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Utility of Serum Free Light Chain Measurements in Multiple Myeloma Patients Not Achieving Complete Response to Therapy

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Abstract

Normalization of the serum free light chain ratio (FLCr) with the absence of bone marrow monoclonal plasma cells following achievement of a complete response (CR) to therapy denotes a stringent CR in multiple myeloma (MM), and is associated with improved overall survival (OS). However, its value in patients achieving <CR is not clear. We hypothesized that patients achieving a normalization of FLCr with initial therapy of MM will have an improved outcome, even in the absence of a CR. We retrospectively evaluated 449 patients with newly-diagnosed MM with measurable disease at baseline, who did not achieve a CR with initial therapy. One hundred fifty three patients (34%) had a normal FLCr while 296 (66%) had an abnormal ratio. Patients with a normal FLCr had a longer progression-free survival (PFS) (29 vs. 16 months, P <.001) and OS (91 vs. 58 months, P <.001). Normalization of FLCr retained its prognostic value in a multivariable model. Our results suggest an important role for sFLC measurement in disease monitoring even in patients who achieve only a partial response to therapy. Obtaining a normal FLCr confers a favorable prognosis independent from other factors, supporting the inclusion of sFLC in all levels of response criteria.

Keywords

serum free light chain ratio; multiple myeloma; response; survival

INTRODUCTION

Monoclonal gammopathies are characterized by secretion of monoclonal protein by the clonal plasma cells, which in the majority of patients is in the form of intact

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AUTHOR CONTRIBUTIONS

MA and SKK designed the study, extracted the data, performed the analysis and wrote the manuscript, SVR, AD, MAG, MQL, FKB, LH, DD, PK, SRH, JAL, and RAK provided patients, and critically reviewed and edited the manuscript.

'Supplementary information is available at Leukemia's website'

AUTHOR DISCLOSURES

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immunoglobulins. In addition to the intact monoclonal proteins, normal as well as clonal plasma cells also secrete kappa and lambda light chains unbound to a heavy chain.(1, 2) These serum free light chains can be quantitated by assays that utilize antibodies against epitopes on the free light chains that are typically hidden when bound to the heavy chain. In the vast majority of patients with monoclonal gammopathies, the clonal plasma cells secrete an excess of one of the light chains, thus disrupting the normal ratio between serum free kappa and lambda light chains.(3-6) In a smaller proportion of patients, clonal PCs only secrete free light chains and a clonal heavy chain cannot be identified.(7)

The proportion of patients with elevated monoclonal free light chains increases with disease progression from monoclonal gammopathy of undetermined significance (MGUS) to smoldering myeloma (SMM) to symptomatic MM. Baseline serum free light chain (sFLC) measurements have been shown to be of prognostic value in all types of monoclonal gammopathies, predicting progression in MGUS and SMM and survival in MM.(3, 5, 8) More importantly, in MM, sFLC measurements allow assessment of response to therapy and have been integrated into the International Myeloma Working Group (IMWG) guidelines for response criteria.(3, 5, 6, 9-18) While it is the primary marker of response among patients with light chain myeloma and those without conventional levels of measurable disease by electrophoresis (<1 g/dl M spike in SPEP or < 200 mg/24 hours in UPEP), it is also a key determinant of the depth of response on all patients with MM. The IMWG response criteria recently defined a new level of response, stringent complete response (sCR), that requires a normalization of serum FLC ratio (FLCr) in addition to the conventional definition of CR with the absence of bone marrow clonal plasma cells.(19) Achievement of a sCR is associated with improved outcomes including overall survival and likely denotes a deeper tumor reduction.

