Title of the Study

A phase I / II study of Lenalidomide with low dose oral cyclophosphamide and low dose dexamethasone (RdC) in AL amyloidosis

Test drug/ investigational product:
Revlimid® (Lenalidomide)
Cyclophosphamide
Dexamethasone

Indication : Primary Systemic (AL) Amyloidosis

A Phase I/II study in patients with Al amyloidosis to assess the feasibility, safety and efficacy of the combination of Lenalidomide with ,ow dose dexamethasone and low dose oral cyclophosphamide in patients with primary systemic Al amyloidosis

Sponsor: Hellenic Cooperative Oncology Group (HeCOG)

Protocol number: RV-PI-178
EudraCT: NCT00981708
Clinicaltrials.gov ID: 2006-007082-36

Phase of study: I/II
Study initiation date (first patient enrolled, or any other verifiable definition) : 05 Feb 2008
Study Completion Date:
Study Coordinator: Prof. Meletios-Athanasios Dimopoulos, Department of Clinical Therapeutics, University of Athens School of Medicine,

This study was conducted in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

Date of the report : 28 Feb 2012

Person responsible for the study report:
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2. Synopsis

Name of Sponsor/Company: **HeCOG**	Individual Study Table Referring to Part of the Dossier	*(For National Authority* *Use only)*
Name of Finished Product: **REVLIMID®**	Volume:	
Name of Active Ingredient: **LENALIDOMIDE**	Page:	

Title of Study: **A phase I / II study of Lenalidomide with low dose oral cyclophosphamide and low dose dexamethasone (RdC) in AL amyloidosis**	
Investigators: **Prof. Meletios A. Dimopoulos, MD, Dr Efstathios Kastritis, MD**	
Study centre(s): **Department of Clinical Therapeutics , Alexandra Hospital**	
Publication (reference):	
Studied period (years): (date of first enrolment) **05-Feb-2008** (date of last completed) **11-Jan-2011**	Phase of development: **phase I/II**

Objectives: Primary objective of the phase I of the study was the determination of maximum tolerated dose (MTD) of RdC and of the phase II of the study was the assessment of the hematologic response rate. Secondary objectives were the determination of hematologic and organ progression free survival, overall survival and safety.

Methodology:

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

In the phase I part of the study, patients were observed for 2 cycles of therapy for determination of dose limiting toxicity (DLT). A standard 3+3 design was followed. If no DLT was encountered in the first 3 patients at a dose level, 3 patients were enrolled at the next dose level. If >1 of 3 patients experienced a DLT, then MTD was considered to have been exceeded. If 1 of 3 patients experienced a DLT, 3 more patients were enrolled at the same dose level (total 6 patients). If no more patients experienced a DLT (1 of 6), 3 patients were enrolled at the next dose level. In case

of ≥2 of 6 patients experiencing a DLT then MTD was considered to have been exceeded. Patients had to have completed at least two cycles of treatment in the previous dose cohort before enrolling patients at the next higher dose level.

In the phase II arm of the study patients received protocol treatment with MTD, as defined in the phase I arm.

All patients received low-dose aspirin (100 mg) as prophylactic antithrombotic treatment throughout the treatment course. If low-dose aspirin was contraindicated or was not considered adequate due to other conditions (atrial fibrillation, previous deep vein thrombosis-DVT, heavy proteinuria) then patients received another form of anti-thrombotic therapy according to our institutional guidelines. Standard supportive care also included a PPI, trimethoprim/sulfamethoxazole and valacyclovir.

Number of patients (planned and analysed): Thirty seven patients (13 in the phase I and 24 in the phase II) received at least one dose of RdC. One patient withdrew consent after she had received RdC for a few days and was excluded from efficacy analysis but was included in safety analysis.

Diagnosis and main criteria for inclusion:

Subjects must meet the following inclusion criteria to be eligible for the study:

Inclusion criteria

1. Understand and voluntarily sign an informed consent form.
2. Age >18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Confirmed diagnosis of AL amyloidosis
5. Need for treatment in the judgment of their treating physician
6. Evaluable or measurable disease defined by any of the following:
   I. Measurable serum free light chains > 10 mg/dL, kappa or lambda, provided κ/λ ratio is abnormal (measurable disease)
   II. monoclonal protein in the serum□1 g/dL (να μπει και στο Ελληνικό κείμενο)
7. ECOG Performance Status (PS) 0, 1, 2 or 3
8. Laboratory test results within these ranges:
   - Absolute neutrophil count ≥ 1.5 x 109/L

- Platelet count < 100 x 109/L
- Serum creatinine > 2.5 mg/dL
- Total bilirubin > 1.5 mg/dL
- AST (SGOT) and ALT (SGPT) > 2 x ULN or > 5 x ULN if hepatic metastases are present.

9. Women of childbearing potential (WCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL 10 – 14 days prior to therapy and repeated within 24 hours of starting study drug and must begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide. Women must also agree to ongoing pregnancy testing. Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential. (See Appendix 1 Pregnancy Testing Guidelines and Acceptable Birth Control Methods.)

10. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast

11. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation. (patients intolerant to ASA may use low molecular weight heparin).

Exclusion criteria

1. Patients with symptomatic multiple myeloma with asymptomatic biopsy confirmed AL amyloidosis

2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).

4. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

5. Use of any other experimental drug or therapy within 28 days of baseline.

6. Known hypersensitivity to thalidomide.

7. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

8. Any prior use of lenalidomide.

9. Concurrent use of other anti-cancer agents or treatments.

10. Known positive for HIV or infectious hepatitis, type A, B or C.

11. ≥ grade 2 peripheral neuropathy

12. Life expectancy < 3 months

13. Concurrent use of steroids (Patients may receive prednisone up to 20 mg/d, or equivalent corticosteroids for concurrent illness or adrenal replacement therapy

Test product, dose and mode of administration, batch number:

Patients received therapy according to the described schedule of Cyclophosphamide, dexamethasone and lenalidomide. Prophylactic anticoagulation with ASA 100 mg / 325 mg was required in all patients who did not have an absolute contraindication or who are not taking or planning on taking either coumadin or heparin product

Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Cyclophosphamide	see below	Oral	Days 1-10	28 days
Dexamethasone	20 mg	Oral	Days 1-4	28 days
Lenalidomide	see below	Oral	Days 1-21	28 days

Dose cohorts:

	Cyclophosphamide	Lenalidomide
Dose level –1	25 mg/m^2	5 mg/d
Dose level 0*	25 mg/m^2	10 mg/d
Dose level +1	50 mg/m^2	10 mg/d
Dose level +2	50 mg/m^2	15 mg/d

* Starting dose.

Duration of treatment: Patients received dexamethasone 20 mg on days 1-4 (80 mg per cycle), oral cyclophosphamide on days 1-10, and lenalidomide on days 1-21 every 28 days for a planned duration of 12 cycles

Reference therapy, dose and mode of administration, batch number: there was no control/reference arm in this study

Criteria for evaluation:

Efficacy: Efficacy was evaluated at the beginning of each cycle or whenever there was a delay >14 days in the beginning of a new cycle. All patients were followed for survival and disease progression. Consensus criteria were used for the definition of organ involvement and assessment of hematologic and organ response (Gertz MA, et al . Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005 Aug;79(4):319-28).

Safety: Adverse events were recorded throughout the study and until 30 days after the last dose of lenalidomide. Patients who received at least one dose of treatment with lenalidomide were

assessable for safety. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

Statistical methods: According to Simon's minimax two stage design(16), in the phase II study 24 patients are required in order to test at α=0.05 the null hypothesis that the rate of hematologic response is less than 5% versus the alternative hypothesis that the rate of hematologic response is at least 25%. Following this design, this phase II trial had a power of 90%.

Progression free survival (PFS) was defined form the date of initiation of RdC until the date of hematologic or organ progression or death by any cause. Overall survival was calculated from the date of 1st dose of RdC until the date of death by any cause or the date of last contact. Survival curves were plotted with the method of Kaplan-Meier and compared by the use of the log-rank test.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Phase I : A DLT was recorded at dose level 1 (an episode of DVT in a patient receiving aspirin as thromboprophylaxis). No DLT was recorded at dose level 2, and this dose (lenalidomide 15 mg per day and p.o. cyclophosphamide 100 mg/day) was further evaluated in the phase II of the study.

Hematologic responses were recorded in all three dose cohorts. On intent to treat, a hematologic response was achieved by 20 (55%) patients, including 3 (8%) with hematologic CR. Among patients who received at least 2 cycles of RdC, hematologic responses were seen in 58% and for patients who received at least 6 cycles of RdC hematologic responses were 88% and in all patients who completed the planned 12 cycles of RdC.

The median time to hematologic response for all patients was 2.54 months (95% CI: 1-4.1) and for patients treated at the maximum tolerated dose was 1.9 months (2 cycles of RdC).

An organ response was recorded in 8 (22%) patients, including 1 cardiac and 8 renal responses (one patient achieved both cardiac and renal response). Organ responses were recorded in both pretreated and previously untreated patients. Because significant improvement in organ function may need several months to occur, organ responses were recorded only in patients who survived enough to achieve a response, thus, 8 of 20 patients (40%) that survived at least 6 months had an organ response.

SAFETY RESULTS:

A total of 242 cycles of RdC were given, 89 in the phase I and 153 in the phase II of the study. The median number of cycles that was given in the phase II of the study was 5, while 47% of patients received at least 6 cycles and 24% received the planned 12 cycles of RdC. Treatment was discontinued before cycle 12 due to disease progression or death in 19 patients, toxicity in 3 patients and patient's refusal to continue therapy due to reasons other than toxicity in 5 patients.

A dose reduction for lenalidomide was required in 9 (27%) patients. Only one patient required reduction of the dose of dexamethasone and two of cyclophosphamide.

