



## Ofatumumab

Updated: April 15, 2020.

## OVERVIEW

### Introduction

Ofatumumab is a recombinant human monoclonal antibody to CD20 a cell surface antigen found on pre-B and mature B lymphocytes and which is approved for use in resistant chronic lymphocytic leukemia. Ofatumumab therapy has not been associated with serum enzyme elevations during therapy or to cases of idiosyncratic, clinically apparent liver injury. However, ofatumumab has potent immunosuppressive activity and its use has been reported to be associated with cases of reactivation of inactive hepatitis B which can be severe and can result in fatality.

### Background

Ofatumumab (oh" fa toom' ue mab) is a human monoclonal IgG1 antibody to the cell surface antigen CD20 (also known as human B lymphocyte restricted differentiation antigen: Bp35), which is found on mature B cells as well as 90% of neoplastic B cell such as occur in chronic lymphocytic leukemia (CLL). CD20 is not present on pro-B cells, hematopoietic stem cells, normal plasma cells or other normal lymphocytes, circulating cells or tissues. Engagement of ofatumumab with CD20 leads to B cell lysis and depletion of circulating and tissue B cells for an extended period, up to 6 to 8 months. There is an accompanying mild decrease in IgM, but no change in IgG or IgA levels. Ofatumumab was approved for use in previously treated, resistant chronic lymphocyte leukemia in the United States in 2009. Ofatumumab is available in liquid solution in single use vials of 100 and 1000 mg (20 mg/mL) under the brand name Arzerra. The dose and regimen varies by indication, but it is usually given intravenously in 300 to 2000 mg amounts in 28 day cycles. Common side effects include infusion reactions, chills, fever, nausea, diarrhea, fatigue, dyspnea, cough, bronchitis, pneumonia, skin rash, neutropenia and infections. Less common, but potentially severe side effects include cutaneous reactions (Stevens Johnson syndrome), tumor lysis syndrome, prolonged neutropenia, thrombocytopenia and anemia. Because of the potential severity of infusion reactions, premedication with antihistamines, acetaminophen and corticosteroids is recommended, and ofatumumab should be administered under close medical observation.

### Hepatotoxicity

Serum aminotransferase elevations are uncommon during ofatumumab therapy and rarely mentioned in large clinical trials of its use in CLL and autoimmune diseases. Clinically apparent liver injury has not been reported with ofatumumab therapy either in prelicensure clinical trials or subsequent to its more widescale clinical use.

On the other hand, ofatumumab is a potent immunosuppressive agent and has been reported to cause reactivation of hepatitis B by the FDA. However, there have been no examples of reactivation published in the medical literature and specific features of the reactivation caused by ofatumumab have not been described.

Typically, HBV reactivation is associated with acute hepatocellular injury similar to acute viral hepatitis that can be severe and lead to acute liver failure and death or need for emergency liver transplantation. If detected early, however, therapy with antiviral agents can blunt the severity of injury. In contrast, rituximab, another monoclonal antibody to CD20 that has been extensively used for several decades, is perhaps the best and mostly commonly described cause of HBV reactivation. Because ofatumumab, like rituximab, is a monoclonal antibody to CD20, it should have a similar effect on inactive or latent hepatitis B.

Reactivation typically occurs in patients who are HBsAg carriers with inactive hepatitis B who undergo chemotherapy for cancer. Reactivation can also occur in persons who have recovered from hepatitis B, who have no detectable HBsAg but have antibody to hepatitis B core antigen (anti-HBc), with or without antibody to HBsAg (anti-HBs) in serum. The onset of liver injury is delayed and may occur after 3 to 6 monthly courses of immunosuppressive therapy. The usual sequence of events is appearance of rising levels of HBV DNA in serum shortly after chemotherapy is started, followed by a rise in levels of HBsAg and HBeAg. When therapy is stopped and immune reconstitution has begun, serum ALT and AST levels start to rise followed by symptoms and jaundice. Reactivation of hepatitis B tends to be severe and the mortality rate in jaundiced cases exceeds 10%. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Restarting chemotherapy can result in recurrence of injury, although concurrent antiviral treatment may block recurrence.