Previous studies have explored the potential role of sFLC in the follow up of non-light chain MM and have produced different conclusions. Mori et al. studied 73 patients who received an induction therapy with novel agents and suggested a prognostic value for the involved FLC (iFLC) level at the time of stem cell mobilization on survival outcomes.(20) In a prior study, Dispenzieri et al. found no utility for adding sFLC measurement two months after therapy with alkylating agents in MM with measurable disease.(8) In a recent Japanese study, Iwama et al. studied the effect of normalization of FLCr after treatment in 126 newly diagnosed MM patients and showed that normal FLCr was associated with longer overall survival (OS) regardless of other factors.(21) However, these studies have not examined the role of FLC measurements in the group of patients with residual intact immunoglobulin monoclonal protein (less than CR) at the time of maximal response following therapy. We designed this study to specifically examine the value of the FLC measurements in a cohort of patients with non-light chain MM, who have residual monoclonal protein on SPEP following initial therapy of myeloma (patients with less than a CR).

PATIENTS AND METHODS

Patients

We initially identified 1346 patients with newly diagnosed multiple myeloma patients seen at the Mayo Clinic in Rochester, MN between January 2004 and December 2011. The dates

were selected based on the date of serum FLC assay becoming routinely available in the clinical laboratory. We then selected patients with measurable disease on serum protein electrophoresis, defined as a serum M-spike ≥1 g/dl at the time of diagnosis. Finally, we excluded all patients with negative immunofixation for monoclonal M-protein in serum and urine, did not have serum FLC results available from the time of their first best response, or had biclonal disease with kappa and lambda FLCs. After applying the inclusion and exclusion criteria a total of 449 patients were included in our study **(Supplementary Figure 1)**. The Mayo Clinic Institutional Review Board, in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act guidelines of 1996, approved the study. An informed consent was obtained from all patients included in the study.

Data was obtained from existing databases and review of medical records. We collected the serum electrophoresis results and sFLC values that corresponded with the date of the best response following diagnosis. M protein measurements were collected serially until the time of the first relapse or last follow date if no relapse was recorded. The FLC assay (FREELITE, The Binding Site, Birmingham, United Kingdom) was performed as part of routine clinical care as previously described. We used the following ranges as our reference for normal FLC values; κ FLC (0.33–1.94 mg/dl), λ FLC (0.57–2.63 mg/dl), and (0.26–1.65) for the sFLC κ/λ ratio (FLCr). dFLC was defined as the absolute difference between the kappa and lambda FLC levels.

Statistical analysis—We examined the impact of both FLCr normalization and normalization of the involved sFLC (iFLC) at the time of best response as well as the value of baseline iFLC levels. For the purpose of analyzing baseline iFLC we dichotomized patients into high (≥10 mg/dL) (n=279) and low (<10 mg/dL) (n=86) levels of the baseline iFLC. Eighty-nine patients did not have a serum FLC assay available at the time of diagnosis.

Statistical analysis was done using JMP® 10 software package (SAS Institute Inc., Cary, NC, USA). Progression-free survival (PFS) and overall survival were analyzed using the Kaplan-Meier method and compared using log rank test. Multivariate analysis was performed using Cox proportional hazards model to assess the influence of a number of variables on PFS and OS.

RESULTS

Patient characteristics

The baseline demographics and disease characteristics of all 449 patients are shown in **Table 1**. The median age of the cohort at the time of diagnosis was 65 (range, 29-91); 13% were older than 75 years and 281 (63%) were male. The estimated median follow up for the whole cohort was 5.5 years (95% CI; 5.0, 5.9); 240 (53%) patients were alive with a median follow up of 4.7 years (range, 0.4 to 10). Three hundred and seventy (82%) patients had relapsed following the initial therapy with a median time to progression (TTP) of 19.5 months (95% CI; 18, 22). The median PFS for the entire cohort was 18.8 months (95% CI; 17, 21) and the OS was 67 months (95% CI; 60, 73); both from diagnosis. Baseline FLC

measurements were available in 360 (80%) patients; 339 (94%) of them had an abnormal FLCr and a dFLC of >= 10 mg/dL was seen in 234 (65%) patients.

