recent phase 2 study.

For the study, researchers led by Dr Franck Morschhauser of Hôpital Claude Huriez in Lille, France, randomly assigned 121 patients with relapsed or refractory DLBCL or FL to receive PoV plus rituximab or PiV plus rituximab. Patients received the agents every 21 days for 1 year, or until disease progression or unacceptable toxicity occurred. Nearly half the patients (46%) were refractory to rituximab. The median number of treatment cycles was 5 for the DLBCL patients and between 6 and 8.5 for the FL patients.

Among 74 patients with DLBCL who were available for follow-up, the efficacy of PoV and PiV were similar: the complete response rates were 14% and 19%, respectively, and the partial response rates were 38% and 35%, respectively. Among the 41 patients with FL who were available for follow-up, the efficacy of PoV appeared to be higher than that of PiV based on a complete response rate of 30% vs 5% (the partial response rate was 30% vs 62%).

The overall safety profiles of both regimens were similar. Adverse events included fatigue, diarrhea, nausea, peripheral neuropathy, and constipation, and grade 3 or 4 adverse events included neutropenia, diarrhea, dyspnea, febrile neutropenia, and peripheral neuropathy. More than one-third of patients had serious adverse events (36%), and nearly one-third discontinued treatment (after a median of 5 doses) because of adverse events (31%).

Studies of PoV plus rituximab in combination with chemotherapy, and with measures to reduce peripheral neuropathy, are ongoing.

Morschhauser F, Flinn I, Advani R, et al. Preliminary results of a phase II randomized study (ROMULUS) of polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed/refractory non-Hodgkin lymphoma (NHL) [EHA abstract S1349]. *Haematologica*. 2014;99(suppl 1).

**Commentary:** The development of rituximab arguably has been the most important advance in the treatment of B-cell malignancies, improving survival in most of the common B-cell histologies. Nevertheless, considerable room for improvement remains, and numerous attempts have been made to improve on the antibody against CD20. Other monoclonal antibodies, including a gaggle of anti-CD20s, have been developed. Whether any is superior to rituximab is a subject of controversy. Radioimmunotherapy has languished and is used in a trivial number of patients per year, to the point where

recent classes of hematology-oncology fellows at my institution were totally unfamiliar with the concept. Bispecific antibodies are in development.

The current abstract (I was one of the coinvestigators) describes results with a pair of antibody-drug-conjugates, PoV and PiV. These constructs include a monoclonal antibody linked to the same toxin as in brentuximab vedotin (Adcetris, Seattle Genetics), which is exceptionally active in Hodgkin lymphoma. Although both agents demonstrated activity, especially when combined with rituximab, the activity of PoV-rituximab appeared to be better and this agent will be the one pursued. However, how to optimize such potentially important agents is unclear. Should they be used in combinations with other novel agents, as substitutes for more conventional drugs in standard regimens, or, less likely, as consolidation treatment following an induction regimen?

### Resistance Mutations Linked to Disease Progression With Ibrutinib in CLL

Despite the high rate of progression-free survival with ibrutinib in patients with CLL, some patients experience progressive disease while on the agent. Now, a study adds to the evidence suggesting that mutations in *BTK* and *PLCγ2* are associated with progressive disease while the patient is on ibrutinib. Ibrutinib is a Bruton's tyrosine kinase inhibitor.

For the study, Dr Kami Maddocks and colleagues at Ohio State University in Columbus, Ohio, evaluated 267 patients who were participating in 3 trials of ibrutinib at their institution. A total of 196 patients were receiving ibrutinib alone, and 71 were receiving ibrutinib in combination with ofatumumab (Arzerra, GlaxoSmithKline).

After a median follow-up of 16.6 months (range, <1 to 42 months), 201 patients were still on ibrutinib and 66 had discontinued the agent. The reasons for discontinuation included progressive disease in 24 patients, toxicity in 8 patients, and transplantation in 4 patients. Of the patients with progressive disease, 16 had Richter's transformation and 8 had progressive CLL. A total of 9 patients with Richter's transformation and 3 patients with progressive CLL had died, although the median survival from date of study had not been reached in progressive CLL.

Ion Torrent deep sequencing was performed at both baseline and relapse on a subset of patients who experienced progressive CLL. This testing revealed that all 6 patients had mutations in *BTK* or *PLCγ2*. As previously reported, 1 patient had mutations in both *PLCγ2* and in *BTK C481S*, 2 patients had a mutation in *BTK C481S*,

1 had a mutation in *BTK C481F*, and 1 had a mutation in *PLCγ2 R665W*. In addition, 2 patients who relapsed outside of the studies had a mutation in *BTK C481S*.

The authors concluded that ibrutinib is a well-tolerated and effective therapy, and that their results using deep sequencing confirm the results of other reports that have found a link between *BTK* and *PLCγ2* mutations and progressive disease among patients taking ibrutinib for CLL.

Maddocks K, Ruppert AS, Lozanski G, et al. Disease progression on ibrutinib therapy is uncommon and is associated with the acquisition of resistance mutations: a single center experience of 267 patients [EHA abstract S1340]. *Haematologica*. 2014;99(suppl 1).

**Commentary:** This report confirms results from other studies that resistance to ibrutinib relates, at least in part, to mutations in *BTK* and *PLCγ2*. Second-generation agents are in development that may circumvent this obstacle. However, as ibrutinib and other small molecules become more widely used, other mechanisms of resistance also may develop. This possibility further strengthens support for the position that treatment regimens should be developed to provide a deeper response, with finite duration of treatment.

