Clinically-suspected cast nephropathy

A retrospective, national, real-world study

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Clinically suspected cast nephropathy: a retrospective, national, real-world study

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ABSTRACT

Presentation with severe acute kidney injury due to cast nephropathy (CN) is a medical emergency in multiple myeloma (MM) with high risk of dialysis-dependent renal failure and death. Accrual of patients with CN into interventional studies is difficult, while phase III trials exclude patients with severe renal insufficiency. Real-world data are warranted. We assessed 2252 patients from the population-based Danish Multiple Myeloma Registry (DMMR), diagnosed 2013-2017. We identified 204 patients with clinically suspected CN, defined as serum creatinine concentration >177 µmol/L and serum free light chain (sFLC) concentration >1000 mg/L at the time of diagnosis. The median age was 72 years. Thirty-one percent of patients presented with dialysis-dependent renal failure. Kidney biopsies were performed in 19% of patients and showed CN in 74% of cases. Despite prompt initiation of bortezomib-based therapy in 94% of patients, 33% of patients died in the first year after diagnosis.

Compared with the rest of the patients in the DMMR with symptomatic MM, patients with clinically suspected CN had worse overall survival (OS) irrespective of transplant eligibility. Achievement of renal recovery was associated with deep reductions of involved sFLC. Achievement of very good partial response or better in the first line of therapy and/or deep reduction of involved sFLC at three months after initiation of therapy were associated with superior OS. In conclusion, MM patients presenting with clinically suspected CN have an alarmingly high one-year mortality when treated with current standards of care. Early and deep hematologic response is crucial for survival.

INTRODUCTION

Renal failure, defined by serum creatinine higher than 177 µmol/L occurs in approximately 20-30% of patients with multiple myeloma (MM) at the time of diagnosis.[1–4] Severe renal impairment requiring hemodialysis occurs in 3-9% of all patients with newly diagnosed MM, and unless renal function is recovered, it leads to considerable mortality during the first months after diagnosis. [1,2,5–10] Myeloma cast nephropathy (CN) is the most common form of monoclonal immunoglobulin-mediated kidney disease.[11,12] It results from the interaction of excessive amounts of monoclonal light chains with Tamm-Horsfall proteins in the distal tubule leading to precipitation of light chains and obstruction of the lumen of the distal nephron.[13,14] Cast nephropathy causes around 70% of the cases of dialysis-dependent renal failure in MM and is a medical emergency requiring prompt intervention to rescue the kidneys from irreversible damage.[12,14–19]

The serum free light chain (sFLC) assay is useful for identifying and monitoring patients with light chain myeloma and is an important tool during the initial screening of patients with unexplained acute renal failure.[14,20–22] In such cases, the finding of a high sFLC concentration with an abnormal sFLC ratio raises the clinical suspicion of CN.[14] Although the histopathologic diagnosis of CN is established by a percutaneous kidney biopsy, in routine clinical practice, the diagnostic yield of this procedure is often

outweighed by the urgent need of anti-myeloma treatment and the risk of procedure-related complications.[14,23,24]

Accrual of patients with clinically suspected CN into clinical trials is challenging. This was demonstrated by two randomized clinical trials with the objective of assessing renal recovery and survival of newly diagnosed patients with MM and CN treated with or without high cut-off hemodialysis.[25,26] Both trials required dialysis-dependent renal failure and histopathologic diagnosis of CN for inclusion. The MYRE study was conducted between 2011 and 2016 at 48 French centers and recruited 98 patients.[25] The EULITE trial was conducted between 2008 and 2013 in 14 British and 2 German centers and recruited 90 patients.[26] While interventional studies struggle to include patients with CN, patients with severe renal failure are excluded from most phase III clinical trials.[27] Real-world data in patients with clinically suspected CN are warranted.

We conducted a retrospective, national, patient chart review in patients with newly diagnosed MM and clinically suspected CN. The aims of our study were to assess baseline characteristics, biopsy results, anti-myeloma treatment, renal recovery and overall survival in this patient group.

METHODS

We used five inclusion criteria to define the study population: (1) Patients had to be registered in the Danish Multiple Myeloma Registry (DMMR) with (2) newly diagnosed MM according to the International Myeloma Working Group (IMWG) criteria[28] between (3) 1st of January 2013 and 31st of December 2017 with (4) a serum creatinine concentration higher than 177 µmol/L and (5) an involved sFLC concentration higher than 1000 mg/L at the time of diagnosis (Figure 1 and Supplementary Figure 1A). The sFLC cutoff of 1000 mg/L was chosen based on kernel density analysis of the percentage of renal failure in relation to involved sFLC concentrations in patients from the DMMR diagnosed 2013-2017 (Supplementary Figure 1B). The DMMR is a national registry that collects baseline and treatment-related data from myeloma patients diagnosed since the 1st of January 2005. The coverage of the population is close to 100%.[29–36] Serum free light chain measurements have been routinely reported to this registry since 1st of January 2013. After identification of patients, investigators from ten Danish centers reviewed patient charts and retrospectively registered predefined data in a designated Research Electronic Data Capture (REDCap) database between 1st of October 2018 and 1st of September 2019. All biopsy reports were reviewed by a nephropathologist for the purposes of this study. Lines of therapy were registered in the first 12 months after MM diagnosis. A line of therapy was defined according to the IMWG guidelines for the determination of the number of prior lines of therapy in MM.[37] The best response to a given line of therapy was defined according to the IMWG uniform response criteria for MM.[38] Time to next treatment (TNT) was defined as the length of time between the date of initiation of a line of therapy and the subsequent line of therapy. Pre-myeloma kidney function was defined based on the latest serum estimated glomerular filtration rate (eGFR) assessment prior to myeloma diagnosis. Grades of Chronic