Treatment and response

The most common first-line therapy was lenalidomide with or without dexamethasone in 212 (47%) patients and additional 34 (8%) patients received cyclophosphamide or melphalan in combination with lenalidomide and dexamethasone. A bortezomib-based regimen was used in 60 (13%) patients and additional 15 (3%) and 4 (1%) patients received bortezomib-lenalidomide-dexamethasone (VRD) and bortezomibthalidomide-dexamethasone (VTD), respectively. A total of 45 (10%) patients received a thalidomide-based regimen and the remaining 79 (18%) patients received conventional therapies. A partial response or better was seen among 363 (81%) of patients including 144 (32%) with a VGPR and 219 (49%) with a PR. The median time to the best first response for the whole cohort was 6.9 months (range: 0.3-83 months). The PFS from diagnosis was 21 months (95% CI; 19, 24) for those achieving a PR or better compared with 7 months (95% CI; 5, 12) for the remainder; P <.001 (**Supplementary figure 2A**). The differences were significant even with the analysis performed after landmarking at 1 year from diagnosis, thus allowing patients adequate time to respond to therapy (**Supplementary figure 2B**). The OS from diagnosis was 73 months (95% CI; 64, 99) for those achieving a PR or better compared with 49 months (95% CI; 32, 58) for the remainder; P <.001 (**Supplementary figure 2C**); and was similar when landmarked at 1 year from diagnosis (**Supplementary figure 2D**).

sFLC response to treatment and outcome

Normalization of FLCr at the time of the best first response was seen in 153 (34%) patients and normalization of iFLC level was seen in 199 (44%) patients. Only 122 patients (27%) achieved both normal iFLC level and FLCr. The median time to the best first response was 10 months (range: 0.7-83 months) in patients who achieved a normal sFLCr and 6 months (range: 0.3-48 months) for patient who did not achieve a normal sFLCr. The proportion of patients with FLCr or iFLC normalization within each IMWG response category is shown in **Figure 1**. Patients, who achieved a normal FLCr had a longer PFS compared to those who did not (29 vs. 16 months, P <.001) (**Figure 2A**), and also had a longer OS (91 vs. 58 months, P< .001) (**Figure 2B**). Patients, who achieved a normal iFLC level as compared to those who did not, had a longer PFS (23 vs. 15 months, P <.001) (**Figure 2C**), and OS (73 vs. 58 months, P< .001) (**Figure 2D**).

We then looked at the difference in survival outcomes after grouping patients who achieved a normal iFLC (n=199) into two groups; those who achieved normal FLCr and those who did not. Among the patients achieving a normal iFLC level, those who achieved a normal FLCr had a longer PFS (30 vs. 20 months, P< .002), and OS (99 vs. 65 months, P= .02) compared with those who did not. However, we saw no significant differences in PFS or OS when grouping patients who achieved a normal sFLC κ/λ ratio into those who achieved a normal iFLC level and those who did not.

We specifically compared survival outcomes of patients who achieved a normal FLCr to those who did not achieve a normal FLCr, within each of the IMWG response categories

(**Table 2**). We found that FLCr normalization had a favorable impact on PFS in each of the three groups (VGPR, PR, and SD+PD). However, when looking at the OS, only patients with partial response (PR) had a better OS associated with a normal sFLC κ/λ ratio.

Finally, in univariable analysis conventional prognostic factors, such as age > 65 years, serum creatinine > 2 mg/dL, ISS stage 3 at diagnosis, LDH > 222) and normalization of FLCr were prognostic for overall survival. In a multivariate model that included all these variables (253 patients with all variables available), normalization of FLCr, ISS stage 3 and LDH > 222 were all prognostic for OS. When iFLC normalization was substituted for FLCr normalization in the same multivariable model, only LDH and ISS were significant. Only a minority of patients had FISH data from diagnosis and hence this was not included in the analysis.

We also attempted to examine the impact of the treatment type on our findings. Among patients receiving lenalidomide containing therapy and those receiving conventional therapies, the impact of FLCr normalization was significant, similar to the overall population. However, in patients receiving bortezomib or thalidomide containing regimens, the findings were not significant, but the small number of patients in these groups limits these comparisons.