Reactivation of HBV in persons who have resolved hepatitis B (anti-HBc without HBsAg in serum) is usually referred to as “reverse seroconversion”, and reactivation in persons with preexisting HBsAg in serum as “typical” or classical HBV reactivation. The two forms of reactivation have somewhat different clinical, biochemical and virology courses. In general, patients with reverse seroconversion have received more rigorous immunosuppression, the latency until onset is longer, peak levels of HBV DNA are lower, and the disease course is more severe than in patients with typical reactivation. The time to appearance of clinically apparent reactivation tends to be 3 to 6 months in patients with typical reactivation, but 12 to 36 months in those with reverse seroconversion. Outcomes may also be different, reverse seroconversion tending to be more severe and more likely to resolve with disappearance of HBsAg than typical reactivation. Exceptions occur in both situations; however, some patients with reverse seroconversion do not revert back to being HBsAg negative, particularly those who have had hematopoietic cell transplantation (HCT). In addition, some patients with classic reactivation of hepatitis B ultimately clear HBsAg as a result of the acute liver injury. Both forms of reactivation appear to be ameliorated by early intervention with oral antiviral therapy, but institution of therapy after appearance of clinical disease and jaundice may not be effective and many instances of fatal reactivation have occurred despite treatment with oral antiviral agents. Many cases of reverse seroconversion have been reported with rituximab therapy; the occurrence with ofatumumab has been implied, but specific cases have not been published.

Likelihood score: E\* (unproven but suspected cause of clinically apparent liver injury).

## Mechanism of Injury

The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to viral antigens. Injury generally arises after immunosuppressive or cancer chemotherapy has stopped or between courses of treatment. Rituximab is also known to cause an acute autoimmune-like hepatitis, unrelated to reactivation. Ofatumumab has not been shown to cause this type of drug-induced liver injury.

## Outcome and Management

Guidelines for management of patients who are to receive ofatumumab recommend routine screening for hepatitis B before starting treatment. Screening should include tests for HBsAg and anti-HBc (and perhaps also

anti-HBs as this may help in management). Prophylaxis with a potent oral, antiviral agent effective against hepatitis B is recommended for all persons who have HBsAg in serum and is suggested for those with anti-HBc without HBsAg. An alternative approach is careful monitoring for HBV DNA during therapy and early institution of antiviral therapy if levels rise. This approach, however, is problematic in that reactivation may occur late during chemotherapy or even after it is completed. The choice of antiviral agents includes lamivudine, telbivudine, adefovir, tenofovir or entecavir. All are given once a day and are extremely well tolerated. Lamivudine is less expensive than the other agents, but is associated with a high rate of antiviral resistance, particularly if given for more than 6 months. Tenofovir and entecavir are the most potent and have high barriers to antiviral resistance, which is important if long term therapy is planned. However, there are no prospectively acquired controlled studies to support use of one of these agents over another. Finally, the appropriate duration of treatment is unclear. The typical recommendation is to continue antivirals for at least 6 months after stopping cancer chemotherapy, but cases of reactivation following withdrawal of antiviral therapy (including fatal instances) have been described and some degree of monitoring during withdrawal of antiviral therapy is appropriate with early re-intervention if HBV DNA levels rise. In patients with anti-HBc without HBsAg, boosting titers of anti-HBs before or in-between treatment courses may be helpful in preventing reactivation. However, patients with lymphoma or autoimmune conditions and those who are receiving ofatumumab generally have poor responses to vaccination and this approach has not been critically evaluated in prospective controlled studies.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Ofatumumab – Arzerra®

### DRUG CLASS

Antineoplastic Agents

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ofatumumab	679818-59-8	Monoclonal Antibody	Not Available

## ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2020

Abbreviations: CLL, chronic lymphocytic leukemia; HCT, hematopoietic cell transplantation; TNF, tumor necrosis factor; PML, progressive multifocal leukoencephalopathy.

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

*(Review of hepatotoxicity of immunosuppressive agents mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the tumor necrosis factor [TNF] alpha antagonists"; no specific discussion of ofatumumab).*

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

*(Textbook of pharmacology and therapeutics).*

Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2009/125326s000\\_MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125326s000_MedR.pdf) (pages 102-181).