Kidney Disease (CKD) were defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2012 Clinical Practice Guidelines; grades 1, 2, 3a, 3b, 4 and 5 were defined by eGFR values of ≥90, 60-89, 45-59, 30-44, 15-29 and <15 ml/min/1.73 m^2, respectively.[39,40] Acute kidney injury (AKI) stage at diagnosis was classified according to the KDIGO 2012 Clinical Practice Guideline for acute kidney injury; stages 1, 2 and 3 were defined as serum creatinine 1.5-1.9 times baseline or ≥25.5 µmol/L increase, 2.0-2.9 times baseline, and 3.0 times baseline or increase in serum creatinine to ≥353.6 µmol/L or initiation of renal replacement therapy, respectively.[41] Kidney function and sFLC concentrations were assessed at the following time points: the date of first sFLC measurement, the end of the first cycle of anti-myeloma therapy, three months after initiation of therapy, six months after initiation of therapy and 12 months after initiation of therapy. Renal response was assessed according to the IMWG criteria for the definition of renal response to anti-myeloma therapy.[42] Renal recovery at the predefined time points was assessed according to the following simplified criteria: In patients with dialysis-dependent renal failure at diagnosis, renal recovery was defined as independence from dialysis. In patients without dialysis-dependent renal failure at diagnosis, renal recovery was defined as an improvement of at least one CKD grade: a rise in eGFR from <15 to ≥15, from 15-29 to ≥ 30, from 45-59 to ≥ 60 or from 60-89 to ≥ 90 ml/min/1.73 m^2. Overall survival (OS) was defined as the length of time between the date of diagnosis and the date of death or last contact. Overall survival data were acquired from the DMMR, which automatically receives updated survival status from the Danish population registry.[43]

STATISTICS

Continuous variables were described with median, range, interquartile range (IQR) and confidence interval (CI). Categorical variables were summarized using the number of observations and percentages as appropriate. Overall survival was estimated and visualized using the Kaplan-Meier method, and log-rang tests were used to assess difference between survival curves. Associations with OS were assessed by Cox proportional hazards regression models, with estimates reported as Hazard Ratios. Statistical analysis was performed with the statistical software R v. 3.6.1 and the add-on packages 'tidyverse', 'ggplot2' and 'ggkm'.[44–47] Data visualizations were performed with R v. 3.6.1 and Microsoft Excel for Office 365.

RESULTS

Study population

In the study period, 2252 patients were registered in the DMMR. Diagnostic serum creatinine concentrations were available in 2249 patients. In addition to serum creatinine, diagnostic sFLC kappa and lambda concentrations were available in 2136 patients. Of these, 297 (14%) patients had a serum creatinine concentration higher than 177 µmol/L and 627 (29%) patients had an involved sFLC

concentration higher than 1000 mg/L. Two hundred and nine patients had both a serum creatinine concentration higher than 177 µmol/L and an involved sFLC concentration higher than 1000 mg/L and were included in the study. Medical records in 5 patients were not accessible. The study population thus consisted of 204 patients. The flow-chart for inclusion and identification of the study population are presented in Figure 1 and Supplementary Figure 1, respectively. Two patients had previously been diagnosed with monoclonal gammopathy of unknown significance (MGUS). Five patients did not receive treatment for MM. Of these, one patient had advanced renal cell carcinoma, one patient had prostate cancer, one patient had pre-existing dialysis-dependent hypertensive nephropathy and two patients chose not to receive treatment for MM due to advanced age. One hundred and ninety-nine patients received therapy. The median age at diagnosis was 72 (IQR: 65; 79) years. One hundred and thirty-six (67%) patients were men. The median serum creatinine and involved sFLC concentrations at diagnosis were 340 (IQR: 243; 530) µmol/L and 5677 (IQR: 2495; 11918) mg/L, respectively. Baseline characteristics are presented in Table 1. Pre-myeloma serum creatinine concentrations were available in 169 (83%) patients and 165 (81%) patients had a pre-myeloma eGFR registered. The median pre-myeloma serum creatinine concentration and eGFR were 89 (IQR: 77; 115) µmol/L and 66 (IQR: 47; 80) ml/min/1.73 m^2, respectively. Nineteen (11%) patients had a pre-myeloma serum creatinine concentration higher than 177 µmol/L. Based on pre-myeloma eGFR, there were 23 (14%) patients with grade 1, 80 (49%) with grade 2, 27 (16%) with grade 3a, 15 (9%) with grade 3b, 16 (10%) with grade 4 and five (2%) with grade 5 CKD. Acute kidney injury stage at diagnosis was assessable in 171 patients. Of these, 17 (10%) had AKI stage 1, 32 (19%) had AKI stage 2 and 122 (71%) had AKI stage 3.