Prognostic impact of sFLC measurements in relation to baseline FLC measurements

The baseline free light chains measurement were available in 360 (80%) of the total cohort. Out of the 360 patients, only 21 (6%) had a normal baseline FLCr, those patients had better OS as compared to the 339 (94%) who had abnormal ratio, (NR vs. 65 months, P= .03). One hundred twenty six (36%) patients had a dFLC of <10 mg/dl at baseline, those patients had a superior OS compared to the remainder of the patients; median not reached vs. 61 months, P= 0.02 (**Figure 3A**). We specifically examined the impact of normalization of FLCr among patients with low or high levels of dFLC at baseline on the PFS and OS. In both groups with low and high levels of dFLC, patients who achieved normal FLCr had a better PFS **(Figure 3B, 3C; respectively)**. However, achievement of normal FLCr improved OS in patients with high baseline dFLC ≥10 **(Figure 3D)** and not in patients with low baseline dFLC. We also examined the specific baseline clinical and laboratory factors associated with normalization of the FLCr (**Table 3**). Lower measures of baseline FLC levels were associated with a higher probability of normalization, as might be expected.

DISCUSSION

Serum free light chain assay provides valuable information in all stages of the disease including precursor states such as MGUS, SMM and plasmacytomas, where it remains an excellent marker of future progression risk.(3, 5, 9) It is the primary marker of hematological response in light chain amyloidosis.(22) It has also been shown to be prognostic in patients with newly diagnosed myeloma, and remains an integral part of the current response criteria with stringent CR defined partly on this assessment. In the current study, we have been able to demonstrate utility for serum FLC measurements in patients who still have a measurable intact immunoglobulin M spike. In addition, the findings raise important questions regarding the biology of free light chain excretion by plasma cells in

relation to intact immunoglobulin. We recognized the prognostic impact of sFLC κ/λ ratio normalization in patients with residual intact monoclonal immunoglobulin in the serum and we show an improved PFS for patients who achieved a normal ratio after the initial therapy regardless of their IMWG response level. This prognostic value was more significant in patients with partial response and was translated into substantially better OS in this group (**Table 2**).

The role of serum FLC measurements was proposed in an earlier preliminary study (Mead et al. 2004), which suggested a possible role of serum FLC measurement in patients with measurable disease. This mainly was based on the fact that FLCs have short half-lives compared to the intact immunoglobulins, and thus could provide a more rapid indicator of tumor reduction in response to therapy; however, this study did not look at the effect of attaining normal serum FLC levels on survival outcomes. More recently, Iwama et al.(21) showed that achieving a normal sFLCr correlated with improved PFS and OS in patients who had a PR or VGPR as their maximal response but this study did not look at the patients with intact immunoglobulins separately and the analysis was done on all multiple myeloma patients.

On the other hand, one large study failed to confirm any prognostic value of follow up measurements of FLC on survival outcomes in newly diagnosed myeloma patients with measurable disease, when added to the M-protein measurements. However, this study cannot be compared methodologically to our study; as the FLC measurements were done at a fixed time point of two months after initiating therapy and the FLC response was measured as a 50% reduction in dFLC, iFLC, or FLCr; with the study focus on the early changes in FLC. In addition, the therapy used in the mentioned study did not include novel agents.(8) In contrast, the current study used the complete normalization of the FLCr as the FLC response criteria at the time of the maximal response (median for the best first response was 6.9 months). However, it should be noted that our study is limited by its retrospective nature and the lack of a predefined schedules for response assessments. Our study is also based on patients seen at a referral center and about 20% of the patient did not have baseline sFLC measurements. Other limitations to our study are the variety of the anti-myeloma therapies used as well as variable duration of the treatments. We have tried to limit the heterogeneity by examining the first response obtained after diagnosis in these patients. Despite these limitations our study is the largest to date looking at the benefit of FLC in monitoring multiple myeloma patients with intact immunoglobulin and our results largely confirms the beneficial role of serial sFLC measurements in this group of patients.

