WM Clinical Trials Network

Jorge Castillo, MD

WM-NET

WM CLINICAL TRIALS GROUP

Published OnlineFirst November 11, 2016; DOI: 10.1158/1078-0432.CCR-16-1918

Clinical Trial Brief Report

Clinical Cancer Research

Prospective, Multicenter Clinical Trial of Everolimus as Primary Therapy in Waldenstrom Macroglobulinemia (WMCTG 09-214)

Steven P. Treon[1], Kirsten Meid[1], Christina Tripsas[1], Leonard T. Heffner[2], Herbert Eradat[3], Ashraf Z. Badros[4], Lian Xu[1], Zachary R. Hunter[1], Guang Yang[1], Christopher J. Patterson[1], Joshua Gustine[1], Jorge J. Castillo[1], Jeffrey Matous[5], and Irene M. Ghobrial[1]

Abstract

Purpose: Everolimus inhibits mTOR, a component of PI3K/AKT prosurvival signaling triggered by MYD88 and CXCR4-activating mutations in Waldenstrom macroglobulinemia.

Experimental design: We evaluated everolimus in a prospective, multicenter study of 33 symptomatic, previously untreated Waldenstrom macroglobulinemia patients. Intended therapy consisted of everolimus (10 mg/day) until progression or unacceptable toxicity. Dose deescalation was permitted. The study was registered at www.clinicaltrials.gov (NCT00976248).

Results: At best response, median serum IgM levels declined from 4,440 to 1,360 mg/dL ($P < 0.0001$), median hemoglobin rose from 10.8 to 12 g/dL ($P = 0.001$), and median bone marrow disease burden declined from 75% to 52.5% in serially biopsied patients. The ORR and major response rates were 72.7% and 60.6%, respectively. Among genotyped patients, nonresponders associated with wild-type MYD88 and mutated CXCR4 status. Median time to response was 4 weeks. Discordance between serum IgM levels and bone marrow disease burden was remarkable. With a median follow-up of 13.1 (range, 1.6–64.6 months), the median time to progression was 21 months for all patients and 33 months for major responders. Discontinuation of everolimus led to rapid serum IgM rebound in 7 patients and symptomatic hyperviscosity in 2 patients. Toxicity led to treatment discontinuation in 27% of patients, including 18% for pneumonitis.

Conclusions: Everolimus is active in previously untreated Waldenstrom macroglobulinemia. IgM discordance is common, and treatment cessation can often lead to rapid serum IgM rebound. Pneumonitis also appears more pronounced in untreated versus previously treated Waldenstrom macroglobulinemia patients. The risks and benefits of everolimus should be carefully weighed against other primary Waldenstrom macroglobulinemia therapy options. *Clin Cancer Res; 23(10); 2400–4. ©2016 AACR.*

VOLUME 27 · NUMBER 23 · AUGUST 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Primary Therapy of Waldenström Macroglobulinemia With Bortezomib, Dexamethasone, and Rituximab: WMCTG Clinical Trial 05-180

Steven P. Treon, Leukothea Ioakimidis, Jacob D. Soumerai, Christopher J. Patterson, Patricia Sheehy, Marybeth Nelson, Michael Willen, Jeffrey Matous, John Mattern II, Jakow G. Dimer, George P. Keogh, Thomas J. Myers, Andy Boral, Ann Birner, Dixie L. Esseltine, and Irene M. Ghobrial

From the Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; New York Oncology and Hematology, Lathem, NY; Rocky Mountain Cancer Center, Denver, CO; Virginia Oncology Associates, Newport News, VA; Littleton Regional Hospital, Littleton, NH; Charleston Hematology Oncology Associates, Charleston, SC; and Millennium: The Takeda Oncology Company, Cambridge, MA.

Submitted October 8, 2008; accepted February 23, 2009; published online ahead of print at www.jco.org on June 8, 2009.

Supported by the Peter and Helen Bing Fund for Waldenström's Macroglobulinemia at the Dana-Farber Cancer Institute, Millennium: The Takeda Oncology Company, and National Institutes of Health Career Development Award No. K23CA097977-03 (S.P.T.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Steven P. Treon, MD, MA, PhD, Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Harvard

A B S T R A C T

Purpose

We examined the activity of bortezomib, dexamethasone, and rituximab (BDR) in patients with symptomatic, untreated Waldenström macroglobulinemia (WM).

