# CLINICAL STUDY REPORT

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|---|---|
| **Clinical Trial:** | Lenalidomide and Dexamethasone for treatment of patients with acute myeloma (light chain)-induced renal failure |
| **Clinical Phase:** | II |
| **Protocol Number:** | LD<br>RV MM CEMSG-354 (Celgene Protocol Number) |
| **EudraCT:** | 2008-006497-15 |
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| **Study initiation date (FPI)** | July 2009 |
| **Study completion date (LPO)** | January 2014 |

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## 1. ETHICS

The study was conducted in accordance with GCP and all applicable local laws and the Declaration of Helsinki, including archiving of study documents.

The protocol was approved by local ethics committees and informed consent was obtained from all patients.

## 2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator: Univ.-Prof. Dr. Heinz Ludwig

*Table 1: List of sites and investigators*

| Site# | Site | Department | Principal Investigator | Patients enrolled |
|---|---|---|---|---|
| 01 | Wilhelminenspital Wien | 1. Medizinische Abteilung | Prof. Dr. Heinz Ludwig | 17 |
| 02 | Med. Universität Wien | Universitätsklinik f. Innere Medizin I, Klin. Abteilung für Hämatologie u. Hämostaseologie | Prof. Dr. Heinz Gisslinger | 0 |
| 03 | Med. Universität Wien | Universitätsklinik f. Innere Medizin I, Klin. Abteilung für Onkologie | Prof. Dr. Johannes Drach | 0 |
| 04 | Klinikum Wels-Grieskirchen GmbH | Abteilung für Innere Medizin IV | Prof. Dr. Josef Thaler | 3 |
| 05 | Universitätsklinikum der PMU Salzburg | Univ. Klinik für Innere Medizin III | Prof. Dr. Richard Greil | 2 |
| 06 | LKH Leoben | Abteilung f. Innere Medizin | Prof. Dr. Felix Keil / OA Dr. Christof Tinchon | 0 |
| 07 | LKH Feldkirch | Interne E | OA Dr. Alois Lang | 1 |
| 08 | General Faculty Hospital, Charles University Prague | 1st Department of Internal Medicine, Division of Haematology | Ass. Prof. Dr. Ivan Spička | 4 |
| 09 | Faculty Hospital Brno and Faculty of Medicine MU Brno | 2nd Internal Clinic | Prof. Dr. Zdenek Adam | 5 |
| 10 | A.ö. KH der Elisabethinen Linz | 1. Interne Abteilung | OA Dr. Hedwig Kasparu | 2 |
| 11 | Universitätsklinikum Leipzig | Selbstständige Abteilung für Hämatologie und Internistische Onkologie | Prof. Dr. Dietger Niederwieser | 1 |

## 3. INTRODUCTION

Renal failure is a frequent complication of multiple myeloma and can be elicited by various factors such as infections, NSAIDs, nephrotoxic antibiotics, iodinated contrast media, hypercalcemia, tumor lysis syndrome, myeloma cell infiltration of the kidney, renal vein or artery thrombosis and, frequently by clonotypic light chains. Renal impairment induced by dehydration, hypercalcemia, anti-inflammatory drugs and infections often is less severe and often reversible[1]. This is in contrast to several forms of light chain induced renal injuries such as glomerular and vascular amyloidosis, light chain deposit disease, light chain proximal tubulopathy with/without Fanconi syndrome, or cast nephropathy, which is the most frequent sequel of kidney-pathogenic light chains and typically associated with much faster deterioration of renal function[2]. In cast nephropathy excessive glomerular filtration of free light chains saturates the clearance mechanism of the proximal tubule[3] and the resulting overflow of light chains into the distal tubule precipitates with Tamm-Horsefall protein particularly in case of high binding affinity of both protein types[4] and altered osmolality. This process results in tubular damage and interstitial inflammation[5].

Light chain-induced acute kidney impairment may be the salient symptom leading to diagnosis of myeloma, or more frequently, a consequence of progressive disease in patients with established diagnosis. The occurrence of this complication has substantial impact on the prognosis with a significantly higher risk for life threatening infections and mortality. In fact, recent surveys from Ireland[6] and UK[7] showed that survival of myeloma patients requiring dialysis during the first weeks after diagnosis of multiple myeloma is in the range of 6 to 11 months and did not improve substantially during the recent years even in spite of availability of novel drugs. In patients with less severe renal impairment survival has been improved, but highly active anti-myeloma therapy is required for seizing the window of opportunity for reversing renal function[8].

Here we evaluate lenalidomide-dexamethasone as treatment for patients with acute light-chain induced renal failure.