Kidney biopsies

A kidney biopsy was carried out in 38 (19%) patients. In 25 (66%) of these patients, the kidney biopsy was performed prior to the diagnosis of MM. The median time from kidney biopsy to MM diagnosis was 4 (IQR: 3; 8) days. In 13 (34%) patients, the kidney biopsy was done after the diagnosis of MM. The median time from MM diagnosis to kidney biopsy was 5 (IQR: 2; 7) days. The histopathologic diagnosis based on the kidney biopsy was CN in 28 (74%) cases. Besides CN, additional diagnoses were reported in 12 patients. These diagnoses were acute tubular necrosis (n=3), acute interstitial nephritis (n=2), pyelonephritis (n=2), interstitial fibrosis (n=2), amyloidosis (n=1), hypertensive blood vessel changes (n=1), chronic interstitial nephritis (n=1), mesangioproliferative glomerulonephritis (n=1) and unspecific chronic changes (n=1). In the 10 biopsied patients who did not have CN, the following diagnoses were reported: renal cell carcinoma (n=2), amyloidosis (n=1), acute tubulointerstitial nephritis (n=1), chronic inflammation with fibrosis (n=1), unspecific changes (n=1), normal tissue (n=1), and unsuitable biopsy (n=3). Baseline clinical characteristics in biopsied patients with and without CN were similar (Supplementary Table 1).

Time from first serum free light chain measurement to initiation of therapy

The first line of anti-myeloma therapy was initiated prior to the first sFLC measurement in three patients (day -3: two patients, day -1: one patient). The median time from the first sFLC measurement to initiation of anti-myeloma therapy was five (IQR: 2; 10) days (Supplementary Figure 2). The time from first sFLC measurement to initiation of therapy in the two patients with previously diagnosed MGUS were 1163 and 1432 days, respectively.

Lines of therapy

Within the first 12 months from diagnosis, 199 patients received one, 44 patients received two, 15 patients received three, four patients received four, two patients received five and one patient received six lines of therapy. High-dose melphalan with autologous hematopoietic stem cell transplantation (HDT-ASCT) was carried out in 51 (25%) patients and was part of the first, second and third line of therapy in 45, four and two patients, respectively. The most frequently used drugs (other than steroids) were bortezomib (n=220), cyclophosphamide (n=100), melphalan (n=38), thalidomide (n=34) and lenalidomide (n=31). The most frequently used first-line regimens were bortezomib-dexamethasone (VD; n=70), cyclophosphamide-bortezomib-dexamethasone (CVD; n=57), bortezomib-melphalan-prednisolone (VMP; n=16), bortezomib-thalidomide-dexamethasone (VTD; n=12) and bortezomib-lenalidomide-dexamethasone (VRD; n=5). Bortezomib was administered as part of the first-line regimen in 188 (94%) patients. The most frequently used second line regimens were CVD (n=8), VMP (n=7), lenalidomide-dexamethasone (RD; n=5), thalidomide-cyclophosphamide-dexamethasone (CTD; n=4), daratumumab-lenalidomide-dexamethasone (DRD; n=3) and VTD (n=3). Hematologic response to the first and second lines of therapy is shown in Supplementary Figure 3. The reduction of involved sFLC concentration at the end of the first cycle of therapy, at three months, six months and twelve months after initiation of therapy is shown in Supplementary Figure 4. A cause of discontinuation was registered in 88% of the administered lines of therapy. The cause of discontinuation was fixed duration regimen in 58 (25%), toxicity in 35 (15%), death in 34 (15%), plateau phase in 34 (15%), progressive disease in 31 (13%), insufficient response in 12 (5%), poor performance status in 11 (5%), patient's choice in 7 (3%), and "other" in 10 (4%) of cases. The causes of discontinuation of the first and second lines of therapy are shown in Supplementary Figure 5. The median TNT between the first and second line of therapy was 46 (24; 101) days.

Dialysis dependency and renal recovery

Renal function was available in 188 patients at the end of the first cycle of therapy, 169 patients at three months, 157 patients at six months and 134 patients at 12 months after initiation of therapy. At these time points, 24%, 17%, 15% and 13% of patients had dialysis-dependent renal failure, respectively (Supplementary Figure 6A). Renal response according to the IMWG criteria is shown in Supplementary

Figure 6B. Renal recovery according to the simplified criteria defined in this study was achieved in 45% of patients at the end of the first cycle of therapy, in 66% of patients three months, in 72% of patients six months, and in 73% of patients 12 months after initiation of therapy (Supplementary Figure 6C). Achievement of renal recovery was associated with deeper reductions of involved sFLC at all time points (p=0.009 at the end of the first cycle of therapy, p=0.001 at three months, and p=0.002 at six months after initiation of therapy; Figure 2).