In conclusion, it appears that obtaining a normal sFLC ratio confers a more favorable prognosis irrespective of the depth of the response, which may represent an effective eradication of a plasma cell subclone that secretes these free light chains. This would be consistent with the prior findings of inferior outcomes seen among patients with myeloma with higher levels of serum FLC at presentation. We suggest an important role for sFLC measurements in disease monitoring even in patients who achieve only a PR to therapy. Conceivably, this can be done at the time the patient achieves their maximal response to a given therapy (instead of serial measurements at every time point) and future studies should be designed to examine if alterations in therapy based on these results will alter long term

outcomes. These results support the inclusion of sFLC at all levels of response included in the current International Myeloma Working Group (IMWG) criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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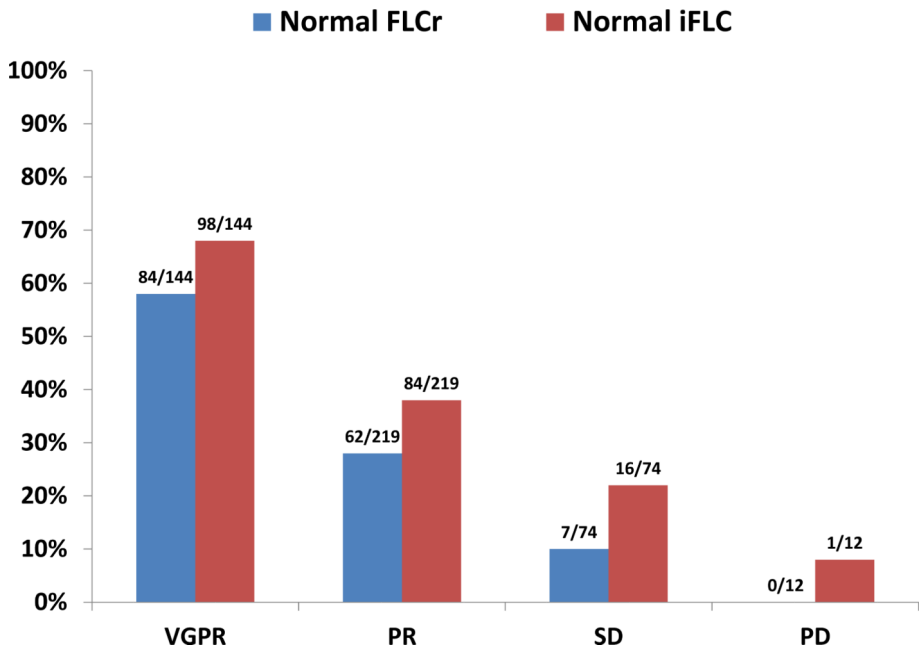

Figure 1.

Proportion of patients with FLCr or iFLC normalization at the time of the best first response within each IMWG response category. *Abbreviations*: PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial remission.