Patients and Methods

A cycle of therapy consisted of bortezomib 1.3 mg/m^2 intravenously; dexamethasone 40 mg on days 1, 4, 8, and 11; and rituximab 375 mg/m^2 on day 11. Patients received four consecutive cycles for induction therapy and then four more cycles, each given 3 months apart, for maintenance therapy. Twenty-three patients received a median of seven cycles of treatment.

Results

Median bone marrow disease involvement declined from 55% to 10% ($P = .0004$), serum immunoglobulin M levels declined from 4,830 to 1,115 mg/dL ($P < .0001$), and hematocrit increased from 29.8% to 38.2% ($P = .0002$) at best response. The overall response rates and major response rates were 96% and 83% with three complete responses, two near complete responses, three very good partial responses, 11 partial responses, and three minor responses. Responses occurred at a median of 1.4 months. With a median follow-up of 22.8 months, 18 of 23 patients remained free of disease progression. Peripheral neuropathy was the most common toxicity, and it resolved to grade ≤ 1 in 13 of 16 patients at a median of 6.0 months. Four of the first seven treated patients developed herpes zoster, resulting in the institution of prophylactic antiviral therapy.

Conclusion

The results demonstrate that BDR produces rapid and durable responses, along with high rates of response and complete remissions in WM. Herpes zoster prophylaxis is necessary with BDR, and reversible peripheral neuropathy was the most common toxicity leading to premature discontinuation of bortezomib in 61% of patients. Exploration of alternative schedules for bortezomib administration that includes weekly dosing should be pursued.

J Clin Oncol 27:3830-3835. © 2009 by American Society of Clinical Oncology

Cancer Therapy: Clinical

Lenalidomide and Rituximab in Waldenstrom's Macroglobulinemia

Steven P. Treon,[1,3] Jacob D. Soumerai,[1] Andrew R. Branagan,[1] Zachary R. Hunter,[1] Christopher J. Patterson,[1] Leukothea Ioakimidis,[1] Luis Chu,[4] Paul Musto,[5] Ari D. Baron,[6] Johannes C. Nunnink,[7] Joseph J. Kash,[8] Terenig O. Terjanian,[9] Paul M. Hyman,[10] Elena L. Nawfel,[11] David J. Sharon,[12] Nikhil C. Munshi,[2,3] and Kenneth C. Anderson[2,3]

Abstract

Purpose: Thalidomide and its more potent immunomodulatory derivative lenalidomide enhance rituximab-mediated antibody-dependent cell-mediated cytotoxicity. We therefore evaluated lenalidomide and rituximab in symptomatic Waldenstrom's macroglobulinemia (WM) patients naive to either agent.

Experimental Design: Intended therapy consisted of 48 weeks of lenalidomide (25 mg/d for 3 weeks and then 1 week off) along with rituximab (375 mg/m^2/wk) dosed on weeks 2 to 5 and 13 to 16. Sixteen patients were enrolled, 12 of whom were previously untreated.

Results: Unexpectedly, we observed an acute decrease in hematocrit in 13 of 16 patients (median hematocrit decrease, 4.8%), which was attributable to lenalidomide patients and which led to cessation of further enrollment on this study. Lenalidomide-related anemia was observed even at doses as low as 5 mg/d and occurred in the absence of hemolysis or other cytopenias. The overall response and major response (<50% decrease in serum IgM) rates were 50% and 25%, respectively, on an intent-to-treat basis. With a median follow-up of 31.3 months, 4 of 8 responding patients have progressed with a median time to progression of 18.9 months.

Conclusion: Lenalidomide produces unexpected but clinically significant acute anemia in patients with WM. In comparison with our previous study with thalidomide and rituximab in an analogous patient population, the responses achieved in WM patients with lenalidomide and rituximab appear less favorable.