## 4. STUDY OBJECTIVES

Primary objective of the study was to assess the tumor response rate and the rate of recovery of renal function in patients with newly established disease and renal failure (glomerular filtration rate (GFR) <50ml/min and creatinine ≥2mg/dl) or in patients with pre-existing MM and renal failure with normal or near normal GFR (≥60ml/min) within the previous 6 weeks.

Secondary objective were determination of

- Progression-free survival, event-free survival
- Overall survival
- Pharmacodynamics of lenalidomide in patients with different categories of renal insufficiency
- Rate of toxicity according to NCI CTCAE criteria, version 3.0

## 5. INVESTIGATIONAL PLAN

This was a non-randomized, multicenter, open-label, single-arm Phase II study.

Patients with either previously unknown MM and acute light chain induced renal failure (GFR <50ml/min and serum creatinine ≥2mg/dl) or patients with previously established MM and normal renal function (GFR ≥60ml/min and serum creatinine ≤ 1.2mg/dl) with progressive disease and acute (within 6 weeks) light chain induced renal failure (GFR <50ml/min and creatinine ≥2mg/dl) were enrolled to the following treatment schedule:

Lenalidomide on days 1 to 21

Dexamethasone, 40mg on days 1-4, 9-12, 17-20 for the first cycle and 40mg once weekly thereafter.

Cycles à 28 days were repeated every 4 weeks. The recommended number of cycles was nine.

Patients were included from July 2009 until January 2013. The last patient finished treatment phase on 26-Sep-2013. The study was closed 6 months after EOT of last patient, i.e. in April 2014.

Patients were included according to the following inclusion criteria:

- Understood and voluntarily signed an informed consent form
- Age ≥18 years at the time of signing the informed consent form
- MM (all stages) with acute light chain induced renal impairment

  a) Patients with previously unknown MM and acute light chain induced renal failure (GFR<50ml/min and serum creatinine ≥2.0 mg/dL) and with further workup revealing light chain induced renal injury with MM as underlying cause

  b) Patients with previously established MM and normal renal function (GFR ≥60ml/min and serum creatinine ≤1.2mg/dl) with progressive disease and acute (within 6 weeks) light chain induced renal failure (GFR<50ml/min and creatinine ≥ 2mg/dL)

  Disease progression was documented by one or more of the following criteria:
    - Increase in serum paraprotein by >25%, or increase of ≥ 50% of 24 hour urine paraprotein excretion
    - Hypercalcemia
    - Progression of bone lesions
    - Decrease in Hb>2g/dl within 4 weeks (not induced by cytotoxic drugs)
    - Increase in bone marrow plasma cell infiltration by > 25%
- All previous medical anti-myeloma therapy (excluding corticosteroids) had to be discontinued at least 3 weeks prior to treatment in this study
- Able to adhere to the study visit schedule and other protocol requirements
- Measurable serum or urine paraprotein
- Laboratory test results within these ranges:
  - Glomerular filtration rate < 50ml/min
  - Serum creatinine ≥ 2.0mg/dL
  - Absolute leukocyte count ≥ 1.5 x $10^9$/L
  - Platelet count ≥ 75 x $10^9$/L if bone marrow plasma cell infiltration (BMPC) was <50% or ≥ 30 x $10^9$/L if BMPC infiltration is ≥50%
  - Total bilirubin ≤ 1.5 mg/dL
  - AST (SGOT) and ALT (SGPT) ≤ 2,5 x ULN
  - *Females of childbearing potential (FCBP) had to*
    - understand that the study medication could have an expected teratogenic risk

- agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she had amenorrhea. This applied unless the subject committed to absolute and continued abstinence confirmed on a monthly basis. The following were effective methods of contraception
  - Implant
  - Levonorgestrel-releasing intrauterine system (IUS)
  - Medroxyprogesterone acetate depot
  - Tubal sterilization
  - Sexual intercourse with a vasectomised male partner only; vasectomy must have been confirmed by two negative semen analyses
  - Ovulation inhibitory progesterone-only pills (i.e., desogestrel)
- agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applied to women of childbearing potential who practiced complete and continued abstinence
- agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of next treatment. This requirement also applied to women of childbearing potential who practiced complete and continued abstinence

Male subjects had to

- agree to use condoms throughout study drug therapy, during any dose interruption and for 28 days after cessation of study therapy if their partner was of childbearing potential and had no contraception
- agree not to donate semen during study drug therapy and for 28 days after end of study drug therapy.

- All subjects had to agree not to share study medication with another person and to return all unused study drug to the investigator
- Disease free of prior malignancies for $\geq$ 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast
- Agreed to take low molecular weight heparin as prophylactic anticoagulation.