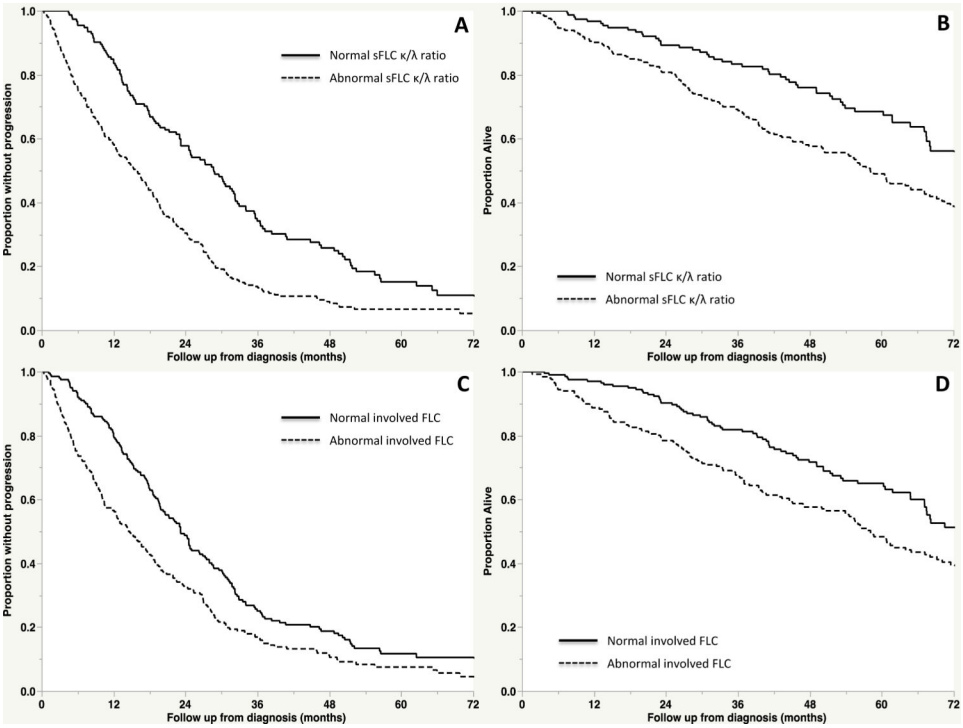

Figure 2.

(A) Progression-free survival; comparing patients achieved normal sFLC κ/λ ratio at the time of the best first response with patients who did not achieve normal sFLC κ/λ ratio, **(B) Overall survival**; comparing patients achieved normal sFLC κ/λ ratio at the time of the best first response with patients who did not achieve normal sFLC κ/λ ratio, **(C) Progression-free survival**; comparing patients achieved normal involved FLC level at the time of the best first response with patients who did not achieve normal involved FLC level, **(D) Overall survival**; comparing patients achieved normal involved FLC level at the time of the best first response with patients who did not achieve normal involved FLC level. NR; not reached.

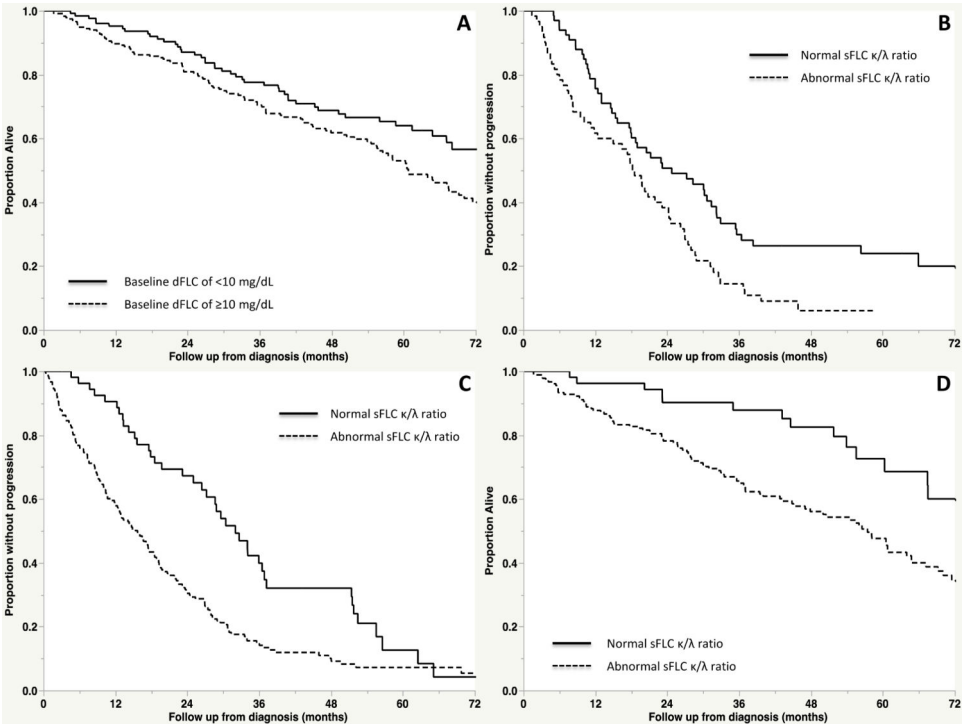

Figure 3.