CLINICAL TRIALS AND OBSERVATIONS

Thalidomide and rituximab in Waldenstrom macroglobulinemia

Steven P. Treon,[1,2] Jacob D. Soumerai,[1] Andrew R. Branagan,[1] Zachary R. Hunter,[1] Christopher J. Patterson,[1] Leukothea Ioakimidis,[1] Frederick M. Briccetti,[3] Mark Pasmantier,[4] Harvey Zimbler,[5] Robert B. Cooper,[6] Maria Moore,[7] John Hill II,[8] Alan Rauch,[9] Lawrence Garbo,[9] Luis Chu,[10] Cynthia Chua,[11] Stephen H. Nantel,[12] David R. Lovett,[13] Hans Boedeker,[14] Henry Sonneborn,[15] John Howard,[16] Paul Musto,[17] Bryan T. Ciccarelli,[1] Evdoxia Hatjiharissi,[1,2] and Kenneth C. Anderson[2,18]

[1]Bing Center for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]New Hampshire Hematology Oncology, Concord; [4]New York Presbyterian Hospital, Weill Medical College, New York, NY; [5]Berkshire Hematology Oncology, Pittsfield, MA; [6]Praxair Cancer Center, Danbury Hospital, CT; [7]Park Ridge Hospital, Hendersonville, NC; [8]Hendersonville Hematology Oncology, NC; [9]New York Oncology Hematology, Albany; [10]Florida Cancer Specialists, Sarasota; [11]Oncology Hematology Care, Cincinnati, OH; [12]British Columbia Cancer Agency, Vancouver General Hospital, Vancouver, BC; [13]Cape Cod Hospital, Hyannis, MA; [14]Bridgton Hospital, ME; [15]Seacoast Cancer Center, Portsmouth, NH; [16]Virginia Oncology Associates, Norfolk; [17]Commonwealth Hematology Oncology, Quincy, MA; and [18]Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA

Thalidomide enhances rituximab-mediated, antibody-dependent, cell-mediated cytotoxicity. We therefore conducted a phase 2 study using thalidomide and rituximab in symptomatic Waldenstrom macroglobulinemia (WM) patients naive to either agent. Intended therapy consisted of daily thalidomide (200 mg for 2 weeks, then 400 mg for 50 weeks) and rituximab (375 mg/m^2 per week) dosed on weeks 2 to 5 and 13 to 16. Twenty-five patients were enrolled, 20 of whom were untreated. Responses were complete response (n = 1), partial response (n = 15), and major response (n = 2), for overall and major response rate of 72% and 64%, respectively, on an intent-to-treat basis. Median serum IgM decreased from 3670 to 1590 mg/dL ($P < .001$), whereas median hematocrit rose from 33.0% to 37.6% ($P = .004$) at best response. Median time to progression for responders was 38 months. Peripheral neuropathy to thalidomide was the most common adverse event. Among 11 patients experiencing grade 2 or greater neuropathy, 10 resolved to grade 1 or less at a median of 6.7 months. Thalidomide in combination with rituximab is active and produces long-term responses in WM. Lower doses of thalidomide (ie, ≤ 200 mg/day) should be considered given the high frequency of treatment-related neuropathy in this patient population. This trial is registered at www.clinicaltrials.gov as #NCT00142116. (Blood. 2008;112:4452-4457)

CLINICAL TRIALS AND OBSERVATIONS

Long-term follow-up of symptomatic patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia treated with the anti-CD52 monoclonal antibody alemtuzumab

Steven P. Treon,[1] Jacob D. Soumerai,[1] Zachary R. Hunter,[1] Christopher J. Patterson,[1] Leukothea Ioakimidis,[1] Brad Kahl,[2] and Michael Boxer[3]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Carbone Cancer Center, University of Wisconsin, Madison, WI; and [3]Arizona Oncology Associates, University of Arizona, Tucson, AZ

CD52 is expressed on malignant cells in lymphoplasmacytic lymphoma (LPL), including IgM-secreting Waldenström macroglobulinemia (WM). We examined the activity of alemtuzumab in 28 symptomatic LPL (27 IgM and 1 IgA) patients. The median prior number of therapies for these patients was 2 (range, 0-5) and 43% had refractory disease. Patients received alemtuzumab at 30 mg IV 3 times weekly for up to 12 weeks after test dosing, and also received hydrocortisone, acyclovir, and Bactrim or equivalent prophylaxis. Patients had a complete response (n = 1), a partial response (n = 9), or a MR (n = 11) for an overall and major response rate of 75% and 36%, respectively. Median serum Ig decreased from 3510 to 1460 mg/dL ($P < .001$ at best response). With a median follow-up of 64 months, the median time to progression was 14.5 months. Hematologic and infectious complications, including CMV reactivation, were more common in previously treated patients and were indirectly associated with 3 deaths. Long-term follow-up revealed late-onset autoimmune thrombocytopenia (AITP) in 4 patients at a median of 13.6 months after therapy, which contributed to 1 death. Alemtuzumab is an active therapy in patients with LPL, but short- and long-term toxicities need to be carefully weighed against other available treatment options. Late AITP is a newly recognized complication of alemtuzumab in this patient population. This study is registered at www.clinicaltrials.gov as NCT00142181. (*Blood*. 2011;118(2):276-281)

Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia

Steven P. Treon,[1] Andrew R. Branagan,[1] Leukothea Ioakimidis,[1] Jacob D. Soumerai,[1] Christopher J. Patterson,[1] Barry Turnbull,[2] Parveen Wasi,[3] Christos Emmanouilides,[4] Stanley R. Frankel,[5] Andrew Lister,[6] Pierre Morel,[7] Jeffrey Matous,[8] Stephanie A. Gregory,[9] and Eva Kimby[10]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]BioBridges, Boston, MA; [3]McMaster University Medical Center, Hamilton, ON; [4]University of California Los Angeles (UCLA) Medical Center; [5]Greenebaum Cancer Center, University of Maryland, Baltimore; [6]Medical Oncology, St Bartholomew's Hospital and Cancer Research, London, United Kingdom; [7]Clinical Hematology, Centre Hospitalier Schaffner, Lens, France; [8]Rocky Mountain Cancer Center, Denver, CO; [9]Rush University Medical Center, Chicago, IL; and [10]Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden

We report the long-term outcome of a multicenter, prospective study examining fludarabine and rituximab in Waldenström macroglobulinemia (WM). WM patients with less than 2 prior therapies were eligible. Intended therapy consisted of 6 cycles (25 mg/m^2 per day for 5 days) of fludarabine and 8 infusions (375 mg/m^2 per week) of rituximab. A total of 43 patients were enrolled. Responses were: complete response (n = 2), very good partial response (n = 14), partial response (n = 21), and minor response (n = 4), for overall and major response rates of 95.3% and 86.0%, respectively. Median time to progression for all patients was 51.2 months and was longer for untreated patients ($P = .017$) and those achieving at least a very good partial response ($P = .049$). Grade 3 or higher toxicities included neutropenia (n = 27), thrombocytopenia (n = 7), and pneumonia (n = 6), including 2 patients who died of non–*Pneumocystis carinii* pneumonia. With a median follow-up of 40.3 months, we observed 3 cases of transformation to aggressive lymphoma and 3 cases of myelodysplastic syndrome/acute myeloid leukemia. The results of this study demonstrate that fludarabine and rituximab are highly active in WM, although short- and long-term toxicities need to be carefully weighed against other available treatment options. This study is registered at clinicaltrials.gov as NCT00020800. (Blood. 2009;113:3673-3678)

RECENT BCWM CLINICAL TRIALS

CLINICAL TRIALS AND OBSERVATIONS

Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia

Steven P. Treon,[1,2] Christina K. Tripsas,[1] Kirsten Meid,[1] Sandra Kanan,[1] Patricia Sheehy,[1] Stacey Chuma,[1] Lian Xu,[1] Yang Cao,[1] Guang Yang,[1] Xia Liu,[1] Christopher J. Patterson,[1] Diane Warren,[1] Zachary R. Hunter,[1] Barry Turnbull,[3] Irene M. Ghobrial,[1,2] and Jorge J. Castillo[1,2]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Harvard Medical School, Boston, MA; and [3]BioBridges Inc., Newton, MA

Key Points

- Carfilzomib, rituximab, and dexamethasone (CaRD) produce overall and CR/VGPR responses in 87% and 36% of frontline WM patients, respectively.
- CaRD activity was not impacted by MYD88 and CXCR4 mutations and represents a neuropathy-sparing option for treating WM patients.