Patients were not allowed to be included in case of the following (exclusion) criteria:

- Acute renal failure due to other causes than light-chain induced nephropathy such as NSAIDS, antibiotics, or other nephrotoxic drugs, or others
- Acute renal failure due to hypercalcemia only, without excretion of nephrotoxic light chains
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would have prevented the subject from signing the informed consent form
- Any prior use of lenalidomide

- Any anti-myeloma therapy within 3 weeks before day 1 of first cycle, with the exception of dexamethasone 40mg (maximum dose 160mg) or corticosteroid equivalent.
- Any other experimental drug or therapy within 3 weeks of baseline
- Any condition, including the presence of laboratory abnormalities, which placed the subject at unacceptable risk if he/she were to participate in the study or confounded the ability to interpret data from the study
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs
- Known positive for HIV or infectious hepatitis, type A, B or C or evidence of any severe active or chronic infection
- Clinical significant heart disease (NYHA status>2)
- Pregnant or breast feeding females
- Anamnesis of thromboembolic complications, such as stroke, myocardial infarction and pulmonary embolism.

Patient characteristics are shown in table 1 and the patient flow during the trial is depicted in the consort diagram (figure 1). The trial had been discontinued after inclusion of 35 patients because of slow enrollment. The 35 patients comprise the intent to treat population (ITT). Four of those died within the first 2 cycles and 5 discontinued therapy (3 due to adverse events, 1 due to progressive disease and 1 due to withdrawal of consent), leaving 26 patients for the per protocol analysis (PP).

*Table 2.* Patient characteristics

| | |
|---|---|
| Number of patients | 35 |
| Age, median (range) | 66 (45-87) |
| Gender, male/female | 20/15 |
| Newly diagnosed / relapsed MM | 28/7 |
| ISS Stage | |
| < I | 0 |
| II | 2 (5.7%) |
| III | 33 (94.3%) |
| ECOG Status 0-1/≥ 2 | 19/16 |
| ß2 microglobulin | 14 mg/l<br>(5.3 – 85.9mg/l) |

| | |
|---|---|
| IgG | 14 (40%) |
| IgA | 3 (9%) |
| κ Light chain<br>λ light chain | 9 (26%)<br>9 (26%) |
| t (4;14)*<br>del17q*<br>1q21* | 4 (13.8%)<br>3 (10.3%)<br>13 (44.8%) |
| t4;14 ± del17q ± 1q21* | 14 (48%) |