Overall survival

The median OS in the study population was 3.7 (95% CI: 2.6; 4.7) years (Supplementary Figure 7A). One-year mortality was 33%. Of the 204 patients with accessible records, 190 (93%), 170 (83%), 158 (77%) and 136 (67%) patients were alive after the first cycle of therapy, at three months, six months and 12 months after initiation of therapy, respectively. There were 1927 patients in the DMMR who did not fulfil the inclusion criteria for this study. The median OS of these patients was 6.1 (95% CI: 5.2; not reached) years. One-year mortality was 13%. Of the 1927 patients, 1393 had symptomatic MM. Compared with the rest of the patients in the DMMR with symptomatic MM, patients with clinically suspected CN had worse OS irrespective of HDT-ASCT-eligibility (p<0.001; Supplementary Figure 7B). One-year mortality was higher in both HDT-ASCT-eligible (6% vs. 2%) and HDT-ASCT-ineligible (43% vs. 20%) patients.

Factors associated with overall survival:

The following baseline variables were associated with OS: age (HR: 1.78; p<0.001), performance status 2 (HR: 2.19; p=0.006), performance status 3 (HR: 6.20; p<0.001), performance status 4 (HR: 6.80; p<0.001), serum albumin (HR: 0.95; p<0.001), beta-2-microglobulin (HR: 1.03; p=0.006), and LDH (HR: 1.00; p=0.022). High-dose melphalan with autologous hematopoietic stem cell transplantation performed in any line of therapy was associated with longer OS (HR 0.26; p<0.001). There was no difference in OS of HDT-ASCT-eligible nor HDT-ASCT-ineligible patients based on the administered first-line regimens (Supplementary Figure 8). In multivariate analysis adjusted for the effects of age, performance status, creatinine, albumin, LDH and HDT-ASCT, very good partial response or better in the first line of therapy (HR 0.46; p=0.002) and involved sFLC reduction to 10% or lower of baseline at three months after initiation of therapy (HR: 0.56; p=0.039) were independently associated with longer OS (Figure 3).

DISCUSSION

Our large real-world study provides nationwide data on the characteristics, treatment, renal recovery and OS of patients with newly diagnosed MM and clinically suspected CN, defined as serum creatinine higher than 177 µmol/L and involved sFLC higher than 1000 mg/L. This disease presentation was found in 10% of all MM patients. Despite the prompt initiation of effective bortezomib-based therapy in 94%

of patients, one third of the patient group died in the first year after diagnosis; a mortality higher than in the rest of the patients registered in the DMMR who were diagnosed in the same period. One-year mortality was especially high in HDT-ASCT-ineligible patients. Patients who survived the crucial first year after diagnosis had comparable survival to the rest of the patients registered in the DMMR. Very good partial response or better in the first line of therapy and deep reduction of involved sFLC at three months resulted in superior OS.

A strength of our study is the description of a group of patients who are underrepresented in clinical trials. Besides the inclusion criteria, the study population was unselected and population-based. All treatment decisions were results of real-world clinical scenarios. As expected, we observed higher one-year mortality than reported in the MYRE and EULITE trials, even though these trials were conducted in more sick populations, having only included patients with dialysis-dependent real failure at the time of diagnosis.[25,26]

A limitation of this study is the lack of systematic histological verification of CN. When performed, kidney biopsies showed CN in 74% of cases, similarly to the findings of previous biopsy studies in MM.[17,18] A kidney biopsy is the only diagnostic method of CN; no threshold sFLC concentration or biomarker is specific for this mechanism of acute kidney injury. It is though generally assumed that CN does not develop in patients with an involved sFLC concentration lower than 500 mg/L.[14] Our data, based on 2136 patients from the DMMR supported the use of a sFLC cutoff of 1000 mg/L for renal failure (Supplementary Figure 1). It is our opinion, that the sFLC assay, despite being unspecific for CN, together with the initial diagnostic work-up, provides sufficient clinical information to initiate acute treatment in most patients. We expect that CN remains a clinically suspected, rather than a histologically verified diagnosis in the future.

The standard frontline treatment in our patient group consisted of CVD induction followed by HDT-ASCT in transplant-eligible patients, and VD in transplant-ineligible patients. Daratumumab is a monoclonal antibody that can be safely administered in patients with renal failure.[48,49] There were only seven patients in our cohort that were treated with daratumumab, which had been reimbursed in Denmark since September 2016. At the time of writing of this manuscript, daratumumab has not yet been granted reimbursement for the frontline treatment of patients with MM in Denmark. However, it is expected, that daratumumab soon will be an available first-line option in MM patients presenting with clinically suspected CN, improving patient outcomes.

In conclusion, MM patients presenting with clinically suspected CN, especially transplant-ineligible patients, have an alarmingly high one-year mortality when treated with current standards of care. Early and deep hematologic response and reduction of toxic free light chains are crucial for survival. The expected inclusion of daratumumab in future first-line regimens will likely improve outcomes in this group of MM patients.