Bortezomib frequently produces severe treatment-related peripheral neuropathy (PN) in Waldenström's macroglobulinemia (WM). Carfilzomib is a neuropathy-sparing proteasome inhibitor. We examined carfilzomib, rituximab, and dexamethasone (CaRD) in symptomatic WM patients naïve to bortezomib and rituximab. Protocol therapy consisted of intravenous carfilzomib, 20 mg/m2 (cycle 1) and 36 mg/m^2 (cycles 2-6), with intravenous dexamethasone, 20 mg, on days 1, 2, 8, and 9, and rituximab, 375 mg/m^2, on days 2 and 9 every 21 days. Maintenance therapy followed 8 weeks later with intravenous carfilzomib, 36 mg/m^2, and intravenous dexamethasone, 20 mg, on days 1 and 2, and rituximab, 375 mg/m^2, on day 2 every 8 weeks for 8 cycles. Overall response rate was 87.1% (1 complete response, 10 very good partial responses, 10 partial responses, and 6 minimal responses) and was not impacted by MYD88^{L265P} or CXCR4^{WHIM} mutation status. With a median follow-up of 15.4 months, 20 patients remain progression free. Grade ≥2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), and cardiomyopathy in 1 patient (3.2%) with multiple risk factors, and PN in 1 patient (3.2%) which was grade 2. Declines in serum IgA and IgG were common. CaRD offers a neuropathy-sparing approach for proteasome inhibitor-based therapy in WM. This trial is registered at www.clinicaltrials.gov as #NCT01470196. (*Blood*. 2014;124(4):503-510)

Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenström macroglobulinemia: long-term follow-up

Jorge J. Castillo,[1,2] Kirsten Meid,[1] Catherine A. Flynn,[1] Jiaji Chen,[1] Maria G. Demos,[1] Maria L. Guerrera,[1] Amanda Kofides,[1] Xia Liu,[1] Manit Munshi,[1] Nicholas Tsakmaklis,[1] Christopher J. Patterson,[1] Guang Yang,[1,2] Zachary Hunter,[1,2] and Steven P. Treon[1,2]

[1]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; and [2]Department of Medicine, Harvard Medical School, Boston, MA

Key Points

- Ixazomib, dexamethasone, and rituximab (IDR) was associated with overall, major, and very good partial response rates of 96%, 77%, and 19%.
- Responses to IDR were durable, with a median PFS of 40 months, and the safety profile was excellent with no grade 4 adverse events.

Proteasome inhibition is a standard of care for the primary treatment of patients with Waldenström macroglobulinemia (WM). We present the long-term follow-up of a prospective, phase II clinical trial that evaluated the combination of ixazomib, dexamethasone, and rituximab (IDR) in 26 treatment-naive patients with WM. IDR was administered as 6 monthly induction cycles followed by 6 every-2-month maintenance cycles. The *MYD88 L265P* mutation was detected in all patients, and *CXCR4* mutations were detected in 15 patients (58%). The median time to response (TTR) and time to major response (TTMR) were 2 and 6 months, respectively. Patients with and without *CXCR4* mutations had median TTR of 3 months and 1 month, respectively ($P = .003$), and median TTMR of 10 months and 3 months, respectively ($P = .31$). The overall, major, and very good partial response (VGPR) rates were 96%, 77%, and 19%, respectively. The rate of VGPR in patients with and without *CXCR4* mutations were 7% and 36%, respectively ($P = .06$). The median progression-free survival (PFS) was 40 months, the median duration of response (DOR) was 38 months, and the median time to next treatment (TTNT) was 40 months. PFS, DOR, and TTNT were not affected by *CXCR4* mutational status. The safety profile was excellent with no grade 4 adverse events or deaths to date. IDR provides a safe and effective frontline treatment option for symptomatic patients with WM. This study was registered at www.clinicaltrials.gov as #NCT02400437.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

CLINICAL TRIALS AND OBSERVATIONS

Ibrutinib and venetoclax as primary therapy in symptomatic, treatment-naïve Waldenström macroglobulinemia

Jorge J. Castillo,[1,2] Andrew R. Branagan,[2,3] David Sermer,[2,4] Catherine A. Flynn,[1] Kirsten Meid,[1] Megan Little,[1] Katherine Stockman,[1] Timothy White,[1] Alexa Canning,[1] Maria L. Guerrera,[1] Amanda Kofides,[1] Shirong Liu,[1] Xia Liu,[1] Kris Richardson,[1] Nicholas Tsakmaklis,[1] Christopher J. Patterson,[1] Zachary R. Hunter,[1] Steven P. Treon,[1,2] and Shayna Sarosiek[1,2]

[1]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Medicine, Harvard Medical School, Boston, MA; [3]Center for Multiple Myeloma, Massachusetts General Hospital, Boston, MA; and [4]Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA

KEY POINTS

- The combination of ibrutinib and venetoclax induced deep and durable responses in treatment-naïve patients with Waldenström macroglobulinemia.
- Planned study therapy was stopped early due to a higher-than-expected occurrence of ventricular arrhythmia in 4 of the 45 participants.