*) FISH cytogenetics available in 29/35 patients

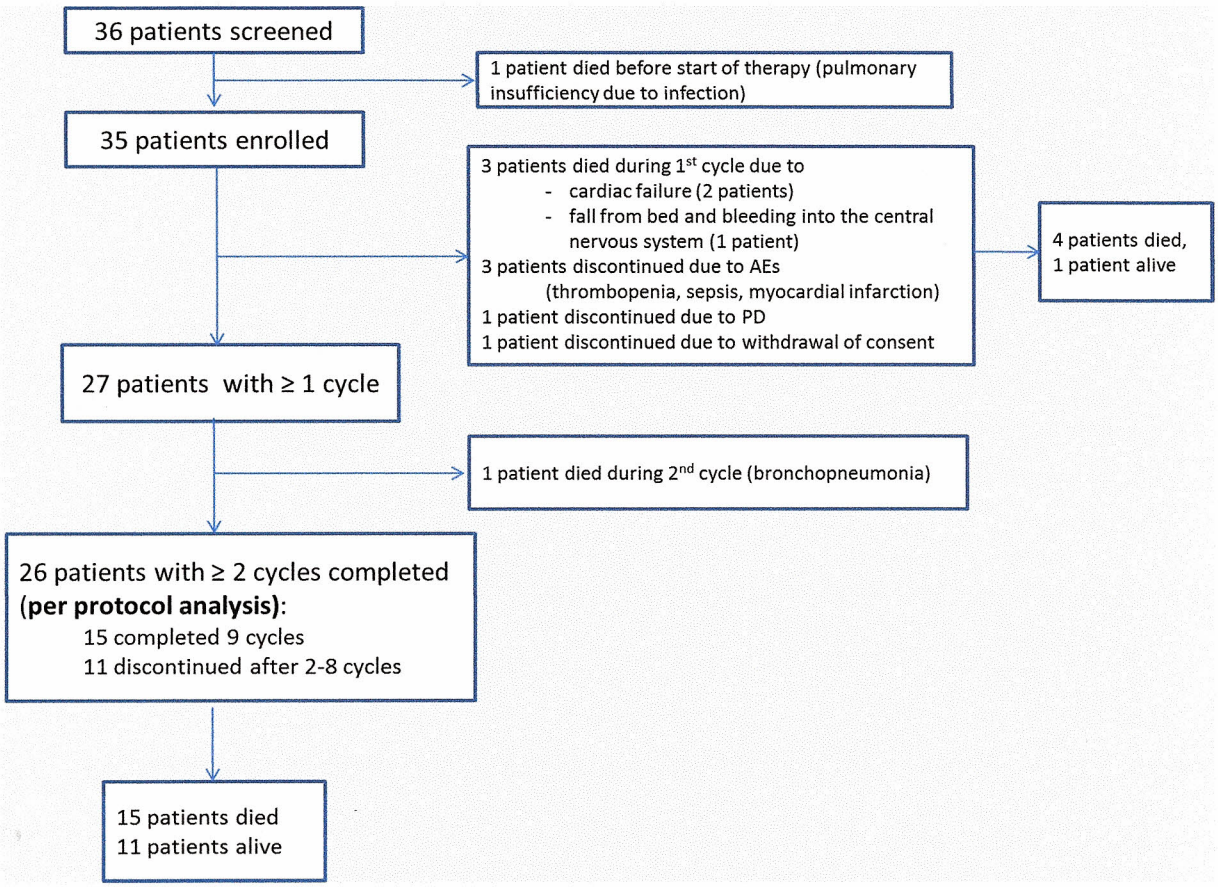



*Figure 1.* Consort diagram of patient flow

Patients were enrolled by 8 participating centers in Austria, Germany and the Czech Republic. All patients gave written informed consent before entering the study. The trial was registered in the EudraCT database (No. 2008-006497-15), was approved by the health authorities and ethical committees in all participating countries, and was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

## 6. EFFICACY EVALUATION

Myeloma response was assessed according to the EBMT Criteria for Multiple Myeloma[9] with the addition of very good partial response (VGPR)[10] as an additional category (reduction of measurable serum paraprotein by ≥90%).

As this was a non-comparative study the estimation of sample size did not present a crucial, but an orientating value. The sample size calculation was based on the assumption that the combination Lenalidomide-dexamethasone showed substantial activity and would induce reversal of renal impairment in ≥ 50% of patients at the end of the therapy. Assuming the rate of reversal with other, conventional therapies to be 20 % (H0 = 20 %), by accrual of 50 eligible patients, the predicted rate of reversal of renal failure would be verified with a power of 95% and significance level of 5% by a two-sided one-grouped Chi-Square-Test.

Assessment of reversal of renal failure was made by calculating the percentage achieving a glomerular filtration rate ≥60ml/min, the percentage increase in glomerular filtration rate and the percentage of reduction in serum creatinine level.

Response rates, PFS, OS and toxicities were calculated by intent-to-treat analysis, but PFS and OS is also shown in the per protocol treated patients and kinetics of eGFR and 24 hour proteinuria are shown in the myeloma response group also. Overall survival and progression-free survival were estimated by the product limit method[11]. Due to the limited sample size multivariate analysis could not be performed. The Kruskal Wallis test[12] was used for comparison of patient groups. For all analyses, the significance endpoint was set to 0.05 and all values reported are two-sided. SPSS, version 17 was used for all analyses.
The following risk factors were tested for possible correlations with myeloma and renal response ($C^{Rrenal}$, $\geq PR^{renal}$), PFS and OS in univariate analysis: age > 65 years, ISS stage III, ECOG <2, ß-2 microglobulin > 5.5mg/ml, albumin < 3.5g/L, hemoglobin < 8.0g/dL, LDH > 226U/L, calcium > 2.24mmol/L, CRP > 5mg/L, CRP > 13.2mg/L, eGFR < 15ml/min, eGFR < 30ml/min, dialysis, baseline platelets < 150.000/µL, cytogenetic risk factors (t (4;14) ± del 17p) and 1q21 ± t(4;14) ± del 17p, reduction of baseline involved FLC > 95%.
Adverse events (AEs) were graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, of the National Cancer Institute[13].

