Predictors of response and survival in a large cohort of 319 Waldenström macroglobulinemia patients treated with ibrutinib monotherapy

Supplemental data

Table S1. Indications to treat in 319 patients with WM treated with ibrutinib monotherapy. The total percentage is higher than 100% because some patients had more than one indication to treat.

Indications	N (%)
Anemia	186 (58%)
Constitutional symptoms	96 (30%)
Hyperviscosity	48 (15%)
Extramedullary disease	29 (9%)
Peripheral neuropathy	23 (7%)
Thrombocytopenia	23 (7%)
Cryoglobulinemia	4 (1%)
Cold agglutinin disease	2 (1%)

Table S2. Patients' characteristics according to *CXCR4* mutational status

Characteristic	CXCR4 WT (n=155)	CXCR4 MUT (n=89)	P-value
Age >65 years, n(%)	96 (62%)	46 (52%)	0.12
Male sex	104 (67%)	56 (63%)	0.51
Hemoglobin <11.5 g/dl	109 (71%)	64 (72%)	0.91
Platelet count <100 K/uL	9 (6%)	21 (24%)	<0.001
Serum IgM level >4,000 mg/dl	58 (37%)	43 (48%)	0.10
Serum IgM level >7,000 mg/dl	5 (3%)	7 (8%)	0.11
Serum β2-microglobulin level >3 mg/l	89 (70%)	40 (59%)	0.13
Serum albumin level ≤3.5 g/dl	49 (33%)	21 (25%)	0.18
Bone marrow involvement ≥60%	73 (52%)	54 (64%)	0.08
IPSSWM			
Low	33 (24%)	19 (25%)	0.71
Intermediate	47 (35%)	22 (29%)	
High	55 (41%)	34 (45%)	
MYD88 wild type	4 (3%)	0 (0%)	0.13
Previously treated	105 (68%)	60 (67%)	0.96

WT: wildtype; MUT: mutated; IPSSWM: International Prognostic Scoring System for Waldenström Macroglobulinemia

Table S3. Patients' characteristics according to *CXCR4* mutation subtype

Characteristic	CXCR4 NS (n=56)	CXCR4 FS (n=31)	P-value
Age >65 years, n (%)	27 (48%)	18 (58%)	0.38
Male sex	33 (59%)	22 (71%)	0.27
Hemoglobin <11.5 g/dl	38 (68%)	26 (84%)	0.10
Platelet count <100 K/uL	11 (20%)	10 (32%)	0.20
Serum IgM level >4,000 mg/dl	28 (50%)	15 (48%)	0.89
Serum IgM level >7,000 mg/dl	5 (9%)	2 (6%)	0.68
Serum β2-microglobulin level >3 mg/l	26 (55%)	13 (65%)	0.46
Serum albumin level ≤3.5 g/dl	14 (26%)	7 (23%)	0.76
Bone marrow involvement ≥60%	32 (58%)	22 (79%)	0.07
IPSSWM			
Low	14 (29%)	4 (17%)	0.16
Intermediate	16 (33%)	5 (21%)	
High	19 (39%)	15 (63%)	
MYD88 wild type	0 (0%)	0 (0%)	1.00
Previously treated	36 (64%)	22 (71%)	0.53

NS: nonsense; FS: frameshift; IPSSWM: International Prognostic Scoring System for Waldenström Macroglobulinemia

Table S4. Univariate and multivariate logistic regression analyses for major and deep response in 319 patients with Waldenström macroglobulinemia treated with ibrutinib monotherapy using continuous variables.