Concurrent Bruton tyrosine kinase and BCL2 inhibition has not yet been investigated in Waldenström macroglobulinemia (WM). We performed an investigator-initiated trial of ibrutinib and venetoclax in symptomatic treatment-naïve patients with MYD88-mutated WM. Patients received ibrutinib 420 mg once daily (cycle 1), followed by a ramp-up of venetoclax to 400 mg daily (cycle 2). The combination was then administered for 22 additional 4-week cycles. The attainment of very good partial response (VGPR) was the primary end point. Forty-five patients were enrolled in this study. The median baseline characteristics were as follows: age 67 years, serum IgM 43 g/L, and hemoglobin 102 g/L. Seventeen patients (38%) carried *CXCR4* mutations. Nineteen patients (42%) achieved VGPR. Grade 3 or higher adverse events included neutropenia (38%), mucositis (9%), and tumor lysis syndrome (7%). Atrial fibrillation occurred in 3 (9%), and ventricular arrhythmia in 4 (9%) patients that included 2 grade 5 events. With a median follow-up of 24.4 months, the 24-month progression-free survival (PFS) and overall survival (OS) rates were 76% and 96%, respectively, and were not impacted by *CXCR4* mutations. The median time on therapy was 10.2 months, and the median time after the end of therapy (EOT) was 13.3 months. Eleven

Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia

Jorge J. Castillo[1,2✉], Kirsten Meid[1], Joshua N. Gustine[1,3], Carly Leventoff[1], Timothy White[1], Catherine A. Flynn[1], Shayna Sarosiek[1,2], Maria G. Demos[1], Maria L. Guerrera[1], Amanda Kofides[1], Xia Liu[1], Manit Munshi[1], Nicholas Tsakmaklis[1], Lian Xu[1], Guang Yang[1], Andrew R. Branagan[2,4], Elizabeth O'Donnell[2,4], Noopur Raje[2,4], Andrew J. Yee[2,4], Christopher J. Patterson[1], Zachary R. Hunter[1] and Steven P. Treon[1,2]

Herein, we present the final report of a single-center, prospective phase II study evaluating ibrutinib 420 mg once daily in 30 treatment-naive patients with Waldenstrom macroglobulinemia (WM). The present study is registered with ClinicalTrials.Gov (NCT02604511). With a median follow-up of 50 months, the overall, major, and VGPR response rates were 100%, 87%, and 30%. The VGPR rate was numerically but not significantly lower in patients with than without *CXCR4* mutations (14% vs. 44%; $p = 0.09$). The median time to a minor response was 0.9 months, and to a major response was 1.9 months, though were longer in those with mutated *CXCR4* at 1.7 months ($p = 0.07$) and 7.3 months ($p = 0.01$). Six patients had disease progression. The median progression-free survival (PFS) was not reached, and the 4-year PFS rate was 76%. There was also a non-significant lower 4-year PFS rate in patients with than without *CXCR4* mutations (59% vs. 92%; $p = 0.06$). The most common treatment-related adverse events were fatigue, upper respiratory infection, and hematoma. Atrial fibrillation occurred in 20% of patients. Ibrutinib monotherapy induced durable responses in treatment-naive patients with WM. *CXCR4* mutations impacted VGPR attainment, time to major response, and 4-year PFS rate.

Leukemia (2022) 36:532–539; https://doi.org/10.1038/s41375-021-01417-9

original reports abstract

Venetoclax in Previously Treated Waldenström Macroglobulinemia

Jorge J. Castillo, MD[1,2]; John N. Allan, MD[3]; Tanya Siddiqi, MD[4]; Ranjana H. Advani, MD[3]; Kirsten Meid, MPH[1]; Carly Leventoff, BA[1]; Timothy P. White, BA[1]; Catherine A. Flynn, NP[1]; Shayna Sarosiek, MD[1,2]; Andrew R. Branagan, MD[2,4]; Maria G. Demos, BA[1]; Maria L. Guerrera, MD[1]; Amanda Kofides, BA[1]; Xia Liu, BA[1]; Manit Munshi, BA[1]; Nicholas Tsakmaklis, BA[1]; Lian Xu, BA[1]; Guang Yang, BA[1]; Christopher J. Patterson, BA[1]; Zachary R. Hunter, PhD[1,2]; Matthew S. Davids, MD[2,3]; Richard R. Furman, MD[3]; and Steven P. Treon, MD, PhD[1,2]

