Prospective, multicenter clinical trial of everolimus as primary therapy in Waldenstrom Macroglobulinemia (WMCTG 09-214).

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Short Title: Everolimus in Waldenstrom Macroglobulinemia
Abstract Word Count: 250
Text Word Count: 2447

Tables: **2**
Figure: **2**
Keywords: Waldenström Macroglobulinemia, Everolimus, MYD88, CXCR4, mTOR

Abstract

Purpose: Everolimus inhibits mTOR, a component of PI3K/AKT pro-survival signaling triggered by MYD88 and CXCR4 activating mutations in Waldenstrom's Macroglobulinemia (WM).

Experimental design: We evaluated everolimus in a prospective, multicenter study of 33 symptomatic, previously untreated WM patients. Intended therapy consisted of everolimus (10 mg/day) until progression or unacceptable toxicity. Dose de-escalation was permitted. The study was registered at www.clinicaltrials.gov (NCT01470196).

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, non-responders associated with wild-type MYD88 and mutated CXCR4 status. Median time to response was 4 weeks. Discordance between serum IgM levels and BM 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 two patients. Toxicity led to treatment discontinuation in 27% of patients, including 18% for pneumonitis.

Conclusions: Everolimus is active in previously untreated WM. 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 WM patients. The risks and benefits of everolimus should be carefully weighed against other primary WM therapy options.

Introduction

The PI3K/AKT pathway is an important survival signaling cascade that supports the growth and survival of malignant lymphoplasmacytic cells (LPC) in Waldenstrom Macroglobulinemia (WM).[1] Activating mutations in MYD88 and CXCR4, found in 95% and 30% of WM patients, respectively, trigger PI3K/AKT signaling.[2-5] Everolimus is an orally administered inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase that is downstream of the PI3K/AKT signaling pathway.[6] Everolimus is approved by the U.S. Food and Drug Administration for treatment of several solid malignancy indications, and shows *in vitro* activity against WM cells.[6] In previous work, we evaluated the activity of everolimus in previously treated WM 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 WM patients. We performed serial bone marrow (BM) biopsies to more fully delineate the impact of therapy on WM 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 WM 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 ≥75 x 10^9/L, absolute neutrophil count (ANC) of $\geq$1.5 X 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 WM Clinical Trials Group (WMCTG Protocol 09-214). All patients provided informed written consent approved by the local institutional review boards (IRB). 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 de-escalations, respectively. Dose re-escalation was not permitted. Re-treatment was permitted once adverse events resolved to grade 1 or less. Filgrastim or transfusional support was permitted to treat hematological 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 4 times daily for prevention of stomatitis during the first three months of everolimus therapy.

Baseline studies consisted of complete blood counts and differential, quantitative serum IgM levels, serum protein electrophoresis, a BM biopsy and aspiration, computed tomography (CT) scans of the chest, abdomen and pelvis (CAP), serum electrolytes, liver function tests (LFTs), amylase, lipase, blood urea nitrogen (BUN), 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 BM 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 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. An allele specific polymerase chain reaction (PCR) assay was used for determination of MYD88^{L265P} using DNA isolated from CD19-selected BM cells as previously described.[1] CXCR4^{WHIM} mutation status was determined by AS-PCR and Sanger sequencing of CD19-selected BM cells.[2]

Statistical analysis

The primary endpoint was determination of overall response rate. Response determinations were made using consensus criteria adapted from the Sixth International Workshop on WM.[11] Secondary endpoints included determination of time to progression, and assessment of safety and tolerability of everolimus. Sample size was predicated on an expected overall response rate 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 post-therapy continuous variables. For categorical variables, a two-tailed Fisher's 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, College Station, TX, USA).

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 12/9/2009, and last patient started therapy on 6/13/2011. The last patient came off study for disease progression on 7/14/2016. The median number of treatment cycles administered was 10.5 (range 1-64.6). All participants are off treatment.