CONFLICT OF INTEREST

AGS: consulting for Janssen
JT: no conflicts of interest
KFI: no conflicts of interest
CTH: no conflicts of interest
EMT: no conflicts of interest
SBP: no conflicts of interest
SBF: no conflicts of interest
CS: no conflicts of interest
MF: no conflicts of interest
MØV: honoraria from Celgene
UCF: no conflicts of interest
DK: no conflicts of interest
TP: consulting for Janssen, Celgene, Takeda, Abbvie, Genmab;
AJV: honoraria from Janssen and Celgene; consulting for Takeda, Sanofi, Oncopeptides

AUTHOR CONTRIBUTIONS

AGS designed the study, created the study database, conducted patient chart review, created figures and wrote the manuscript.
JT carried out data analysis, statistics, created figures and participated in the writing of the manuscript.
KFI entered patients in the study database and participated in the writing of the manuscript.
CTH entered patients in the study database and participated in the writing of the manuscript.
EMT entered patients in the study database and participated in the writing of the manuscript.
SBP entered patients in the study database and participated in the writing of the manuscript.
SBF entered patients in the study database and participated in the writing of the manuscript.
CS entered patients in the study database and participated in the writing of the manuscript.
entered patients in the study database and participated in the writing of the manuscript.
MF entered patients in the study database and participated in the writing of the manuscript.
MØV entered patients in the study database and participated in the writing of the manuscript.
UCF entered patients in the study database and participated in the writing of the manuscript.
DK entered patients in the study database and participated in the writing of the manuscript.
TP: supervised the design of the study and participated in the writing of the manuscript.
AJV: entered patients in the study database, supervised the study and participated in the writing of the manuscript

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DATA AVAILABILTY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to Danish data protection regulations.

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LEGENDS

Figure 1

Flow-chart of the study population

In the study period (2013-2017), 2252 patients were registered in the Danish Multiple Myeloma Registry. Diagnostic serum creatinine concentrations were available in 2249 patients. In addition to serum creatinine, diagnostic serum free light chain kappa and lambda concentrations were available in 2136 patients. Of these, 297 (14%) patients had a serum creatinine concentration higher than 177 µmol/L and 627 (29%) patients had an involved serum free light chain concentration higher than 1000 mg/L. Two hundred and nine patients had both a serum creatinine concentration higher than 177 µmol/L and an involved serum free light chain concentration higher than 1000 mg/L and were included in the study. Medical records in 5 patients were not accessible. The study population thus consisted of 204 patients. Pre-myeloma kidney function was defined based on the latest serum estimated glomerular filtration rate (eGFR) assessment prior to myeloma diagnosis. Grades of Chronic Kidney Disease (CKD) were defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2012 Clinical Practice Guidelines; grades 1, 2, 3a, 3b, 4 and 5 were defined by eGFR values of ≥90, 60-89, 45-59, 30-44, 15-29 and <15 ml/min/1.73 m^2, respectively. Fourteen percent, 49%, 16%, 9%, 10% and 2% of patients had pre-myeloma CKD grades 1, 2, 3a, 3b, 4 and 5, respectively. Acute kidney injury (AKI) stage at diagnosis was classified according to the KDIGO 2012 Clinical Practice Guideline for acute kidney injury; stages 1, 2 and 3 were defined as serum creatinine 1.5-1.9 times baseline or ≥25.5 µmol/L increase, 2.0-2.9 times baseline, and 3.0 times baseline or increase in serum creatinine to ≥353.6 µmol/L or initiation of renal replacement therapy, respectively. At diagnosis, 10%, 19% and 71% of patients had AKI stage 1, 2 and 3, respectively.

Abbreviations: DMMR=Danish Multiple Myeloma Registry; pt.s=patients; sFLC=serum free light chain; CKD=chronic kidney disease; AKI=acute kidney injury

Figure 2

Renal recovery by reduction of serum involved free light chain concentration

Stacked columns showing achievement of renal recovery at different time points by reduction of involved serum free light chain concentration. Reduction of involved free light chain to ≤10% of baseline is shown on the left in red, reduction to 11-50% of baseline is shown in the middle in blue and reduction to >50% of baseline is shown on the right in purple. In patients with dialysis-dependent renal failure at diagnosis, renal recovery was defined as independence from dialysis. In patients without dialysis-dependent renal failure, renal recovery was defined as a rise in estimated glomerular filtration rate from <15 to ≥15, from 15-29 to ≥ 30, from 45-59 to ≥ 60 or from 60-89 to ≥ 90 ml/min/1.73 m^2. Achievement

