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.*

Introduction

The PI3K/AKT pathway is an important survival signaling cascade that supports the growth and survival of malignant lymphoplasmacytic cells in Waldenstrom macroglobulinemia (1). Activating mutations in MYD88 and CXCR4, found in 95% and 30% of Waldenstrom macroglobulinemia patients, respectively, trigger PI3K/AKT signaling (2–5). Everolimus is an orally administered inhibitor of mTOR, a serine–threonine kinase that is downstream of the PI3K/AKT signaling pathway (6). Everolimus is approved by the FDA for the treatment of several solid malignancy indications and shows *in vitro* activity against Waldenstrom macroglobulinemia cells (6). In previous work, we evaluated the activity of everolimus in previously treated Waldenstrom macroglobulinemia patients (7). The overall response rate (ORR) using consensus criteria was 73%, and 50% of patients achieved a major response (8). The median progression-free survival (PFS) was 21 months in this study (9). Toxicities were common, with grade 3 or higher adverse events observed in 67% of patients (8, 9). We therefore examined the safety and efficacy of everolimus in previously untreated, symptomatic Waldenstrom macroglobulinemia patients. We performed serial bone marrow biopsies to more fully delineate the impact of therapy on Waldenstrom macroglobulinemia disease burden and also assessed the impact of MYD88 and CXCR4 mutations on treatment outcome. We present herein the first report from this prospective, multicenter study.

Patients and Methods

Symptomatic Waldenstrom macroglobulinemia patients requiring therapy based on consensus recommendations (10) and who were previously untreated were eligible to enroll. To meet eligibility, patients must have had a platelet count of $\geq 75 \times 10^9$/L, absolute neutrophil count of $\geq 1.5 \times 10^9$/L. Patients with symptomatic hyperviscosity, known history of active or chronic hepatitis B or C, uncontrolled diabetes, or severe or uncontrolled medical conditions that prohibited study participation were excluded.

The study was conducted by the Waldenstrom macroglobulinemia Clinical Trials Group (WMCTG Protocol 09-214). All

[1]Bing Center for Waldenstrom's Macroglobulinemia at the Dana-Farber Cancer Institute; and Harvard Medical School, Boston, Massachusetts. [2]Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia. [3]Jonsson Comprehensive Cancer Center, UCLA School of Medicine, Los Angeles, California. [4]Greenebaum Cancer Center, University of Maryland, Baltimore, Maryland. [5]Rocky Mountain Cancer Center, Denver, Colorado.

Corresponding Author: Steven P. Treon, Dana Farber Cancer Institute, 450 Brookline Avenue, M546, Boston, MA 02215. Phone: 617-632-5880; Fax: 617-632-4862; E-mail: steven_treon@dfci.harvard.edu

doi: 10.1158/1078-0432.CCR-16-1918

patients provided informed written consent approved by the local Institutional Review Boards. Intended therapy consisted of self-administered oral everolimus (10 mg/day). Patients were treated until progression or unacceptable toxicity. Each treatment cycle was 4 weeks. Dose reduction for grade 3 or higher adverse events was permitted as follows: 7.5 mg daily, 5.0 mg daily, and 5.0 mg every other day for the first, second, and third dose deescalations, respectively. Dose reescalation was not permitted. Retreatment was permitted once adverse events resolved to grade 1 or less. Filgrastim or transfusional support was permitted to treat hematologic adverse events. Patients were strongly encouraged to use 5 mL of an oral dexamethasone solution (0.5 mg/5mL) to swish and spit up to four times daily for prevention of stomatitis during the first 3 months of everolimus therapy.

Baseline studies consisted of complete blood counts and differential, quantitative serum IgM levels, serum protein electrophoresis, a bone marrow biopsy and aspiration, CT scans of the chest, abdomen and pelvis (CAP), serum electrolytes, liver function tests, amylase, lipase, blood urea nitrogen, creatinine, and serum β_2-microglobulin levels, lipid panel, and glucose. Patients were assessed for efficacy and toxicity on the first day of cycles 2, 3, and thereafter every 12 weeks. A bone marrow biopsy and aspiration, and CT scans of CAP (if extramedullary disease was present at baseline) were required at 24 weeks, and thereafter as clinically indicated, including to confirm complete response (CR) or suspected disease progression.