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 ($p<0.0001$). Pre-therapy, 23/33 (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$). Among 24 patients with serial BM biopsies, the median BM involvement declined from 75% (range 2-95%) to 52.5% (range 6-95%) at best response ($p=0.03$). Discordance between serum IgM levels and BM disease burden was common (**Figure 1**). For 24 patients who had a repeat BM biopsy by week 26, the median change in serum IgM was -47.9% (range 3.8% to -88.5%, while the synchronous change in BM disease burden was -13.3% (range -36.8% to 200%) ($r=0.23$; $p=0.26$). In 8 (33.3%) of these patients, the BM disease burden had increased, with a median increase of 43% (range 25% to 200%), while the serum IgM level decreased by a median of 41% (range -75.7% to 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 (MR; n=4); for an overall response rate (ORR) and major response (PR or better) rate of 72.7% (95% CI 57.5-87.9%) and 60.6% (95% CI 43.9-77.3%), respectively. No patient achieved a complete response. Overall and major

response rates were not impacted by the International Scoring System for WM (ISSWM) 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 4/21 (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% 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), while 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 **Figure 2.** The median time to progression was 21 months (95% CI 11-39 months). By univariate analysis, neither baseline BM disease burden >50% versus $\leq$50% (p=0.95), serum IgM >4,000 versus $\leq$4,000 mg/dL (p=0.59), nor hemoglobin >11 versus $\leq$11 g/dL (p=0.16) levels were associated with increased risk for progression. Dose de-escalation (<10 mg/day versus 10 mg/day) was also not associated 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 versus 5 months, respectively; HR=4.350, 95% CI 3.9-113 months, p=0.0011).

Toxicities

Grade 2 or higher toxicities that were at least possibly related to protocol therapy are presented in **Table 2**. The most common non-hematological treatment related Grade ≥2 toxicities included mucositis (27.3%), infection (21.2%), rash (21.2%), fatigue (18.2%), and pneumonitis (18.2%). Treatment related hematological 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: non-response (n=6); progressive disease (n=15); pneumonitis (n=5); withdrawal of consent (N=3) that included one patient for recurring grade 2 stomatitis; non-compliance (N=2), and prolonged study drug hold for unrelated infection.

Following discontinuation of everolimus, rapid increases in serum IgM levels were common. In seven 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 WM patients. Everolimus inhibits mTOR, a serine-threonine kinase that contributes to PI3K/AKT directed growth and survival signaling in WM.[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 response interpretation since consensus criteria for response in WM primarily rely on changes in serum IgM levels. IgM discordance has been observed with other therapeutics used to treat WM patients including rituximab and ofatumumab that can increase, while bortezomib and ibrutinib can decrease serum IgM levels independent of changes in BM tumor burden.[13-17] A bystander effect for the "IgM flare" by rituximab has been proposed wherein immune cells release IL-6 though interactions with the Fc domain of rituximab prompting IgM release by WM cells.[18] The BTK substrate STAT5A regulates IgM secretion in WM 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). While the study numbers are small for a meaningful analysis, the one patient with MYD88 wild-type was a non-responder, 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, WM 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 WM 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 WM patients. Patients with major responses exhibited longer PFS than those with minor responses or stable disease (i.e. 33 versus 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 WM, and may reflect the broad pro-survival signaling cascades induced by MYD88 and/or CXCR4 activating mutations that include canonical NFkB, 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 (18%) patients 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 WM patients (18% versus 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 frontline versus previously treated CLL patients.[20] The impact of previous treatment status on T-reg immune cell function may have contributed for differences in autoimmune activity between frontline and previously treated patients exposed to idelalisib, and may be relevant in WM 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 $\geq$3 events) in this study compared to our experience in previously treated patients, and likely reflected the routine use of an oral swish and spit dexamethasone solution during the first three 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 WM patients. Discordance between serum IgM levels and BM 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 to our experience in previously treated WM patients. The risks and benefits of everolimus should carefully be weighed against other available treatment options for the primary therapy of WM. Current NCCN and WM consensus guidelines support use of everolimus in relapsed/refractory WM disease, and appear reasonable in view of the risk/benefit identified for everolimus in this frontline study.[21,22]

Acknowledgements

Supported by Novartis Inc., that provided study drug and research funding, Peter Bing M.D., 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.

Authorship

SPT designed the study. SPT, LH, HE, AZB, JJC, JM, and IMG provided treatment to study patients, and collected study data. KM, CT, JG, CJP coordinated the study and/or provided regulatory oversight. SPT and KM analyzed the study data. LX, GY, and ZRH performed MYD88 and CXCR4 genotyping and/or signaling studies. All authors reviewed the manuscript, provided input, and approved its submission. SPT wrote the first draft of the manuscript.

Conflicts of Interest

SPT and IMG received research funding from Novartis Inc. JJC received honoraria from Alexion, Biogen, Celgene and Otsuka, and research funding from Abbvie, Gilead, Millennium and Pharmacyclics.