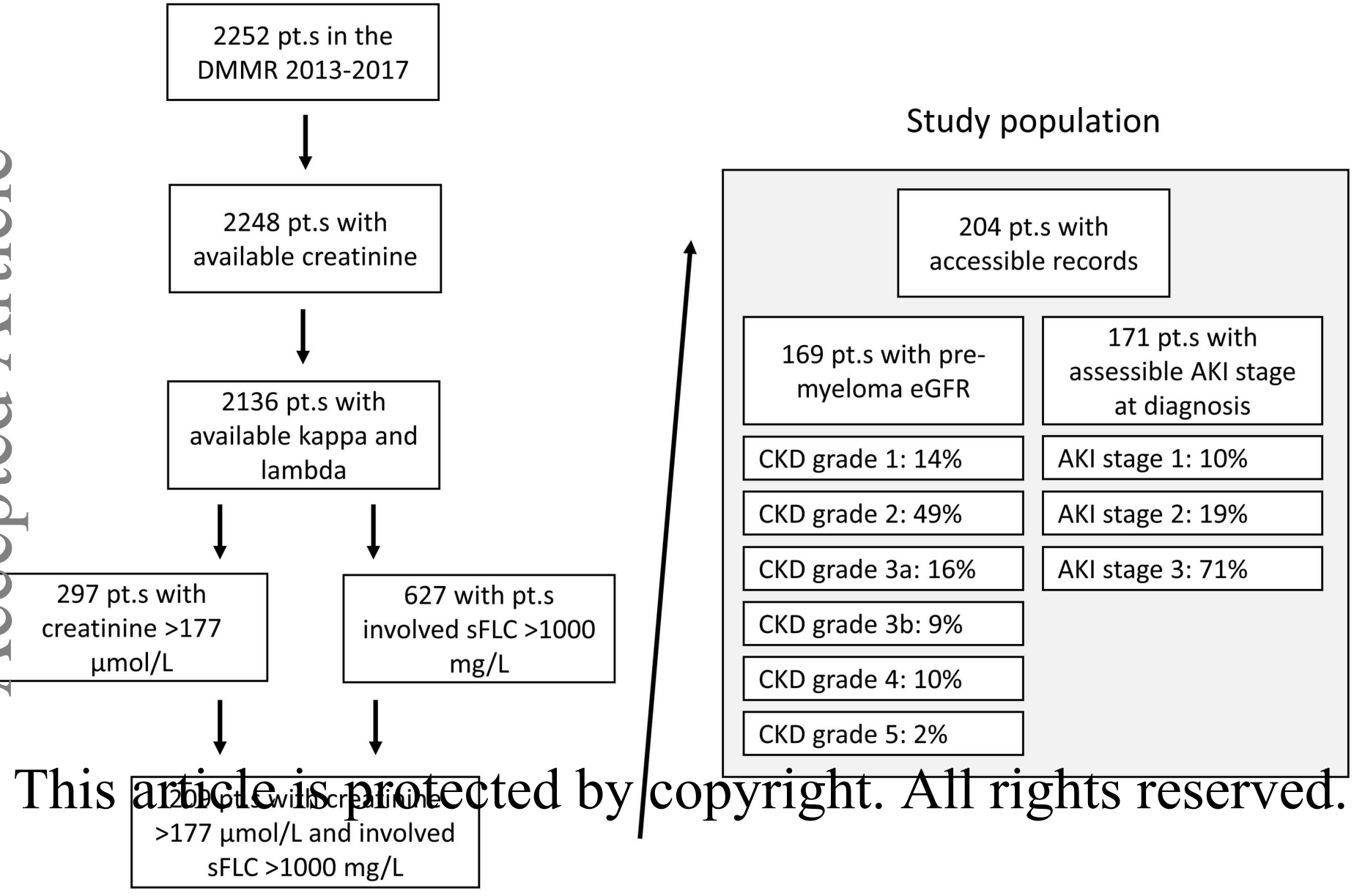
of renal recovery was associated with deeper reductions of involved sFLC at all time points (p=0.009 at the end of the first cycle of therapy, p=0.001 at three months, and p=0.002 at six months after initiation of therapy).
Abbreviations: sFLC= serum involved free light chain; C1=end of first cycle of anti-myeloma therapy, M3=three months after initiation of anti-myeloma therapy, M6=six months after initiation of anti-myeloma therapy, M12=twelve months after initiation of anti-myeloma therapy.