*(FDA website with medical review that formed the basis of the initial approval of ofatumumab as therapy for CLL mentions that there were no hepatic deaths and few liver related serious adverse events but recommended product label warning about reactivation of HBV because of the experience with rituximab).*

Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol.* 2000;62:299–307. PubMed PMID: 11055239.

*(Among 71 Chinese patients with HBsAg who underwent cancer chemotherapy [not with rituximab] for various malignancies, 15 developed reactivation of HBV, including 6 with jaundice and 3 with acute liver failure, but none died).*

Hagenbeek A, Gadeberg O, Johnson P, Pedersen LM, Walewski J, Hellmann A, Link BK, et al. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood.* 2008;111:5486–95. PubMed PMID: 18390837.

*(In a pilot study of ofatumumab in 40 patients with refractory lymphoma, "no significant changes in serum chemistry were observed").*

Coiffier B, Lepage S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MH, Wooldridge J, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood.* 2008;111:1094–100. PubMed PMID: 18003886.

*(Pilot study of ofatumumab in escalating doses once weekly for 4 weeks in 33 patients with refractory CLL, the maximum tolerated dose was not reached, one patient developed "cytolytic hepatitis"; a 74 year old man who had elevated tests the day of the first infusion, but also had abnormal values before therapy).*

Østergaard M, Baslund B, Rigby W, Rojkovich B, Jorgensen C, Dawes PT, Wiell C, et al. Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, phase I/II study. *Arthritis Rheum.* 2010;62:2227–38. PubMed PMID: 20506254.

*(Two studies of ofatumumab in patients with resistant rheumatoid arthritis given two infusions of ofatumumab [at 3 different doses] or placebo 2 weeks apart in 264 patients; B cell depletion occurred in all doses and response rates ranged from 40-49% [vs 11% in controls]; side effects were common, but usually mild to moderate in severity and no significant changes were found in routine laboratory results).*

Ofatumumab (Arzerra) for CLL. *Med Lett Drugs Ther.* 2010;52(1341):51–2. PubMed PMID: 20585286.

*(Concise review of efficacy, safety and cost of ofatumumab in CLL shortly after its approval in the US; mentions that severe side effects include infusion reactions, cytopenias, opportunistic infections and progressive multifocal leukoencephalopathy [PMLE]; no mention of hepatotoxicity or ALT elevations).*

Taylor PC, Quattrocchi E, Mallett S, Kurrasch R, Petersen J, Chang DJ. Ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naive, rheumatoid arthritis patients with an inadequate response to

methotrexate: a randomised, double-blind, placebo-controlled clinical trial. *Ann Rheum Dis.* 2011;70:2119–25. PubMed PMID: 21859685.

*(Among 260 patients with rheumatoid arthritis treated with ofatumumab or placebo [two infusions 2 weeks apart], clinical responses at week 24 were more frequent with ofatumumab [50%] than placebo [27%], and common side effects were rash [21%] and urticaria [12%], but there were no liver related serious adverse events and ALT elevations were not reported).*

Nightingale G. Ofatumumab: a novel anti-CD20 monoclonal antibody for treatment of refractory chronic lymphocytic leukemia. *Ann Pharmacother.* 2011;45:1248–55. PubMed PMID: 21896924.

*(Review of the mechanism of action, pharmacology, efficacy and safety of ofatumumab; no mention of hepatotoxicity or ALT elevations).*

Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). *Pharmacoepidemiol Drug Saf.* 2012;21:1216–20. PubMed PMID: 22821419.

*(Analysis of spontaneous adverse event reporting of PML in the US between 2004-2010 identified 635 cases with higher than expected number of cases from several immunosuppressive monoclonal antibodies, including rituximab [n=124], natalizumab [123] and efalizumab [12], but not ofatumumab).*

Hwang JP, Vierling JM, Zelenetz AD, Lackey SC, Loomba R. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. *Support Care Cancer.* 2012;20:2999–3008. PubMed PMID: 22933131.

*(Review of reactivation of HBV from chemotherapy stresses need for routine screening for HBV markers, particularly for patients who are to receive rituximab).*

Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. *JAMA.* 2013;310:1664. PubMed PMID: 24150447.