$MYD88^{L265P}$ and $CXCR^{WHIM}$ mutation genotyping

MYD88 and CXCR4 genotyping was performed for patients enrolled at the Dana Farber Cancer Institute (DFCI; Boston, MA). An allele-specific PCR assay was used for the determination of $MYD88^{L265P}$ using DNA isolated from CD19-selected bone marrow cells as described previously (1). $CXCR4^{WHIM}$ mutation status was determined by AS-PCR and Sanger sequencing of CD19-selected bone marrow cells (2).

Statistical analysis

The primary endpoint was determination of ORR. Response determinations were made using consensus criteria adapted from the Sixth International Workshop on Waldenstrom macroglobulinemia (11). Secondary endpoints included determination of time to progression and assessment of safety and tolerability of everolimus. Sample size was predicated on an expected ORR of $\geq$70% and a minimal acceptable response rate of 50% based on assumptions derived from our previous published experience with everolimus (8, 9). PFS was defined as the time between initiation of therapy and date of progression, death, or last follow-up. Patients without disease progression (including those taken off study for toxicity) were censored at the date of their last evaluation. For categorical univariate analyses, the Kaplan–Meier method for incomplete observations was used to estimate PFS curves, which were compared using the log-rank test. A Wilcoxon rank-sum test was used for analysis of pre- and posttherapy continuous variables. For categorical variables, a two-tailed Fisher exact test was used. P values $\leq$0.05 were considered statistically significant. All graphics and calculations were obtained using STATA 13.1 (StataCorp LP).

Patients and disease characteristics

Thirty-three patients were enrolled, and their baseline characteristics are shown in Table 1. The first patient started on therapy on December 9, 2009, and the last patient started therapy on June 13, 2011. The last patient came off study for disease progression on July 14, 2016. The median number of treatment cycles administered was 10.5 (range, 1–64.6). All participants are off treatment.

Table 1. Baseline characteristics for all patients enrolled on study

	Median	Range
Age (years)	62	40–79
Gender (M/F)	24/9	N/A
Serum IgM (mg/dL)	4,440	959–10,256
Serum IgA (mg/dL)	99	14–556
Serum IgG (mg/dL)	884	187–2,620
Hemoglobin (g/dL)	10.9	7.8–15.7
Platelet (mm^3)	214,000	84,000–448,000
β_2-Microglobulin (mg/L)	3.3	0.7–24.2
ISSWM score (L/I/H)	13/9/11	N/A
Extramedullary disease	10 (30.3%)	N/A
Bone marrow involvement (%)	70	2–95

NOTE: Number of patients with low (L), intermediate (I), and high (H) risk ISSWM score is shown.

Abbreviations: F, female; ISSWM, International Scoring System for Waldenstrom macroglobulinemia (12); M, male.

Response

Median IgM levels for all 33 patients declined from 4,440 mg/dL (range, 959–10,256 mg/dL) at baseline to 1,360 (range, 146–7,100 mg/dL) at best response ($P < 0.0001$). Pretherapy, 23 of 33 (69.7%) patients had a serum IgM level $\geq$3,000 mg/dL; following treatment, 8 of 33 (12.9%) patients had a serum IgM level $\geq$3,000 mg/dL ($P = 0.0004$). Among 24 patients with serial bone marrow biopsies, the median bone marrow involvement declined from 75% (range, 2%–95%) to 52.5% (range, 6%–95%) at best response ($P = 0.03$). Discordance between serum IgM levels and bone marrow disease burden was common (Fig. 1). For 24 patients who had a repeat bone marrow biopsy by week 26, the median change in serum IgM was −47.9% (range, 3.8% to −88.5%), whereas the synchronous change in bone marrow disease burden was −13.3% (range −36.8%–200%; $r = 0.23$; $P = 0.26$). In 8 (33.3%) of these patients, the bone marrow disease burden had increased, with a median increase of 43% (range, 25%–200%), whereas the serum IgM level decreased by a median of 41% (range, −75.7%–3.8%). No serum IgM flare was observed.