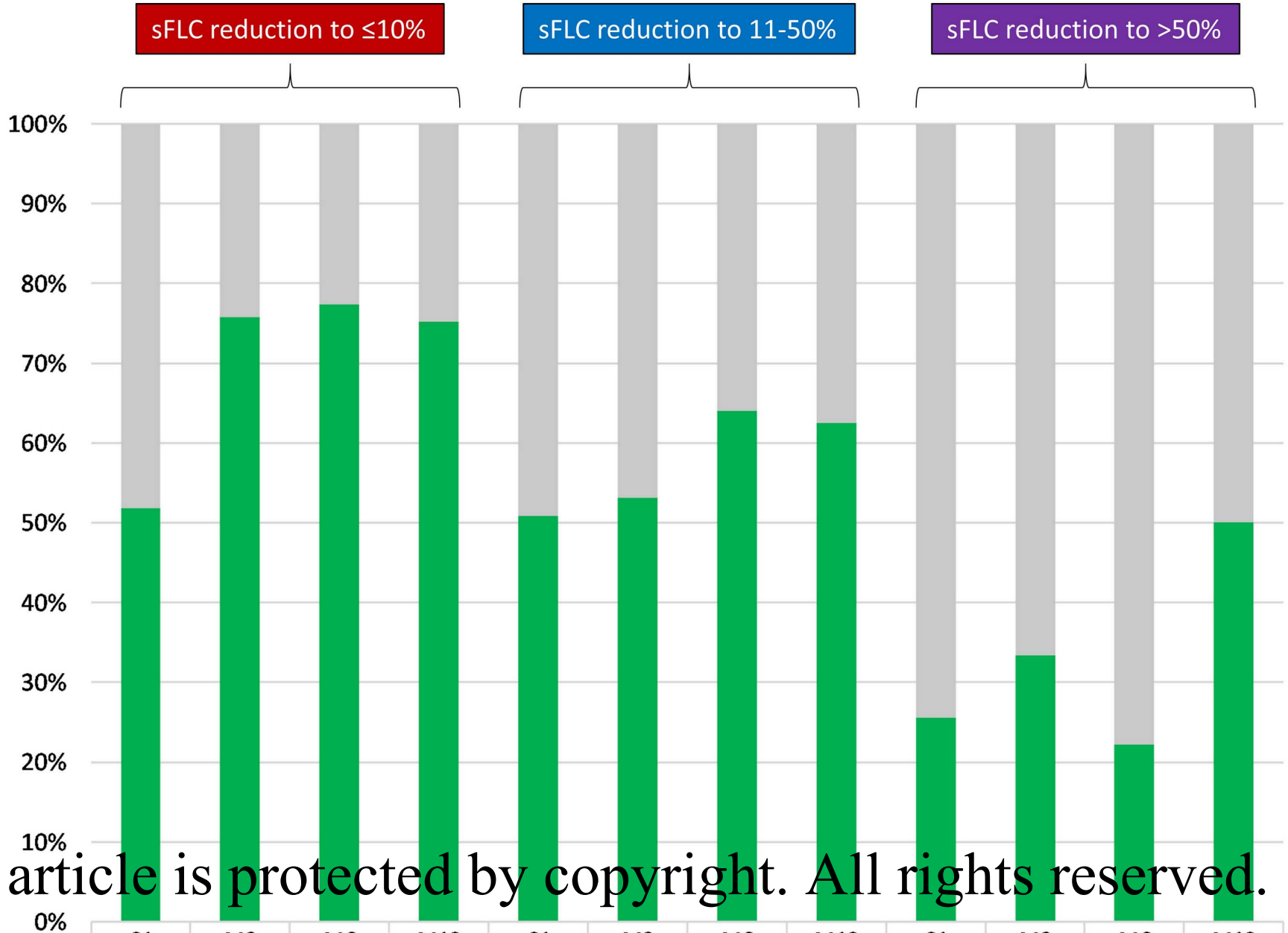
Figure 3
Overall survival by response to first line of therapy and reduction of involved serum free light chain concentration three months after initiation of therapy

Kaplan-Meier curves showing overall survival by hematologic response to the first line of therapy (A) and reduction of involved serum free light chain concentration at three months after initiation of therapy (B). A: Patients achieving very good partial response or better (shown in blue) have superior survival compared to patients achieving a partial response or worse (shown in red). In order to eliminate bias, only patients with assessable response in their first line of therapy were included in this analysis.
B: Patients achieving reduction of involved free light chain concentration to ≤10% of baseline three months after initiation of therapy (shown in blue) have superior survival compared to patients with involved serum free light chain concentration >10% of baseline (shown in red).
Abbreviations: PR=partial response; VGPR=very good partial response