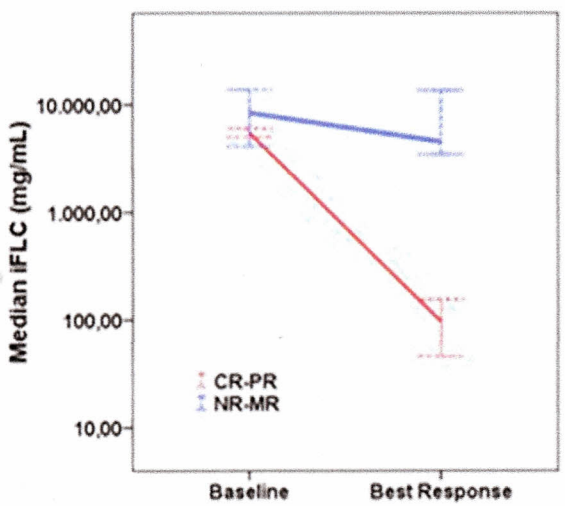
### Response

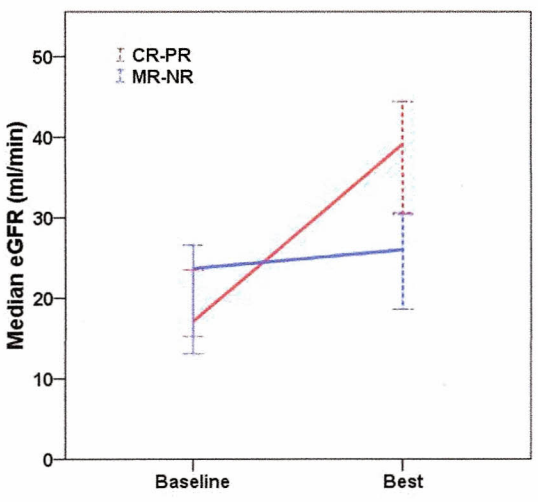
The trial had been discontinued after inclusion of 35 patients because of slow enrollment. The 35 patients comprise the intent to treat population (ITT). Four of those died within the first 2 cycles and 5 discontinued therapy (3 due to adverse events, 1 due to progressive disease and 1 due to withdrawal of consent), leaving 26 patients for the per protocol analysis (PP). After a median follow up of 17.7 months, myeloma response to therapy was noted in 25/35 (71.4%) of the ITT population. Seven patients (20%) had CR, 3 (8.6%) VGPR, 14 (40%) PR, and 1 (2.9%) MR. Median time to first myeloma response was 28 days, and time to best myeloma response was 92 days. Median baseline concentration of involved free light chains in the ITT population was 5.465mg/L (range: 147–42.700mg/L) and 8350mg/L (range: 234– 35.500mg/L) in patients reaching ≥PR and ≤MR,

respectively, and decreased significantly to a median of 95.75mg/L (range: 11.3–5.630mg/L, p <0.001) in the former, but only to a median of 4500mg/L (234–18.705mg/L, p=0.5) in the latter group, respectively (figure 2A).

Renal response was observed in 16 (45.7%) of 35 patients of the ITT group, with 5 (14.2%), 4 (11.4%) and 7 (20%) showing $CR^{renal}$, $PR^{renal}$, and $MR^{renal}$, respectively. Median time to renal response was 28 days and median time to best renal response 157 days. Median eGFR increased significantly in patients with ≥PR from 17.1ml/min at baseline to 39.1ml/min at best response (p<0.001), and from 23.7ml/min to 26.0ml/min in patients with ≤ MR in the ITT population (p=0.469) (figure 2B). The respective figures in the PP group are 17.1ml/min and 39.1ml/min in patients with ≥PR (p<0.001), and 14.85ml/min and 18.65ml/min, respectively, in those with ≤MR (figure 2C).

24 hour proteinuria in the PP group at baseline was lower, albeit not significantly lower (p=0.052) in patients with subsequent myeloma response compared to non-responders (3.371mg/24hrs (410–13.872mg/24hrs) vs. 8.173mg/24 hrs (6.374–9.972mg/24hrs)) (figure 2D). The protein excretion decreased substantially during the first treatment cycle in both groups, but the decline was more pronounced in patients with myeloma response both at day 28 (473mg/24hrs (60–1.604mg/24hrs) vs. 2.310mg/24hrs (1.080– 3.540mg/24hrs), (p=0.034)) and at time of best renal response (213mg/24hrs (40– 850mg/24hrs) vs. 1.810mg/24 hrs (79–3.540mg/24hrs), (p=0.676)). All seven patients with CR had normalization of 24 hour proteinuria (median 119mg/24h (59-192mg/24hrs)). The greatest decline in 24hrs proteinuria was noted in patients with renal response (baseline: median: 3.360mg/24hrs (range 1.000–6.350mg/24hrs), at day 28: median 480mg/24hrs (60-1.600mg/24hrs), at best response: median 192mg/24hrs (40–588mg/24hrs)). Thirteen patients were dialysis dependent at baseline and 5 of them became dialysis independent. The maximal decline in 24 hour proteinuria did not differ between patients who became dialysis independent (260mg/24hrs (130-420mg/24hrs) or not (270mg/24hrs (60–3.540mg/24hrs), (p=0.831)).