Following treatment, the median hemoglobin level for all patients rose from 10.8 to 12 g/dL ($P = 0.001$) at best response. Categorical responses were as follows: very good partial response (VGPR; $n = 1$), partial response (PR; $n = 19$), minor response ($n = 4$), for an ORR and major response (PR or better) rate of 72.7% [95% confidence interval (CI), 57.5%–87.9%] and 60.6% (95% CI, 43.9%–77.3%), respectively. No patient achieved a CR. Overall and major response rates were not impacted by the International Scoring System for Waldenstrom macroglobulinemia score (12).

MYD88 and CXCR4 somatic mutation status was evaluable in 21 patients. Twenty (95.2%) genotyped participants expressed $MYD88^{L265P}$. The overall and major response rates in these patients were 71.4% and 52.4%, respectively. One patient with MYD88 wild type did not respond. $CXCR4^{WHIM}$ mutations were present in 4 of 21 (19.2%) genotyped participants, all of whom were $MYD88^{L265P}$ mutated. The ORR for patients with CXCR4 wild type and WHIM mutations were 81.3% and 50%, respectively ($P = 0.25$). Major response attainment occurred in 62.5%

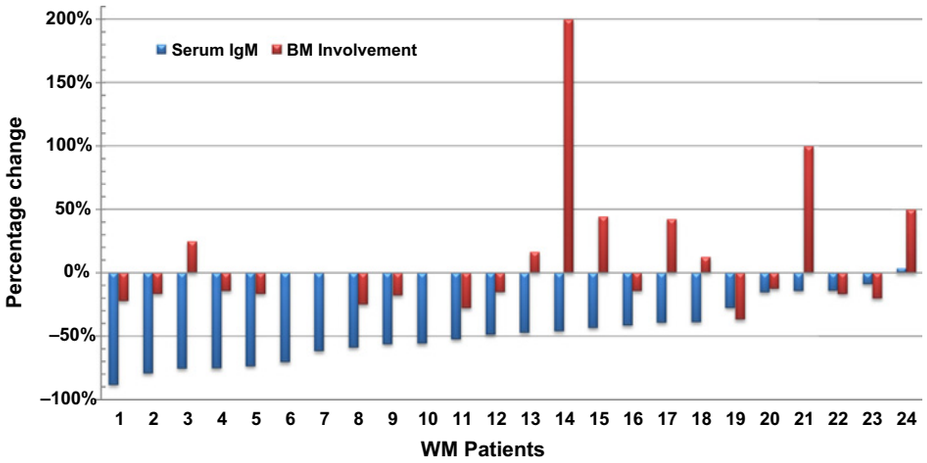

Figure 1.
Synchronous changes for serum IgM levels and bone marrow disease burden assessed for 24 patients who underwent serial bone marrow (BM) biopsies by 26 weeks. $r = 0.23$; $P = 0.26$ by Spearman ρ test for correlation of serum IgM and bone marrow disease burden for all 24 patients. WM, Waldenstrom macroglobulinemia.

and 25% of patients with CXCR4 wild type and WHIM mutations, respectively ($P = 0.56$). Among responders, the median time to at least a minor response was 1 month (range, 1–9 months), whereas the median time to a major response was 2 months (range, 1–27 months).

Time to progression

With a median follow-up of 13.1 months (range, 1.6–64.6 months), all patients were alive. All patients are off treatment. The Kaplan–Meier curve for PFS for all patients appears in Fig. 2. The median time to progression was 21 months (95% CI, 11–39 months). By univariate analysis, neither baseline bone marrow disease burden >50% versus ≤50% ($P = 0.95$), serum IgM >4,000 versus ≤4,000 mg/dL ($P = 0.59$), nor hemoglobin >11 versus ≤11 g/dL ($P = 0.16$) levels were associated with increased risk for progression. Dose deescalation (<10 mg/day vs. 10 mg/day) was also not associated with increased risk of progression ($P = 0.34$). Categorical response attainment was associated with progression risk. Patients achieving a PR or better had a longer PFS versus those with less than a PR (33 vs. 5 months, respectively; HR = 4.350; 95% CI, 3.9–113 months, $P = 0.0011$).