Major response	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	p	OR (95% CI)	p
Age at WM diagnosis, years	1.02 (0.99-1.04)	0.23		
Male sex	1.19 (0.69-2.06)	0.53		
Hemoglobin level, g/dl	0.81 (0.70-0.94)	**0.005**	0.83 (0.65-1.06)	0.14
Platelet count, k/ul	1.00 (0.99-1.00)	0.19		
β2-microglobulin level, mg/l	1.21 (1.01-1.47)	**0.04**	1.00 (0.82-1.22)	0.97
Albumin level, g/dl	0.73 (0.40-1.36)	0.33		
Serum IgM level, mg/dl	0.99 (0.99-1.00)	0.77		
Bone marrow, %	1.01 (1.00-1.02)	**0.004**	1.01 (0.99-1.03)	0.14
Previously treated	0.92 (0.52-1.64)	0.78		
CXCR4 mutated	0.33 (0.17-0.61)	**<0.001**	0.19 (0.08-0.43)	**<0.001**
CXCR4 WT	1.00		1.00	
CXCR4 NS	0.24 (0.12-0.48)	**<0.001**	0.14 (0.06-0.34)	**<0.001**
CXCR4 FS	0.69 (0.25-1.87)	0.47	0.49 (0.12-2.05)	0.33
Deep response	**Univariate analysis**		**Multivariate analysis**	
Variables	OR (95% CI)	p	OR (95% CI)	p
Age at WM diagnosis, years	0.99 (0.98-1.02)	0.94		
Male sex	1.08 (0.65-1.82)	0.76		
Hemoglobin level, g/dl	0.83 (0.72-0.95)	**0.009**	0.83 (0.65-1.04)	0.11
Platelet count, k/ul	1.00 (1.00-1.01)	**0.01**	1.00 (1.00-1.01)	**0.01**
β2-microglobulin level, mg/l	1.05 (0.93-1.18)	0.44		
Albumin level, g/dl	0.56 (0.32-0.97)	**0.04**	0.80 (0.36-1.77)	0.58
Serum IgM level, mg/dl	0.99 (0.99-0.99)	**0.001**	0.99 (0.99-0.99)	**0.001**
Bone marrow, %	1.01 (1.00-1.02)	**0.04**	1.01 (0.99-1.02)	0.06
Previously treated	1.31 (0.76-2.25)	0.33		
CXCR4 mutated	0.34 (0.18-0.66)	**0.001**	0.39 (0.18-0.83)	**0.01**
CXCR4 WT	1.00		1.00	
CXCR4 NS	0.26 (0.11-0.61)	**0.002**	0.29 (0.11-0.75)	**0.01**
CXCR4 FS	0.53 (0.21-1.31)	0.17	0.64 (0.22-1.85)	0.41

WT: wild type; NS: nonsense; FS: frameshift

MYD88 mutational status was not included as sample size for *MYD88* wild type status was small (n=8)

Table S5. Causes of death in 53 patients with WM treated with ibrutinib

Cause of death	N (%)
WM progression	20 (40)
Cardiac amyloidosis	4 (8)
Lung infection	4 (8)
Cardiac arrest/sudden death	4 (8)
Cerebrovascular accident	2 (4)
Interstitial lung disease	2 (4)
Heart failure	1 (2)
Myocardial infarction	1 (2)
Other cancers	8 (16)
DLBCL	3
Esophageal cancer	2
Head and neck cancer	1
Prostate cancer	1
Acute myeloid leukemia	1
Unknown	7 (14)

Table S6. Univariate and multivariate Cox proportional-hazard regression analyses for progression-free survival and overall survival in 319 patients with Waldenström macroglobulinemia treated with ibrutinib monotherapy using continuous variables.

Progression-free survival	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age at WM diagnosis, years	1.00 (0.98-1.03)	0.82		
Male sex	1.09 (0.67-1.78)	0.72		
Hemoglobin level, g/dl	0.86 (0.76-0.98)	**0.02**	0.89 (0.75-1.05)	0.17
Platelet count, k/ul	0.99 (0.99-0.99)	**0.01**	0.99 (0.99-1.00)	0.07
β2-microglobulin level, mg/l	1.09 (0.99-1.21)	0.08		
Albumin level, g/dl	0.59 (0.36-0.97)	**0.04**	0.57 (0.31-1.06)	0.07
Serum IgM level, mg/dl	0.99 (0.99-1.00)	0.56		
Bone marrow, %	1.00 (0.98-1.00)	0.34		
Previously treated	1.40 (0.77-2.53)	0.27		
CXCR4 mutated	2.31 (1.41-3.79)	**0.001**	2.09 (1.23-3.56)	**0.006**
CXCR4 WT	1.00			
CXCR4 NS	2.93 (1.71-5.00)	**<0.001**	2.76 (1.55-4.95)	**0.001**
CXCR4 FS	1.49 (0.68-3.23)	0.32	1.30 (0.58-2.90)	0.52
Overall survival	**Univariate analysis**		**Multivariate analysis**	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age at WM diagnosis, years	1.08 (1.05-1.11)	**<0.001**	1.08 (1.04-1.12)	**<0.001**
Male sex	1.55 (0.81-2.95)	0.18		
Hemoglobin level, g/dl	0.75 (0.63-0.88)	**0.001**	0.80 (0.64-0.99)	**0.047**
Platelet count, k/ul	0.99 (0.99-0.99)	**0.02**	0.99 (0.99-0.99)	**0.045**
β2-microglobulin level, mg/l	3.01 (1.27-7.18)	**0.01**	0.99 (0.86-1.14)	0.87
Albumin level, g/dl	0.45 (0.26-0.78)	**0.005**	0.65 (0.31-1.35)	0.25
Serum IgM level, mg/dl	1.00 (1.00-1.00)	0.40		
Bone marrow, %	1.00 (0.99-1.01)	0.70		
Previously treated	1.46 (0.67-3.15)	0.34		
CXCR4 mutated	1.37 (0.74-2.53)	0.31		
CXCR4 WT	1.00			
CXCR4 NS	1.42 (0.71-2.85)	0.32		
CXCR4 FS	1.49 (0.61-3.64)	0.39		