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Legends

Table 1. Baseline characteristics for all patients enrolled on study. ISSWM, International Scoring System for WM.[12] Number of patients with low (L); intermediate (I); and high (H) risk ISSWM score is shown.

Table 2. Adverse events at highest grade for an individual patient that were possibly, probably or definitely associated with protocol therapy; (%) denotes number of events.

Figure 1. Synchronous changes for serum IgM levels and bone marrow disease burden assessed for 24 patients who underwent serial serial bone marrow biopsies by 26 weeks. *r*=0.23; p=0.26 by Spearman's Rho test for correlation of serum IgM and bone marrow disease burden for all 24 patients.

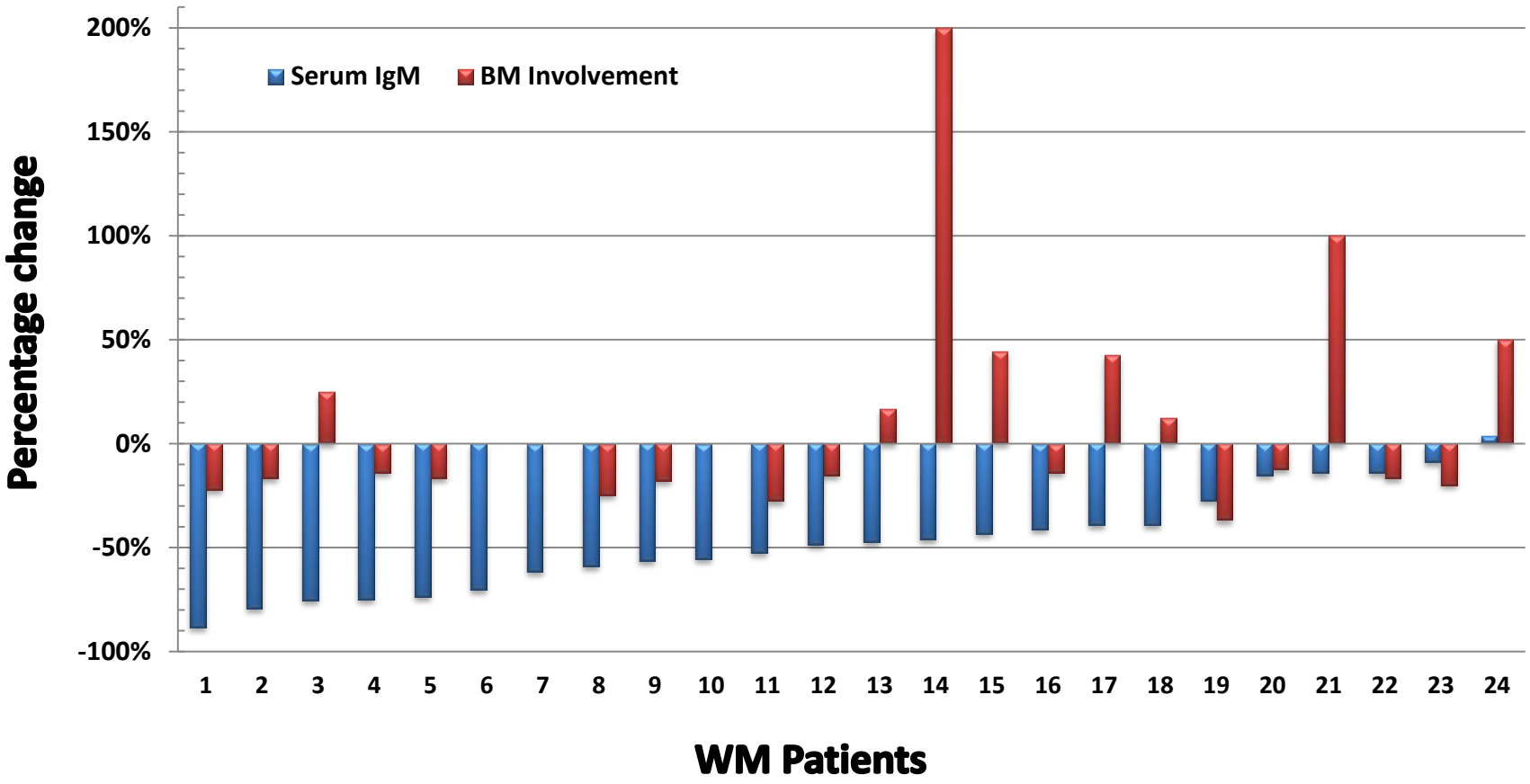
Figure 2. Progression-free survival following everolimus therapy in 33 symptomatic untreated Waldenstrom's macroglobulinemia patients. Kaplan Meier curve with 95% confidence intervals for progression free survival is shown for the 33 WM patients treated with everolimus.