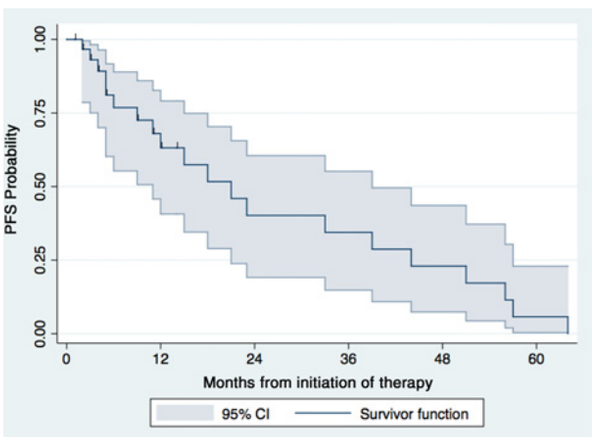

Figure 2.
PFS following everolimus therapy in 33 symptomatic untreated Waldenstrom macroglobulinemia patients. Kaplan–Meier curve with 95% CIs for PFS is shown for the 33 Waldenstrom macroglobulinemia patients treated with everolimus.

Toxicities

Grade 2 or higher toxicities that were at least possibly related to protocol therapy are presented in Table 2. The most common nonhematologic treatment-related grade ≥2 toxicities included mucositis (27.3%), infection (21.2%), rash (21.2%), fatigue (18.2%), and pneumonitis (18.2%). Treatment-related hematologic toxicities that were at least grade ≥2 included anemia (27.3%), neutropenia (18.2%), and thrombocytopenia (15.2%). Dose reduction due to adverse events occurred in 9 patients, with dose reduction to 7.5 mg ($n = 5$) and 5.0 mg ($n = 2$) daily, and 5.0 mg ($n = 2$) every other day. Treatment was discontinued in 32 patients, with reasons for discontinuation as follows: nonresponse ($n = 6$), progressive disease ($n = 15$), pneumonitis ($n = 5$), withdrawal of consent ($n = 3$) that included one patient for recurring grade 2 stomatitis, noncompliance ($n = 2$), and prolonged study drug hold for unrelated infection.

Following discontinuation of everolimus, rapid increases in serum IgM levels were common. In 7 patients, serum IgM levels showed at least a doubling. In these patients, serum IgM levels increased from a median of 1,410 (range, 306–2,880 mg/dL) to 4,670 (range, 2,510–5,910 mg/dL) at a median of 39 days (range, 18–95 days) following discontinuation of everolimus. Four of these patients underwent plasmapheresis, including two for symptomatic hyperviscosity, and two to prevent a rituximab-related IgM flare with subsequent therapy.

IgA and IgG hypogammaglobulinemia

At baseline, median serum IgA and IgG levels were 99 and 884 mg/dL, respectively. Following therapy, at last individual patient assessment, median serum IgA and IgG levels declined to 44 and 447 mg/dL, respectively ($P = 0.49$ and $P = 0.23$, respectively).

Discussion

In this prospective, multicenter study, we examined the single-agent activity of everolimus in symptomatic, untreated Waldenstrom macroglobulinemia patients. Everolimus inhibits mTOR, a serine–threonine kinase that contributes to PI3K/AKT-directed growth and survival signaling in Waldenstrom macroglobulinemia (6, 7). Activating mutations in both MYD88 and CXCR4 trigger PI3K/AKT signaling (1, 2). Our findings showed that everolimus was associated with overall and major responses in 72.7% and 60.6%, respectively, using consensus criteria (11). However, the frequent finding of IgM discordance complicated

Table 2. Adverse events at highest grade for an individual patient that were possibly, probably, or definitely associated with protocol therapy