*(News report of the FDA alert to physicians of the high risk of HBV reactivation in patients receiving ofatumumab or rituximab).*

Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, Kao WY, et al; Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study. *Hepatology.* 2014;59(6):2092–100. PubMed PMID: 24002804.

*(Among 150 patients with non-Hodgkin lymphoma who had anti-HBc without HBsAg in serum and were treated with rituximab containing regimens without prophylaxis and followed with monthly testing for HBV DNA, 27 [18%] developed HBV reactivation 3-57 weeks after starting chemotherapy [6 after stopping], 12 developed HBsAg, 7 HBeAg and 10 ALT elevations despite prompt therapy with entecavir, but none had acute liver failure or died).*

Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, Kim JS, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. *Eur J Cancer.* 2013;49:3486–96. PubMed PMID: 23910494.

*(Retrospective analysis of rates of HBV reaction in 340 patients with lymphoma receiving rituximab based chemotherapy identified HBV reactivation in 45 of 162 [28%] of HBsAg positive and 10% of HBsAg negative but anti-HBc positive patients, risk factors being lack of antiviral prophylaxis and absence of anti-HBs and failures of prophylaxis being mostly due to lamivudine rather than entecavir).*

Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol.* 2013;31:2765–72. PubMed PMID: 23775967.

*(Among 80 Chinese patients with lymphoma and anti-HBc without HBsAg in serum, 41 received entecavir and 39 were monitored during rituximab based chemotherapy; reactivation of HBV occurred in 2% on entecavir [1 patient after stopping prophylaxis] versus 18% of controls; while HBsAg reverse seroconversion occurred in 0% on entecavir and 10% of controls; only 1 patient developed hepatitis and none had acute liver failure).*

Martin ST, Cardwell SM, Nailor MD, Gabardi S. Hepatitis B reactivation and rituximab: a new boxed warning and considerations for solid organ transplantation. *Am J Transplant.* 2014;14:788–96. PubMed PMID: 24592928.

*(Commentary on the boxed warning for rituximab and ofatumumab published by the FDA in September 2013, questioning the need for prophylaxis in patients undergoing solid organ transplant who typically receive a single dose of rituximab and in whom there have been few reports of reactivation).*

Sorensen PS, Lisby S, Grove R, Derosier F, Shackelford S, Havrdova E, Drulovic J, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. *Neurology.* 2014;82:573–81. PubMed PMID: 24453078.

*(Among 38 patients with relapsing multiple sclerosis treated with two infusions of 3 doses of ofatumumab or placebo 2 weeks apart and followed for 24 weeks, new brain lesions were less on magnetic resonance imaging after ofatumumab therapy and "results of clinical laboratory tests... were unremarkable").*

Mikulska M, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, Di Grazia C, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. *Clin Microbiol Infect.* 2014;20(10):O694–701. PubMed PMID: 24575948.

*(Among 754 patients undergoing hematopoietic cell transplantation, 14 patients developed HBV reactivation, occurring among the 137 who had anti-HBc without HBsAg before transplant at a rate of 2% at one year rising to 26% at 7 years; risk factors included lack of HBV immunity in the donor and length of therapy with cyclosporine).*

Yazici O, Sendur MA, Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. *World J Gastroenterol.* 2014;20:6716–24. PubMed PMID: 24944464.

*(Systematic review of studies of HCV reactivation in patients receiving monoclonal antibody and immunomodulatory therapies for cancer found little evidence that hepatitis C is worsened, but advised caution regardless).*

Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, et al. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371:213–23. PubMed PMID: 24881631.

*(Among 391 patients with relapsed or refractory CLL treated with daily ibrutinib or monthly infusions of ofatumumab overall survival was better with ibrutinib as were serious adverse events [57% vs 47%], but there were no liver related serious adverse events and no mention of elevations in ALT levels).*

Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology.* 2015;61:703–11. PubMed PMID: 25412906.

*(Review of the pathogenesis, clinical course, treatment and prevention of HBV reactivation in patients receiving immunosuppressive or anticancer therapies, with particular focus on rituximab and ofatumumab).*

Korycka-Wołowiec A, Wołowiec D, Robak T. Ofatumumab for treating chronic lymphocytic leukemia: a safety profile. *Expert Opin Drug Saf.* 2015;14:1945–59. PubMed PMID: 26566719.