Table 1.

	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 (mm3)	214,000	84,000-448,000
B_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

Table 2.

	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%)


Serum IgM
BM Involvement
200%
150%
100%
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-50%
-100%
Percentage change
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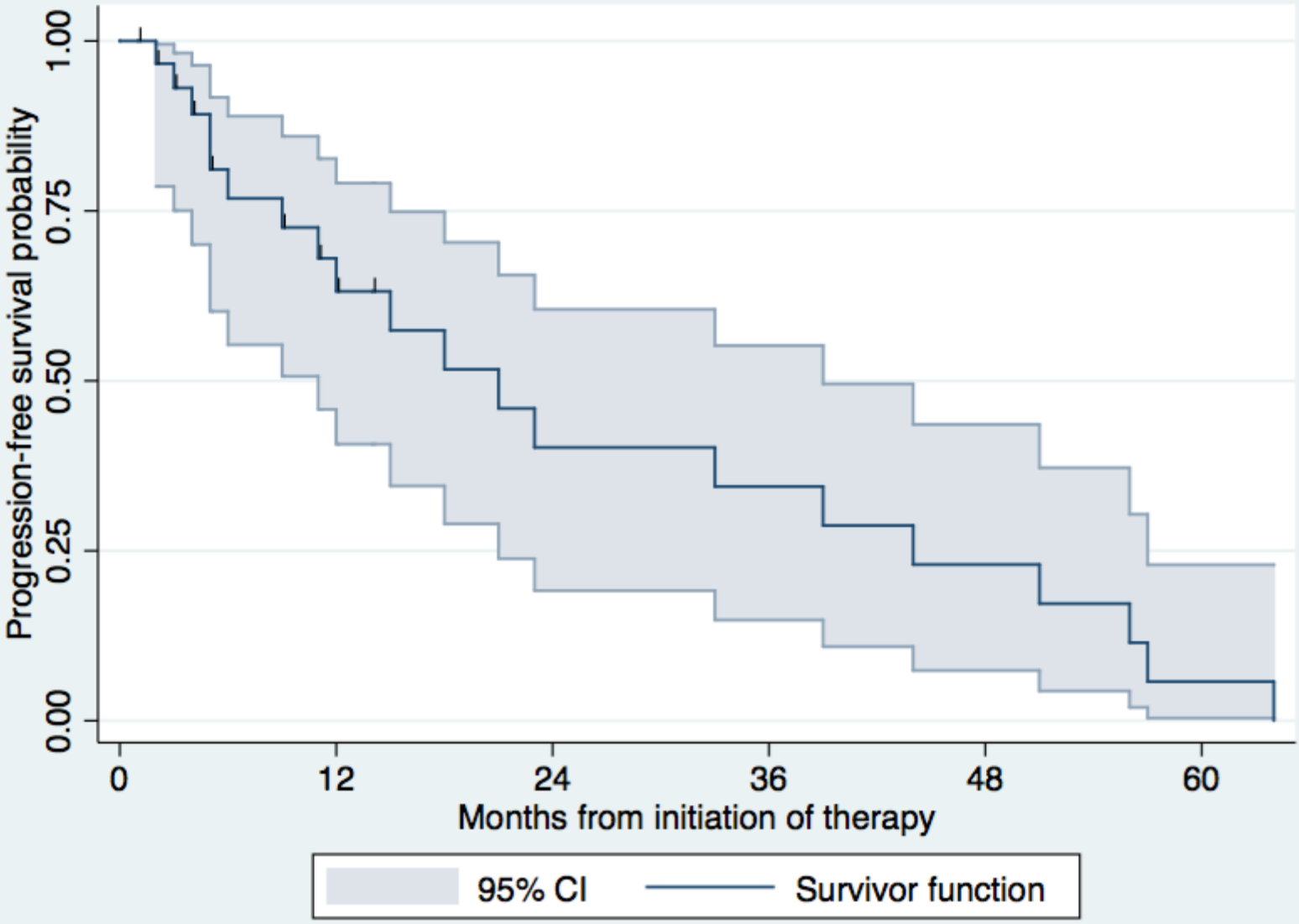
WM Patients


Progression-free survival probability
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
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Months from initiation of therapy
95% CI
Survivor function