WT: wild type; NS: nonsense; FS: frameshift

MYD88 mutational status was not included as the sample size for *MYD88* wildtype status was small (n=8)

Figure S1. Categorical response to ibrutinib monotherapy in 319 patients with WM (A), according to CXCR4 mutational status (B), and according to CXCR4 mutation subtype
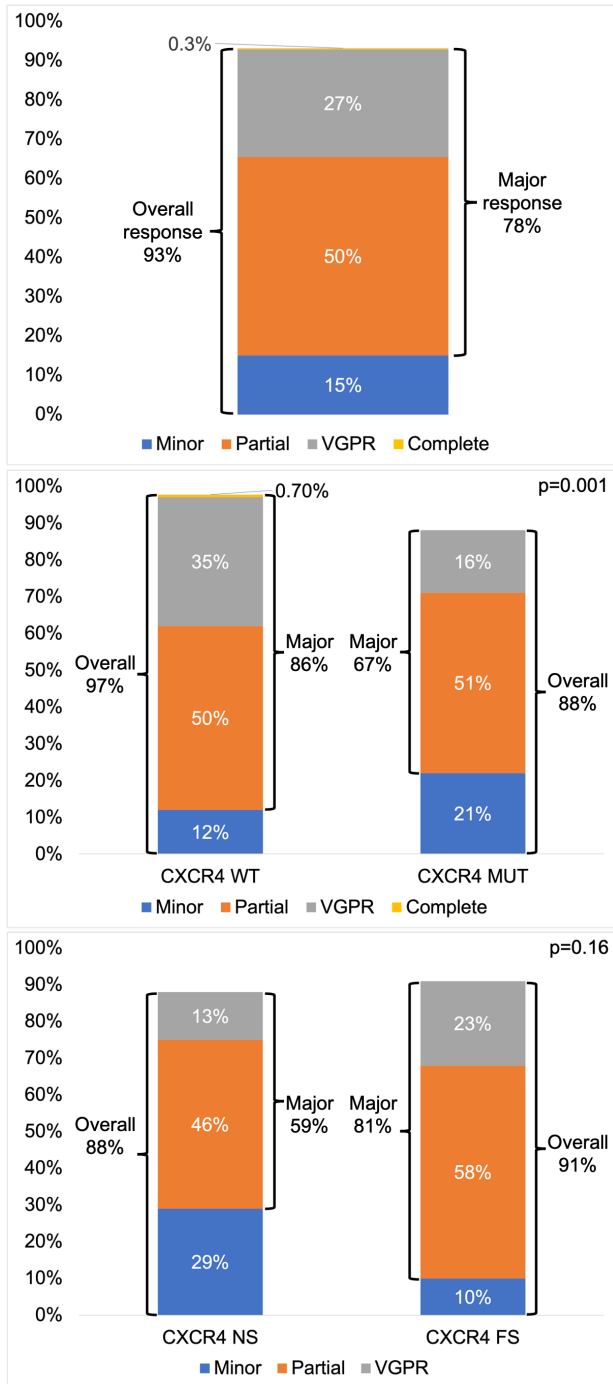
Figure S2. PFS estimates according to the proposed PFS score in patients age >65 years (A), ≤65 years (B), serum IgM level ≥4,000 mg/dl (C), serum IgM level <4,000 mg/dl (D), hemoglobin level <11.5 g/dl (E), hemoglobin level ≤11.5 g/dl (F), previously treated (G), and previously untreated (H)