*(Review of the efficacy and safety of ofatumumab in CLL mentions that the major non-hematologic toxicity is infections [20%] which can be severe, but that hepatic toxicity is uncommon).*

van Oers MH, Kuliczowski K, Smolej L, Petrini M, Offner F, Grosicki S, Levin MD, et al; PROLONG study investigators. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncol.* 2015;16:1370–9. PubMed PMID: 26377300.

*(Among 474 patients with CLL treated with ofatumumab or no therapy for 19 months, progression free survival was better with treatment and adverse events included lymphopenia, anemia thrombocytopenia and infusion reactions; no mention of ALT elevations or hepatotoxicity).*

Moreno C, Montillo M, Panayiotidis P, Dimou M, Bloor A, Dupuis J, Schuh A, et al. Ofatumumab in poor-prognosis chronic lymphocytic leukemia: a phase IV, non-interventional, observational study from the European Research Initiative on Chronic Lymphocytic Leukemia. *Haematologica.* 2015;100:511–6. PubMed PMID: 25596264.

*(Among 103 patients with poor prognosis CLL treated with ofatumumab and followed in an observational study, the overall response rate was low [22%] but therapy was usually well tolerated and 4 subjects with anti-HBs did not develop reactivation of hepatitis B, although specific details were not provided).*

Quattrocchi E, Østergaard M, Taylor PC, van Vollenhoven RF, Chu M, Mallett S, Perry H, et al. Safety of repeated open-label treatment courses of intravenous ofatumumab, a human anti-CD20 monoclonal antibody, in rheumatoid arthritis: results from three clinical trials. *PLoS One.* 2016;11:e0157961. PubMed PMID: 27336685.

*(Among 483 patients with rheumatoid arthritis in 3 clinical trials of ofatumumab given intravenously in up to 7 courses, adverse events were common, particularly infusion reactions which typically were worse with the initial infusions and lessened thereafter, infections occurred in 32-53% of subjects but no patient had reactivation of hepatitis B, one patient developed acute hepatitis B that led to hepatic failure and death; no mention of ALT elevations or hepatotoxicity).*

van Imhoff GW, McMillan A, Matasar MJ, Radford J, Ardeschna KM, Kuliczowski K, Kim W, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The ORCHARRD study. *J Clin Oncol.* 2017;35:544–51. PubMed PMID: 28029326.

*(Among 447 patients with relapsed or refractory diffuse large B cell lymphoma treated with 3 cycles of ofatumumab- or rituximab based combination chemotherapy, response rates were similar [38% vs 42%] as were severe adverse event rates which included neutropenia and acute renal failure, but hepatotoxicity and ALT elevations were not mentioned).*

Flinn IW, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G, Delgado J, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood.* 2018;132:2446–55. PubMed PMID: 30287523.

*(Among 319 patients with relapsed or refractory CLL treated with ofatumumab [twice monthly] or duvelisib [daily] adverse events for ofatumumab included infusion reactions [19%], neutropenia [21%], anemia [10%], thrombocytopenia [6%] and aminotransferase elevations [3%], but there were no drug related severe hepatic adverse events).*

Rosenbaum CA, Jung SH, Pitcher B, Bartlett NL, Smith SM, Hsi E, Wagner-Johnston N, et al. Phase 2 multicentre study of single-agent ofatumumab in previously untreated follicular lymphoma: CALGB 50901 (Alliance). *Br J Haematol.* 2019;185:53–64. PubMed PMID: 30723894.

*(Among 51 patients with follicular lymphoma treated with ofatumumab [500 or 1000 mg] monthly for up to 9 months, the most frequent adverse events were fatigue and pain, infusion reactions and lymphopenia, anemia and thrombocytopenia; serum ALT or AST elevations arose in ~15% of patients but were all transient, asymptomatic and less than twice ULN).*

Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood*. 2019;133:2031–42. PubMed PMID: 30842083.

*(In long term follow up of [median 44 months] of patients participating in a controlled trial of ofatumumab vs ibrutinib [Byrd 2014], ibrutinib recipients still demonstrated a superior survival rate and there were no hepatic adverse events reported with long term use of either agent).*