	Grade 2	Grade 3	Grade 4	Grade ≥2
Abdominal discomfort	2 (6.1%)	0 (0%)	0 (0%)	2 (6.1%)
Anorexia	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Anemia	7 (21.2%)	2 (6.1%)	0 (0%)	9 (27.3%)
Diarrhea	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)
Dyspnea	0 (0%)	1 (3.0%)	0 (0%)	1 (3.0%)
Fatigue	3 (9.1%)	3 (9.1%)	0 (0%)	6 (18.2%)
Fever	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)
Hyperglycemia	2 (6.1%)	1 (3.0%)	0 (0%)	3 (9.1%)
Hypertriglyceridemia	2 (6.1%)	0 (0%)	0 (0%)	2 (6.1%)
Hypoxia	0 (0%)	1 (3.0%)	0 (0%)	1 (3.0%)
Infection	5 (15.2%)	2 (6.1%)	0 (0%)	7 (21.2%)
Leukopenia	3 (9.1%)	1 (3.0%)	0 (0%)	4 (12.1%)
Mucositis	9 (27.3%)	0 (0%)	0 (0%)	9 (27.3%)
Neutropenia	4 (12.1%)	2 (6.1%)	0 (0%)	6 (18.2%)
Pneumonitis	3 (9.1%)	3 (9.1%)	0 (0%)	6 (18.2%)
Rash	7 (21.2%)	0 (0%)	0 (0%)	7 (21.2%)
Thrombocytopenia	0 (0%)	5 (15.2%)	0 (0%)	5 (15.2%)
Vomiting	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)
Weakness	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)

NOTE: % denotes number of events.

response interpretation, as consensus criteria for response in Waldenstrom macroglobulinemia primarily rely on changes in serum IgM levels. IgM discordance has been observed with other therapeutics used to treat Waldenstrom macroglobulinemia patients, including rituximab and ofatumumab that can increase, whereas bortezomib and ibrutinib can decrease serum IgM levels independent of changes in bone marrow tumor burden (13–17). A bystander effect for the "IgM flare" by rituximab has been proposed wherein immune cells release IL6 through the interactions with the Fc domain of rituximab prompting IgM release by Waldenstrom macroglobulinemia cells (18). The BTK substrate STAT5A regulates IgM secretion in Waldenstrom macroglobulinemia cells, and its selective inhibition by ibrutinib has been proposed to contribute to its discordant findings (17). However, the PI3K/AKT pathway is not a known contributor to STAT5A signaling, and other on-target signaling events, as well as off-target effects that contribute to IgM production and secretion could be impacted by everolimus.

The impact of MYD88 and CXCR4 mutations on response activity was also investigated. Genotyping was performed for 21 patients (all at DFCI). Although the study numbers are small for a meaningful analysis, the one patient with MYD88 wild type was a nonresponder, while the overall and major response rates were lower in CXCR4 mutated patients. Wild-type MYD88 and $CXCR4^{WHIM}$ mutation status were also associated with lower overall and major clinical responses to ibrutinib (17). In preclinical studies, Waldenstrom macroglobulinemia cells transduced with $CXCR4^{WHIM}$ receptors showed resistance to everolimus as well as ibrutinib following SDF-1a stimulation (5, 19). The use of CXCR4 antagonists sensitized Waldenstrom macroglobulinemia cells transduced with $CXCR4^{WHIM}$ receptors to the effects of everolimus and ibrutinib in these studies. Combination studies with CXCR4 antagonists may be of interest with everolimus, as well as other agents, such as ibrutinib, whose responses are impacted by CXCR4 mutations.

The median PFS observed in this study of untreated patients was similar (21 months) to that observed in our previous, multicenter study of everolimus in previously treated Waldenstrom macroglobulinemia patients. Patients with major responses exhibited longer PFS than those with minor responses or stable disease (i.e., 33 vs. 5 months). Only one patient attained a VGPR, and none a CR precluding an analysis on the impact of deeper (i.e., VGPR or better) categorical attainment on PFS. The lack of CR attainment observed in this trial is not uncommon in Waldenstrom macroglobulinemia and may reflect the broad prosurvival signaling cascades induced by MYD88 and/or CXCR4-activating mutations that include canonical NFκB, PI3K/AKT, and MAPK/ERK signaling (4, 5).