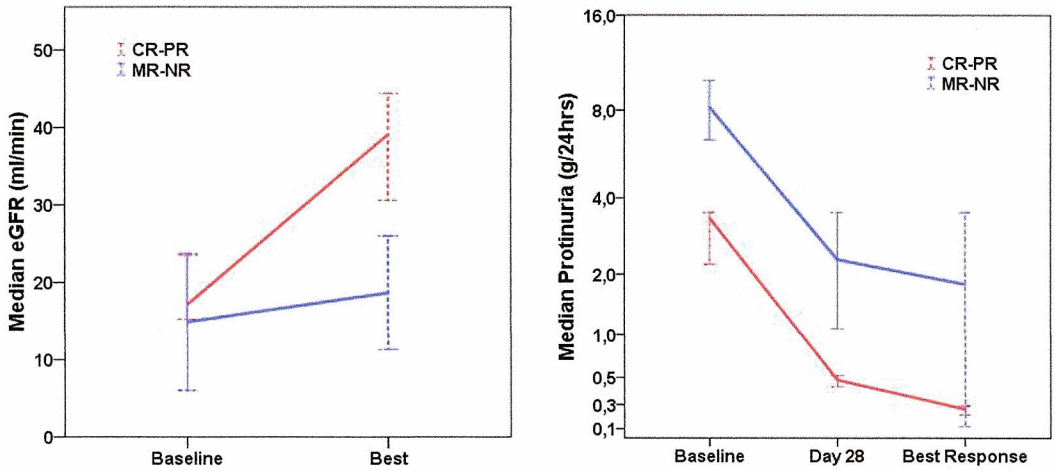



*Figure 2.* A. ITT population; median (range) of involved free light chain concentrations at baseline and at best response in patients with CR-PR compared to the NR-MR population. B. ITT population; median (range) of eGFR in patients with CR-PR or MR-NR at baseline and at best response. C: PP population; median eGFR at in patients with CR-PR and those with MR-NR at baseline and at best response. D. PP population; median 24 hrs proteinuria in patients with CR-PR and those with MR-NR at baseline, day 28 and at best response

Median PFS and OS were 5.5 and 21.8 months, respectively, in the ITT and 12.1 and 31.4 months, respectively, in the PP group (figure 3).

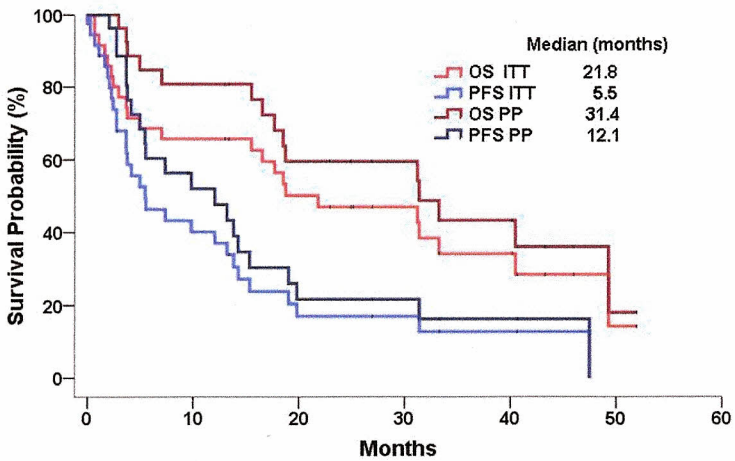



*Figure 3.* Progression-free and overall survival in the intent to treated (ITT) and the per protocol (PP) treated patient population

Univariate analysis in the ITT group revealed significant correlations between myeloma response (≥ PR) and renal response ($p<0.017$), age >65 years ($p<0.01$) LDH ($p<0.044$), PFS ($p<0.004$), and OS ($p<0.014$). Renal response was, in addition associated with PFS ($p<0.01$), and OS ($p<0.048$), and expectedly with >95% reduction in levels of involved

FLC (p<0.036, table 2). High CRP levels (>13.2 mg/L) were associated with shorter OS (p<0.045), and ECOG status ≤1 correlated with PFS (p<0.029).
Patients who discontinued the trial within the first 2 cycles tended to be slightly older (median age 71 vs. 66 years, p=0.186), and had higher baseline CRP levels (23.6 vs 12.63 mg/L, p=0.462). Also they showed a tendency for more aggressive disease manifested by higher LDH levels (267 vs. 222 U/L, p=0.157).