PURPOSE BCL2 is overexpressed and confers prosurvival signaling in malignant lymphoplasmacytic cells in Waldenström macroglobulinemia (WM). Venetoclax is a potent BCL2 antagonist and triggers in vitro apoptosis of WM cells. The activity of venetoclax in WM remains to be clarified.

PATIENTS AND METHODS We performed a multicenter, prospective phase II study of venetoclax in patients with previously treated WM (NCT02677324). Venetoclax was dose-escalated from 200 mg to a maximum dose of 800 mg daily for up to 2 years.

RESULTS Thirty-two patients were evaluable, including 16 previously exposed to Bruton tyrosine kinase inhibitors (BTKis). All patients were *MYD88 L265P*-mutated, and 17 carried *CXCR4* mutations. The median time to minor and major responses was 1.9 and 5.1 months, respectively. Previous exposure to BTKis was associated with a longer time to response (4.5 *v* 1.4 months; $P < .001$). The overall, major, and very good partial response rates were 84%, 81%, and 19%, respectively. The major response rate was lower in those with refractory versus relapsed disease (50% *v* 95%; $P = .007$). The median follow-up time was 33 months, and the median progression-free survival was 30 months. *CXCR4* mutations did not affect treatment response or progression-free survival. The only recurring grade ≥ 3 treatment-related adverse event was neutropenia (n = 14; 45%), including one episode of febrile neutropenia. Laboratory tumor lysis without clinical sequelae occurred in one patient. No deaths have occurred.

CONCLUSION Venetoclax is safe and highly active in patients with previously treated WM, including those who previously received BTKis. *CXCR4* mutation status did not affect treatment response.

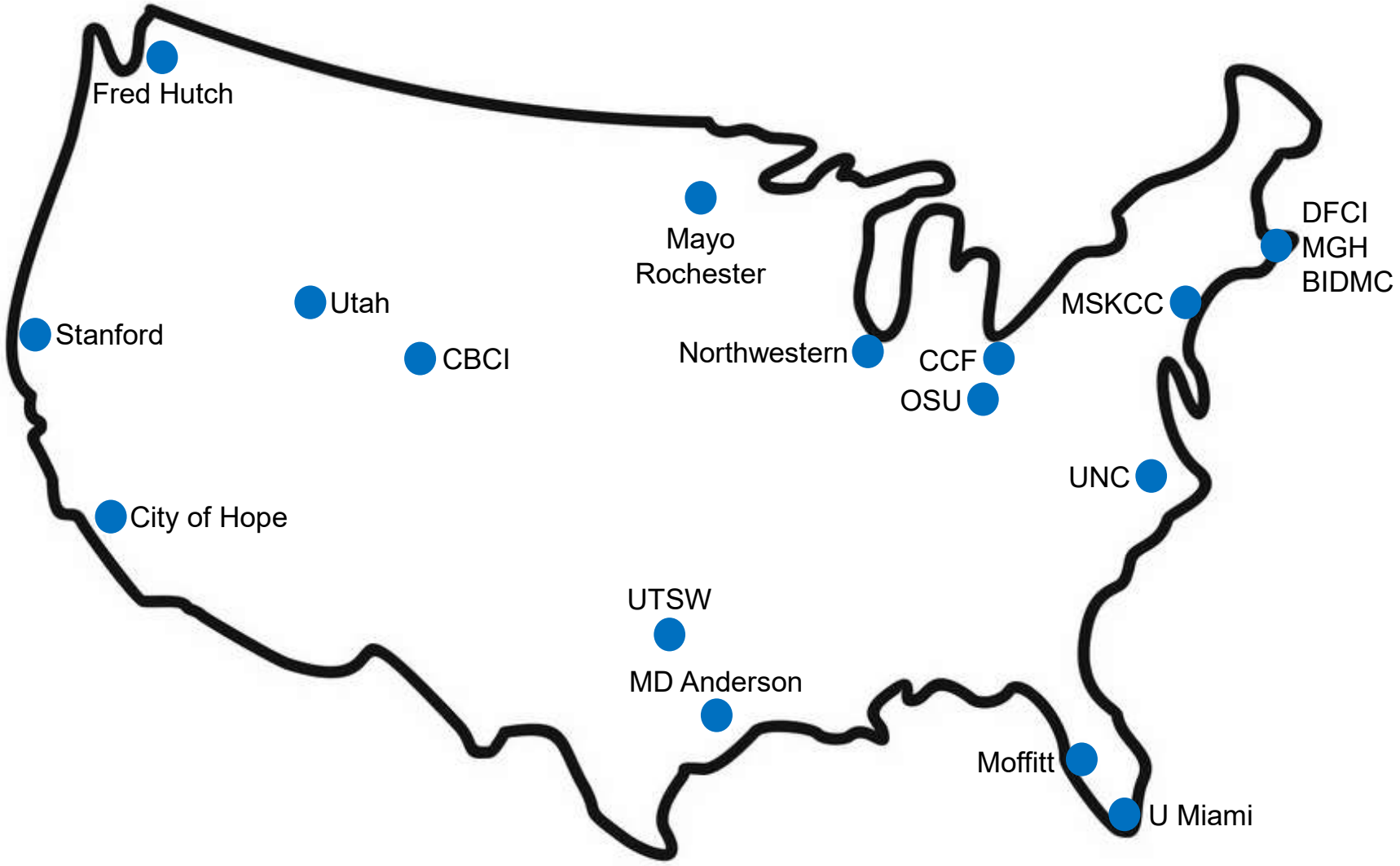
J Clin Oncol 40:63-71. © 2021 by American Society of Clinical Oncology