(A) Overall survival; comparing patients with baseline dFLC of <10 mg/dL to patients with baseline dFLC of ≥10 mg/dL, **(B) Progression-free survival**; showing the impact of FLCr normalization at the time of the best first response among patients with low (<10 mg/dL) of dFLC at baseline, **(C) Progression-free survival**; showing the impact of FLCr normalization at the time of the best first response among patients with high levels (≥10 mg/dL) of dFLC at baseline, **(D) Overall survival**; showing the impact of FLCr normalization at the time of the best first response among patients with high levels (≥10 mg/dL) of dFLC at baseline.

Table 1

Baseline clinical characteristics and responses to therapy (N =449)

Variables	All patients N=449
Age at diagnosis, years, Median (range)	**65 (29-91)**
Male, n (%)	**281 (63)**
Heavy chain subtype	
IgA, n (%)	**91 (20)**
IgG, n (%)	**351 (78)**
Other Subtypes, n (%)	**7 (2)**
Free light chain isotype	
Kappa, n (%)	**304 (68)**
Lambda, n (%)	**145 (32)**
FLC measurements	
Baseline dFLC ≥ 10 mg/dL, n (%) ^	**234 (65)**
Baseline involved-uninvolved FLC ratio ≥ 100, n (%) ^^	**156 (43)**
Baseline iFLC ≥ 10 mg/dL, n (%) ^^^	**237 (65)**
Initial treatment	
IMiD-based initial treatment, n (%)	**291 (65)**
Bortezomib-based initial treatment, n (%)	**60 (13)**
Bortezomib-IMiD combination, n (%)	**19 (4)**
Other types initial treatments, n (%)	**79 (18)**
Best first hematologic response*	
VGPR, n (%)	**144 (32)**
PR, n (%)	**219 (49)**
SD, n (%)	**74 (16)**
PD, n (%)	**12 (3)**
Number of patients who had ASCT before the first relapse, n (%)	**161 (36)**

•Abbreviations: ASCT, autologous hematopoietic stem cell transplantation; FLC, free light chain; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial remission.

* Classified by IMWG criteria

^ Eighty nine patients were missing

^^ Ninety patients were missing

^^^ Eighty four patients were missing

Table 2

Effect of FLCr normalization on survival outcomes grouped by IMWG response categories

	SD+PD			PR			VGPR		
	FLCr		*p*-value	FLCr		*p*-value	FLCr		*p*-value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
N	**7**	**79**		**62**	**157**		**84**	**60**	
PFS, month, median (95%CI)	27 (14, 36)	6 (4, 10)	0.008	26 (20, 36)	17 (13, 20)	0.0005	29(23, 34)	21(18, 26)	0.02
OS, months, median (95%CI)	68 (49, 68)	41 (30, 57)	NS	NR (65, NR)	61 (50, NR)	0.004	91 (67, 107)	73 (59, NR)	NS

Abbreviations: NR; statistically not reached, NS; not significant

Table 3

Univariate analysis of clinical variables affecting FLCr and iFLC normalization

Variables	FLCr normalization, n (%)		OR (95% CI)	p-value	iFLC normalization, n (%)		OR (95% CI)	p-value
	Yes	No			Yes	No		
Age at diagnosis								
=<65	72(31)	158(69)	0.7 (0.5, 1.2)	.22	113(49)	117(51)	1.5(1.1, 2.2)	.02
Light chain isotype								
Lambda	59(41)	86(59)	1.5 (1, 2.3)	.04	66(46)	79(55)	1.1(0.7, 1.6)	>.7
iFLC level at diagnosis								
<10 mg/dL	105(38)	174(62)	2.5 (1.4, 4.4)	.002	140(50)	139(50)	4.4(2.4, 8)	<.0001
dFLC at diagnosis								
<10 mg/dL	66(52)	60(48)	3.7 (2.3, 5.9)	<.0001	87(69)	39(31)	5.9(3.7, 9.4)	<.0001
Involved-uninvolved FLC ratio at diagnosis								
<100	89(44)	114(56)	3.3 (2, 5.3)	<.0001	108(53)	95(47)	2.9(1.9, 4.5)	<.0001
Best first response								
≥PR	147(40)	217(60)	8(3.6, 17.7)	<.0001	182(50)	182(50)	4.2(2.4, 7.5)	<.0001