*Table 3.* Univariate analysis of correlations between myeloma and renal response and clinical parameters

| INTENT TO TREAT POPULATION | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Myeloma Response** | | | **Renal Response** | | |
| | **OR/HR** | **P <** | **95%CI** | **OR/HR** | **P <** | **95%CI** |
| **Age >65 yrs** | 0,097 | 0,010 | 0,160-0,176 | 0,359 | 0,146 | 0,090-1,430 |
| **LDH >226U/L** | 0,167 | 0,044 | 0,029-0,953 | 0,700 | 0,601 | 0,184-2,664 |
| **Red. iFLC >95%** | 0,097 | 0,010 | 0,016-0,576 | 0,214 | 0,036 | 0,051-0,902 |
| **Renal Response** | 8,500 | 0,017 | 1,458-49,539 | - | - | - |
| **PFS** | 0,251 | 0,004 | 0,099-0,636 | 0,364 | 0,010 | 0,169-0,787 |
| **OS** | 0,252 | 0,014 | 0,084-0,757 | 0,416 | 0,048 | 0,174-0,992 |

Of the 4 patients who died during the first 2 cycles, 3 died within cycle 1. Two of them died due to cardiac failure which likely is a consequence of the cardiotoxicity of high dose dexamethasone, and one due to cerebral bleeding. Overall, 23 patients had died, 14 (40%) due to progressive disease, 3 each due to infection (3 (9%), or cardiac toxicity (3 (9%), and 3 (9%) due to complications of the disease or therapy.

## 7. SAFETY EVALUATION

Grade 3/4 anemia was the most frequent haematological toxicity seen in 15 (43%), followed by thrombocytopenia in 8 (23%) and neutropenia in 5 (15%) patients. Other non-hematologic adverse events consisted mainly of grade 3/4 infection in 13 (38%) followed by cardiac toxicity in 4 (11%) patients. Grade 3 diarrhea and vomiting/emesis were noted in 1 (3%) patient each.

Adverse Events were coded according to WHO drug dictionary code. A total of n=412 adverse events were observed. Myeloma related symptoms or complications such as bone pain, fractures, grade ≤ 2 anemia (Hb ≥ 8g/dl), grade ≤ 2 thrombopenia (≥ 75.000/µl) and grade ≤ 2 neutropenia (≥ 1000/µl) did not have to be reported. Adverse events belonged to the following System Organ Class (SOC) categories (table 3). Blood and lymphatic system disorders were most frequent, followed by gastrointestinal disorders and infections.

*Table 3:* frequency of adverse events per SOC category

| ***SOC category*** | ***Frequency*** |
|---|---|
| Blood and lymphatic system disorders | 86 |
| Gastrointestinal disorders | 53 |
| Infections and infestations | 47 |
| Metabolism and nutrition disorders | 42 |

| | |
|---|---|
| General disorders and administration site conditions | 37 |
| Skin and subcutaneous tissue disorders | 27 |
| Nervous system disorders | 21 |
| Musculoskeletal and connective tissue disorders | 20 |
| Psychiatric disorders | 18 |
| Respiratory, thoracic and mediastinal disorders | 16 |
| Vascular disorders | 9 |
| Cardiac disorders | 9 |
| Renal and urinary disorders | 6 |
| Investigations | 5 |
| Eye disorders | 4 |
| Ear and labyrinth disorders | 3 |
| Injury, poisoning and procedural complications | 3 |
| Reproductive system and breast disorders | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 |
| Hepatobiliary disorders | 1 |
| SOC uncoded | 1 |
| ***Total*** | ***412*** |

56 Serious Adverse Events (SAE´s) were reported, 29 of these were related to at least one investigational medicinal product (see table 4). 9 SAE´s were related to both study drugs, lenalidomide and dexamethasone, 16 SAE´s were related to either study drug (lenalidomide or dexamethasone). In 4 SAE´s relationship to study drug was unknown. No SAE was classified as SUSAR.

*Table 4:* SAE reports related to at least one study drug

| SAE # | SAE diagnosis | Study timepoint at onset | Date of onset | Outcome | Date of outcome (recovery, death, ...) | Causality |
|---|---|---|---|---|---|---|
| **Observation period from 29-Jul-2009 to 30-Nov-2009** | | | | | | |
| 01 01 | dysnoea, blood in sputum, pneumonia | Cycle 1 | 25-Sep-09 | Recovered | 20-Oct-09 | related (lenalidomide, dexa-methasone) |
| 01 02 | pneumonia | Cycle 1 | 12-Oct-09 | Recovered | 19-Oct-09 | related (lenalidomide, dexa-methasone) |
| **Observation period from 01-Dec-2009 to 30-Nov-2010** | | | | | | |
| 01 06 | hyper-glycaemia | Cycle 4 | 09.Dec.09 | Recovered | 15-Dec-09 | related (dexa-methasone) |