Table 1
Baseline characteristics

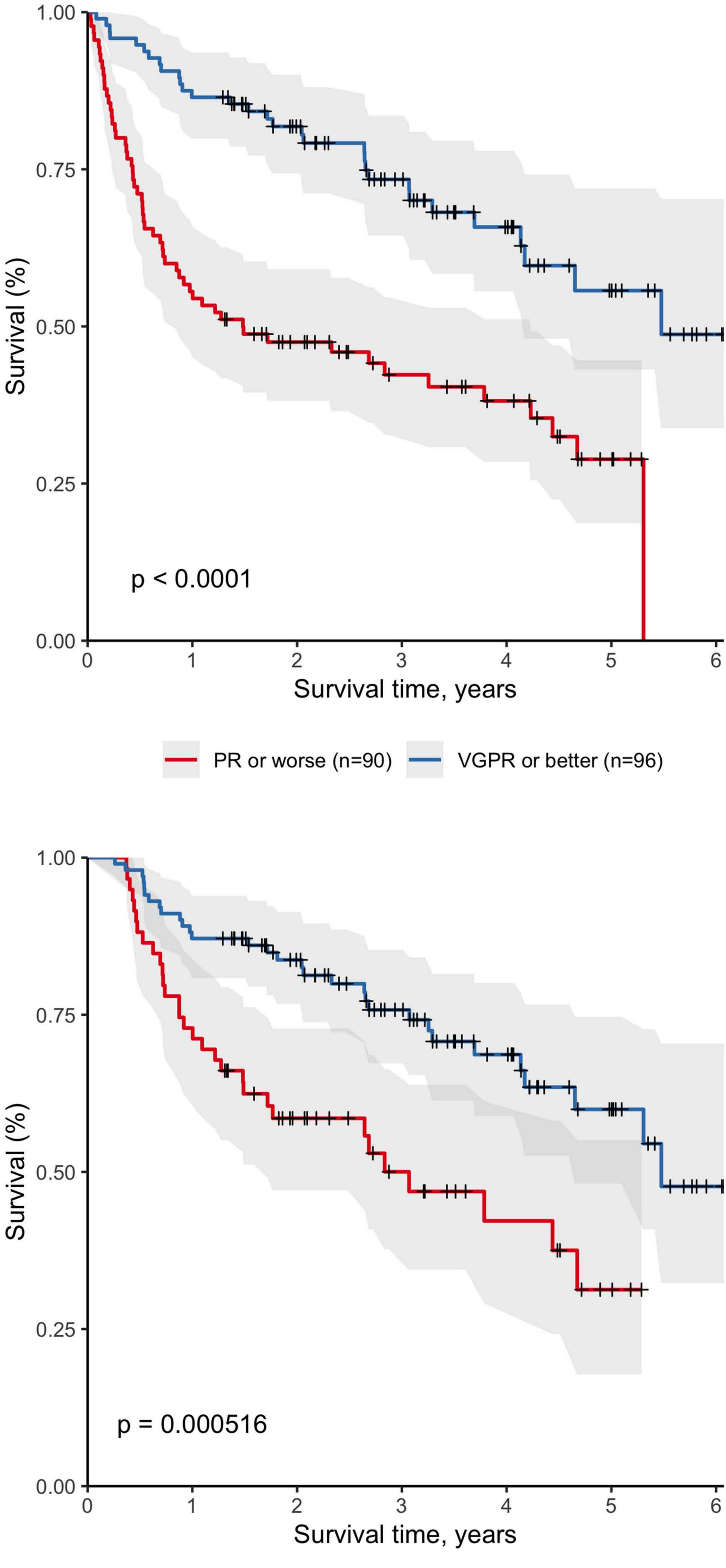
Abbreviations: %=percentage; IQR=interquartile range; n obs.=number of observations; LDH=lactatdehydrogenase; sFLC=serum free light chain; PS=Eastern Cooperative Oncology Group Performance Status; ISS=International Staging System; FISH=Fluorescence in situ hybridization; AKI=acute kidney injury





	C1	M3	M6	M12	C1	M3	M6	M12	C1	M3	M6	M12
no renal recovery	40	24	26	26	28	22	9	9	32	8	7	1
renal recovery	43	75	89	79	29	25	16	15	11	4	2	1

A



B

Table 1

Baseline characteristics of the study population

Baseline variable	category present (%)	Median (IQR)	n obs.
Age		72 (64; 79)	204
Age ≤ 65 years	55 (27)		204
Male sex	136 (67)		204
Hemoglobin (mmol/L)		5.9 (5.3; 6.5)	203
Hemoglobin <6.2 mmol/L	123 (61)		203
Creatinine (µmol/L)		340 (243; 530)	204
Ionised calcium (mmol/L)		1.26 (1.2; 1.49)	174
Ionised Calcium ≥1.345 (mmol/L)	59 (34)		174
β2 microglobulin (mg/L)		14 (10; 20)	176
Albumin (g/L)		34 (29; 39)	204
LDH (U/L)		214 (178; 260)	198
Bone marrow clonal plasma cell infiltration (%)		50 (30; 66)	199
Serum M-protein present	175 (86)		204
Serum M-protein (g/L)		12 (3; 30)	160
Involved sFLC (mg/L)		5677 (2495; 11918)	204
Serum M-protein isotype: IgA	38 (22)		177
Serum M-protein isotype: IgG	73 (41)		177
Serum M-protein isotype: light chain	63 (36)		177
Serum M-protein isotype: other	3 (2)		177
Urine M-protein present	104 (51)		203

Urine M-protein (g/L)		1.01 (0.45; 1.7)	62
Urine M-protein (g/day)		1.9 (1.08; 3.99)	14
Urin M-protein isotype: kappa	52 (54)		96
Urin M-protein isotype: lambda	44 (46)		96
Osteolytic lesion	122 (60)		204
Spinal cord compression	3 (2)		204
Amyloidosis	6 (3)		204
Dialysis-dependent renal failure	64 (31)		204
PS 0	57 (29)		197
PS 1	67 (34)		197
PS 2	45 (23)		197
PS 3	19 (10)		197
PS 4	9 (5)		197
ISS I	2 (1)		176
ISS II	9 (5)		176
ISS III	165 (94)		176
FISH with del17p /t(4;14) /t(14;16)	29 (21)		139
AKI stage 1	17 (10)		171
AKI stage 2	32 (19)		171
AKI stage 3	122 (71)		171

Abbreviations: %=percentage; IQR=interquartile range; n obs.=number of observations; LDH=lactatdehydrogenase; sFLC=serum free light chain; PS=Eastern Cooperative Oncology Group Performance Status; ISS=International Staging System; FISH=Fluorescence in situ hybridization; AKI=acute kidney injury