Drug-related toxicity was responsible for discontinuation of everolimus in 9 (27%) patients, including 5 for pneumonitis. In total, 6 patients (18%) experienced treatment-related pneumonitis that resulted in hospitalization for 3 patients. The incidence of grade 2 or higher treatment-related pneumonitis was higher in this study versus that observed by us in our study with everolimus monotherapy in previously treated Waldenstrom macroglobulinemia patients (18% vs. 8%). Treatment-related pneumonitis has also been reported with idelalisib and may represent a class effect for therapeutics that target PI3K/AKT signaling. A higher incidence of autoimmune-related events, including pneumonitis, has also been observed with idelalisib in first-line versus previously treated CLL patients (20). The impact of previous treatment status on Treg immune cell function may have contributed for differences in autoimmune activity between first-line and previously treated patients exposed to idelalisib and may be relevant in Waldenstrom macroglobulinemia patients undergoing everolimus therapy (20). Steroids were effective in the treatment of everolimus-related pneumonitis, which resolved in all patients. Oral mucositis, a known side effect of everolimus, was less pronounced (no grade ≥3 events) in this study compared with our experience in previously treated patients and likely reflected the routine use of an oral swish and spit dexamethasone solution during the first 3 months of everolimus therapy as a preventative. Despite this measure, mucositis occurred at a grade 2 level in 27% of patients and contributed to early study withdrawal for one patient. Minimal systemic steroid absorption was likely associated with the oral swish and spit dexamethasone solution. Cytopenias were also commonly observed adverse events, particularly grade 2 or higher anemia that was seen in 27% of patients.

The study findings show that everolimus is active in previously untreated Waldenstrom macroglobulinemia patients. Discordance between serum IgM levels and bone marrow disease burden is remarkable, and cessation of everolimus can produce rapid rebounds in serum IgM levels. Toxicity resulted in premature discontinuation of therapy in 27% of patients and included pneumonitis that appeared more common in this study compared with our experience in previously treated Waldenstrom macroglobulinemia patients. The risks and benefits of everolimus should carefully be weighed against other available treatment options for the primary therapy of Waldenstrom macroglobulinemia. Current NCCN and Waldenstrom macroglobulinemia consensus guidelines support use of everolimus in relapsed/refractory Waldenstrom macroglobulinemia disease and appear reasonable in view of the risk/benefit identified for everolimus in this first-line study (21, 22).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.P. Treon, I.M. Ghobrial
Development of methodology: S.P. Treon
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.P. Treon, C. Tripsas, L.T. Heffner, H. Eradat, A.Z. Badros, G. Yang, J.J. Castillo, J. Matous, I.M. Ghobrial
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.P. Treon, K. Meid, C. Tripsas, Z.R. Hunter, J. Gustine, J.J. Castillo, I.M. Ghobrial
Writing, review, and/or revision of the manuscript: S.P. Treon, K. Meid, C. Tripsas, L.T. Heffner, H. Eradat, A.Z. Badros, J.J. Castillo, I.M. Ghobrial
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.P. Treon, K. Meid, C. Tripsas, L. Xu, C.J. Patterson, J. Gustine
Study supervision: S.P. Treon, A.Z. Badros
Other (accrual of patients): J. Matous

Acknowledgments

This work was supported by Novartis Inc., that provided the study drug and research funding, Peter Bing, the Edward and Linda Nelson Fund for WM Research, the D'Amato Fund for Genomic Discovery, and the Bauman Fund for Waldenstrom's Macroglobulinemia Research.

Received July 29, 2016; revised October 5, 2016; accepted October 24, 2016; published OnlineFirst November 11, 2016.