| SAE # | SAE diagnosis | Study timepoint at onset | Date of onset | Outcome | Date of outcome (recovery, death, ...) | Causality |
|---|---|---|---|---|---|---|
| 08 08 | atrial flutter | Cycle 2 | 21.Jan.10 | Recovered | 22-Jan-10 | related (lenalidomide, dexa-methasone) |
| 01 10 | pulmonary embolism | Cycle 8 | 10-Apr-10 | Recovered | 15-Apr-10 | related (lenalidomide, dexa-methasone) |
| 08 11 | sudden death at home | Cycle 6 | 26-Apr-10 | Death | n.a. | unknown |
| 09 17 | bronchopneumonia | Cycle 1 | 21-Jul-10 | Recovered | 09-Aug-10 | related (lenalidomide, dexa-methasone) |
| 09 20 | bronchopneumonia; ischemic stroke | Cycle 2 | 21-Sep-10 | Death | n.a. | unknown |
| 09 21 | heart failure | Cycle 3 | 04.Oct.10 | Recovered | 19-Oct-10 | related (lenalidomide, dexa-methasone) |
| 05 24 | exanthema | Cycle 3 | 30.Nov.10 | Recovered | 02-Dec-10 | related (lenalidomide) |
| **Observation period from 01-Dec-2010 to 30-Nov-2011** | | | | | | |
| 01 28 | general weakness, thrombopenia G4 | Cycle 1 | 03-Mar-11 | Recovered | 09-Mar-11 | related (lenalidomide) |
| 01 29 | cardiac arrhythmia | Cycle 1 | 16-Mar-11 | Recovered | 17-Mar-11 | related (lenalidomide) |
| 01 30 | general weakness, nausea, symptomatic anemia G4 with dyspnoe and T-negativation V1-V5 and consecutive cardiac decompensation, thrombopenia G4 | Cycle 2 | 23-Mar-11 | Recovered | 03.Apr.11 | related (lenalidomide, dexa-methasone) |
| 08 32 | cardiac arrest | Cycle 1 | 08.Apr.11 | Death | 08.Apr.11 | unknown |
| 08 34 | sepsis, paralytic ileus, respiratory failure | Cycle 1 | 25.Apr.11 | Death | 17.Jun.11 | unknown |

| SAE # | SAE diagnosis | Study timepoint at onset | Date of onset | Outcome | Date of outcome (recovery, death, ...) | Causality |
|---|---|---|---|---|---|---|
| 09 35 | exanthema | Cycle 3 | 10.May11 | Recovered | 18.May11 | related (lenalidomide) |
| 01 37 | febrile neutropenia Gr. 4 | Cycle 5 | 11.Jul.11 | Recovered | 22.Jul.11 | related (lenalidomide) |
| 01 38 | thrombocytopenia G4 | Cycle 5 | 27.Jul.11 | Recovered | 03.Oct.11 | related (lenalidomide) |
| 01 39 | bone pain, spondylodiscitis | Cycle 7 | 10.Aug | Recovered | 31.Aug.11 | related (dexa-methasone) |
| 01 40 | soor oesophagitis | Cycle 1 | 27.Oct.11 | Recovered | 22.Nov.11 | related (dexa-methasone) |
| 01 41 | dyspnoea, general weakness | Cycle 1 | 09.Nov.11 | Recovered | 16.Nov.11 | related (dexa-methasone) |
| **Observation period from 01-Dec-2011 to 30-Nov-2012** | | | | | | |
| 01 46 | sore | Cycle 1 | 03.Feb.12 | Recovered | 13.Feb.12 | related (dexamethasone) |
| 01 47 | neutropenia | Cycle 4 | 03.Feb.12 | Recovered | 10.Feb.12 | related (lenalidomide) |
| 01 49 | hyperglycaemia G3 | Cycle 4 | 30.Apr.12 | Recovered | 29.May12 | related (dexamethasone) |
| 01 50 | thrombopenia G4 | Cycle 1 | 07.May12 | Ongoing until death on 01.Jul.12 | | related (lenalidomide) |
| 01 51 | vomitus G3 | Cycle 2 | 01.Jun.12 | Recovered | 06.Jun.12 | related (lenalidomide) |
| 01 52 | hypocalcaemia G4 | Cycle 5 | 08.Jun.12 | Recovered | 12.Jun.12 | related (lenalidomide) |
| **Observation period from 01-Dec-2012 to 30-Nov-2013** | | | | | | |
| 01 53 | Soor-oesophagitis | Cycle 2 | 02.Dec.12 | Recovered | 13.Dec.12 | related (lenalidomide, dexamethasone) |

| SAE # | SAE diagnosis | Study timepoint at onset | Date of onset | Outcome | Date of outcome (recovery, death, ...) | Causality |
|---|---|---|---|---|---|---|
| 10 54 | Bronchopulmunal infection | Cycle 1 | 26.Dec.12 | Recovered | 15.Jan.13 | related (lenalidomide, dexamethasone) |

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