### Ibrutinib Bests Ofatumumab in Trial of Previously Treated CLL

Ibrutinib improved progression-free survival, overall survival, and response rate more than ofatumumab among patients with previously treated CLL or SLL, according to a phase 3 trial.

Results from the trial, called RESONATE (Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia), were presented by Dr Peter Hillmen of the Leeds Teaching Hospitals in Leeds, United Kingdom.

For the study, researchers randomly assigned 391 patients with relapsed or refractory CLL or SLL to receive ibrutinib or the anti-CD20 antibody ofatumumab. After a median of 9.4 months, progression-free survival was significantly longer with ibrutinib than with ofatumumab (median not reached vs 8.1 months; hazard ratio [HR], 0.215; CI, 0.146-0.317;  $P < .0001$ ). This represented a 78.5% reduction in the risk of progressive disease or death. Overall survival also was longer with ibrutinib than with ofatumumab (median not reached for both arms; HR, 0.434; CI 0.238-0.789,  $P = .0049$ ). This represented a 56.6% reduction in the risk of death. Finally, the overall response rate was significantly higher with ibrutinib than with ofatumumab (42.6% vs 4.1%;  $P < .0001$ ). A separate analysis of progression-free survival, overall survival, and overall response rate in patients with

del(17p13.1) or those with disease refractory to purine analogue also favored ibrutinib.

In the publication of their results in the *New England Journal of Medicine* after the conference, the researchers concluded that “ibrutinib was superior to ofatumumab in difficult-to-treat patients with refractory CLL or SLL, as measured by progression-free survival, overall survival, and response.” They pointed out that this improvement was observed across all subgroups that were examined, including patients who were resistant to chemoimmunotherapy and those with del(17p13.1).

Hillmen P, Brown JR, O'Brien S, et al. Randomized comparison of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia / small lymphocytic lymphoma: results from the phase III PCYC-1112 RESONATE™ trial [EHA abstract S693]. *Haematologica*. 2014;99(suppl 1).

Byrd JC, Brown JR, O'Brien S, Barrientos JC, et al; RESONATE investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.

**Commentary:** Ibrutinib has provided exciting activity in patients with relapsed and refractory CLL as well as in older, treatment-naïve patients. Of importance has been its impressive activity in patients with deletions in 17p. The present study demonstrates that ibrutinib is more effective than ofatumumab. The latter was associated with a rather pathetic complete and overall response rate, supporting the limited use of the agent in the hematology-oncology community. However, we now have 2 approved regimens in previously treated CLL: ibrutinib and idelalisib-rituximab. Which of these 2 approaches is preferable remains to be determined, yet the approval indications are quite different, the latter being for patients who are unable to tolerate chemotherapy because of myelotoxicity and/or comorbidities. The future of both will likely be in novel combinations, while the future of ofatumumab continues to fade.

## Bleomycin and Dacarbazine Essential to ABVD for Early-Stage HL

Bleomycin and dacarbazine are essential components of therapy for early-stage favorable Hodgkin lymphoma (HL), the final results of a study confirm. The agents are part of standard treatment for this condition, which consists of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved-field radiotherapy (IFRT).

The German Hodgkin Study Group (GHSG) HD13 study, presented by Dr Karolin Behringer of the

University Hospital of Cologne, Germany, included 1710 patients with early-stage favorable HL. Starting in January 2003, patients were randomly assigned to receive 2 cycles of ABVD, ABV, AV, or AV, followed by IFRT. Patients in the AV and ABV arms had elevated rates of adverse events, so these arms were closed in September 2005 and February 2006, respectively, and recruitment continued in the ABVD and AVD arms. A total of 1710 patients were randomized into the 4 treatment arms by September 2009, and 1502 patients were part of the final analysis because they did not fulfill any exclusion criteria.

After 5 years of treatment, the freedom from treatment failure (FFTF) rate was 93.1% with ABVD, 81.4% with ABV, 89.2% with AV, and 77.1% with AV. The FFTF rate was lower in the ABV and AV arms compared with ABVD, and the noninferiority of AV compared with ABVD could not be confirmed with respect to the predefined margin. Overall survival was excellent and did not differ between the treatment arms, with 5-year estimates of 97.6% for ABVD, 94.1% for ABV, 97.6% for AV, and 98.1% for AV. The rate of acute toxicities, which included leukopenia, hair loss, and nausea/vomiting, ranged from 26.3% with AV to 32.7% with ABVD.

The researchers concluded that neither dacarbazine nor bleomycin could be safely omitted from the ABVD regimen without a relevant loss in efficacy. The reduction in tumor control did not translate into poorer overall survival, however.

Behringer K, Goergen H, Borchmann P. Impact of bleomycin and dacarbazine within the ABVD regimen in the treatment of early-stage favorable Hodgkin lymphoma: final results of the GHSG HD13 trial [EHA abstract S1290]. *Haematologica*. 2014;99(suppl 1).

**Commentary:** The investigators are to be commended for conducting this important study. However, there is considerable room for disagreement with their conclusions. There was a difference of nearly 4% in FFTF that favored ABVD over AV, but without a survival advantage and with considerably greater toxicity. Thus, my interpretation of these results is that they support prior impressions that bleomycin adds little to efficacy but considerable unnecessary toxicity. I believe these data show that bleomycin can be eliminated from the ABVD without compromising the outcome of patients with HL.

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