References

1. Leleu X, Jia X, Runnels J, Ngo HT, Moreau A-S, Farag M, et al. The Akt pathway regulates survival and homing in Waldenstrom macroglobulinemia. Blood 2007;110:4417–26.
2. Xu L, Hunter Z, Yang G, Zhou Y, Cao Y, Liu X, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood 2013;121:2051–8.
3. Xu L, Hunter ZR, Tsakmaklis N, Cao Y, Yang G, Chen J, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenström macroglobulinaemia. Br J Haematol 2016;172:735–44.
4. Yang G, Buhrlage S, Tan L, Liu X, Chen J, Xu L, et al. HCK is a survival determinant transactivated by mutated MYD88, and a direct target of ibrutinib in Waldenstrom macroglobulinemia. Blood 2016;127:3237–52.
5. Cao Y, Hunter ZR, Liu X, Xu L, Yang G, Chen J, et al. The WHIM-like CXCR4S338X somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's macroglobulinemia. Leukemia 2015;29:169–76.
6. Houghton PJ. Everolimus. Clin Cancer Res 2010;16:1368–72.
7. Roccaro AM, Sacco A, Jia X, Banwait R, Maiso P, Azab F, et al. Mechanisms of activity of the TORC1 inhibitor everolimus in Waldenstrom macroglobulinemia. Clin Cancer Res 2012;18:6609–22.
8. Ghobrial IM, Gertz M, LaPlant B, Camoriano J, Hayman S, Lacy M, et al. Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory Waldenström macroglobulinemia. J Clin Oncol 2010;28:1408–14.
9. Ghobrial IM, Witzig TE, Gertz M, LaPlant B, Hayman S, Camoriano J, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom macroglobulinemia. Am J Hematol 2014;89:237–42.
10. Kyle RA, Treon SP, Alexanian R, Barlogie B, Björkholm M, Dhodapkar M, et al. Prognostic markers and criteria to initiate therapy in Waldenström's macroglobulinemia: consensus panel recommendations from the second international workshop on Waldenström's macroglobulinemia. Semin Oncol 2003;30:116–120.
11. Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth international workshop. Br J Haematol 2013;160:171–6.
12. Morel P, Duhamel A, Gobbi P, Dimopoulos MA, Dhodapkar MV, McCoy J, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood 2009;113:4163–70.
13. Dimopoulos MA, Zervas C, Zomas A, Kiamouris C, Viniou NA, Grigoraki V, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab. J Clin Oncol 2002;20:2327–33.
14. Treon SP, Branagan AR, Hunter ZR, Santos D, Tournhilac O, Anderson KC, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. Ann Oncol 2004;15:1481–3.
15. Furman RR, Eradat H, Switzky JC, Hayman SR, Hofmeister CC, Avignon NA, et al. A Phase II trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia. Blood 2011;116:1795.
16. Treon SP, Hunter ZR, Matous J, Joyce RM, Mannion B, Advani R, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03–248. Clin Cancer Res 2007;13:3320–5.
17. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med 2015;372:1430–40.
18. Yang G, Gong P, Ioakimidis T, Xu L, Hunter Z, Sun J, et al. The IgM flare following rituximab and IVIG administration in Waldenstrom's macroglobulinemia is related to IL-6 production by bystander immune cells, possibly through stimulation of the FcgammaRIIa receptor. Blood 2009;114:Abstract 761.
19. Roccarro AM, Sacco A, Jimenez C, Maiso P, Moschetta M, Mishima Y, et al. C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood 2014;123:4120–31.
20. Lampson BL, Matos T, Kim HT, Morgan EA, Rassenti L, Davids MS, et al. Idelalisib given front-line for the treatment of chronic lymphocytic leukemia results in frequent and severe immune-mediated toxicities. Blood 2015;126:497.
21. National Comprehensive Cancer Network. Waldenstrom macroglobulinemia, version 2.2016. Available from: www.nccn.org.
22. Leblond V, Kastritis E, Advani R, Ansell SM, Buske C, Castillo JJ, et al. Treatment recommendations for waldenstrom macroglobulinemia from the eighth international workshop for WM. Blood 2016;128:1321–8.