MISSION

A sustainable think-tank
to support clinical research collaborations
in Waldenström macroglobulinemia

VISION

To improve the lives of patients with Waldenström macroglobulinemia through scientifically driven clinical research


Fred Hutch
Mayo
Rochester
DFCI
MGH
BIDMC
Utah
MSKCC
Stanford
CBCI
Northwestern
CCF
OSU
UNC
City of Hope
UTSW
MD Anderson
Moffitt
U Miami

Staff

- Director: Jorge J. Castillo (DFCI)
- Project manager: Search ongoing
- Research coordinator: Search ongoing
- Meeting planner: Lorraine Martinez (DFCI)

Clinical trials – late development

- Loncastuximab tesirine for previously treated WM (NCT05190705)
  - PI
    - Shayna Sarosiek (DFCI)
  - Collaborators
    - Prashant Kapoor (Mayo)
    - Mary Kwok (Fred Hutch)
  - Status
    - Active, enrolling

Clinical trials – late development

- Epcoritamab for previously treated WM
  - PI
    - Gottfried von Keudell (BIDMC)
  - Collaborators
    - Larry Anderson (UT Southwestern)
    - Chris Dittus (UNC)
  - Status
    - DFCI/BIDMC IRB approved

Clinical trials – late development

- Zanubrutinib, bendamustine and rituximab for treatment-naïve WM (ZEBRA)
  - PI
    - Andrew Branagan (MGH)
  - Collaborators
    - Larry Anderson (UT Southwestern)
    - Jeff Matous (CBCI)
  - Status
    - FDA comments received and addressed

Clinical trials – early development

- Pirtobrutinib, venetoclax and rituximab (PROVE-IT)
  - Frontline treatment
  - PI: Lia Palomba (MSKCC)

- ABV338 (anti-BCMA bispecific antibody)
  - Late relapse (2+ previous lines of therapy)
  - PI: Prashant Kapoor (Mayo)

Database

- Create a US-based WM registry
- Understand treatment patterns and outcomes in the US
- Answer questions unlikely to be answered by clinical trials
- Leads
  - Prashant Kapoor (Mayo)
  - Yazeed Sawalha (Ohio State)
  - Georgios Pongas (U Miami)

Biorepository

- Post-hoc studies in WM-NET clinical trial samples
- Potential to expand to other types of samples
- Lead
  - Sheeba Thomas (MD Anderson)

STRATEGIC PARTNERS

- The Kaplan Family Fund
- The Kissam Family Fund
- The Siegel Family Fund
- The Brettschneider Family Fund
- The WMR Fund