The most common hematologic toxicities included neutropenia and anemia (see Table) - no platelet or RBCs transfusions were required. G-CSF support was required only in one patient – after a reduction of the dose of lenalidomide no G-CSF was required again. Fatigue, non-neutropenic infections, and rash were the most common non-hematologic toxicities (see Table). No significant neurotoxicity was recorded. Fatigue was the most common reason for dose reductions of lenalidomide. Infections were also common; however no neutropenic infections were recorded. Most of the febrile episodes were associated with symptoms of upper respiratory tract infection and were treated on outpatient basis with oral antibiotics. Two patients in the phase II of the study, both of whom had severe nephrotic syndrome, died due to non-neutropenic sepsis. Rash was common (33% of patients), but required dose reduction in only 2 patients. No patient discontinued therapy due to a skin rash.

Most patients (83%) received low-dose aspirin and the rest received either LMWH (14%) or coumadin (3%). Two episodes of DVT were recorded, the first occurred in the phase I of the study, and the second in a patient with heavy proteinuria receiving LMWH. One patient died due to complications that followed an acute MI, while on treatment with RdC. A coronary angiography showed a 2 vessel disease. Another patient with cardiac involvement and 3-vessel coronary artery disease died suddenly 7 days after the initiation of therapy with RdC. Finally, a patient suffered a stroke after the 11th cycle of RdC. In all the above episodes, patients were receiving aspirin.

CONCLUSION: The oral combination of lenalidomide with low dose steroids and low dose cyclophosphamide is feasible and results in significant response rates with a manageable toxicity

profile. RdC could be an additional option especially for patients with preserved organ function and low levels of cardiobiomarkers who relapse after bortezomib or ASCT or Melphalan with dexamethasone. For patients at moderate or high risk RdC may not be able to alter their outcome.

Date of the report: **28 Feb 2012**

3. Contents

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
DMC	Data Monitoring Committee
DTIC	Dacarbazine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
GM-CSF	Granulocyte/macrophage colony stimulating factor, sargramostim, (Leukine, Prokine)
GCP	Good clinical practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IFN	Interferon
IL-2	Interleukin-2
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LD	Longest diameter
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activity
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PR	Partial response
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TPP	Therapeutics Product Programme
TSH	Thyroid stimulating hormone

TTP	Time to progression
WBC	White blood cell (count)
WCBP	Women of child bearing potential
WHO	World Health Organization

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study was reviewed and approved by the

- Local ethics committee (Scientific Review Board of Alexandra Hospital) (Protocol Number 248/18.12.2006 – 6/2/2007)
- National Ethics Committee (Protocol Number 43688/26-07-07 – EED decision Number 36/07 – Chair: D. Athanasiades)

5.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3 PATIENT INFORMATION AND CONSENT

All patients gave informed consent prior to any procedure related to the study. Pre-screening all subject were informed in detail by study physicians (M.A Dimopoulos, E. Kastritis, M. Roussou) for the procedures of the study and treatment options. After the patient had read the ICF and the physicians answered all questions, and after the subject signed the ICF, the screening procedures initiated. An informed consent (in Greek) is provided in Appendix 16.1.3

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator: Prof. Meletios A. Dimopoulos, MD

Co-Investigators: **Dr. Esftathios Kastritis, MD**

Dr.Maria Roussou, MD

Department of Clinical Therapeutics, University of Athens School of Medicine

Monitoring: **Mina Petropoulou**

Evita Fragou

Authors of the report: Dr. Esftathios Kastritis, MD

Department of Clinical Therapeutics, University of Athens School of Medicine

7. INTRODUCTION

Current treatments for primary systemic light chain (AL) amyloidosis are based on alkylating agents, such as the combination of standard dose melphalan with dexamethasone (MDex), or, for some selected patients, high dose melphalan (HDM) with autologous stem cell support (ASCT)(1, 2). For patients who fail initial therapy and are either refractory or relapsed, there is no standard therapy. Novel agents such as thalidomide, bortezomib and lenalidomide, offer new treatment options for patients with AL amyloidosis. However, due to multiorgan involvement, many patients with AL cannot tolerate standard doses of novel agents. Thus, thalidomide at standard doses was not well tolerated (3-5) while bortezomib is active in AL amyloidosis (6, 7) but is associated with peripheral neuropathy, orthostatic hypotension, constipation or diarrhea.

Lenalidomide with dexamethasone was active in AL amyloidosis in two phase II trials, although standard doses were poorly tolerated and dose reductions were required in most patients (8, 9). In patients with newly diagnosed myeloma, lenalidomide in combination with low dose dexamethasone was better tolerated than its combination with high dose dexamethasone.(10). and combinations of lenalidomide with alkylating agents is feasible and effective in both newly diagnosed (11) and relapsed myeloma (12). Based on the above data, we initiated a phase I/II study to explore the feasibility, define doses and evaluate the activity of an oral regimen based on the combination of lenalidomide with low dose dexamethasone and low dose oral cyclophosphamide (RdC) in patients with AL amyloidosis.

8. STUDY OBJECTIVES

Primary objectives

Phase I arm

- Assess the maximum tolerated dose of lenalidomide in combination with Cyclophosphamide and Dexamethasone in patients with AL amyloidosis.

Phase II arm

- Assess the hematologic response rate of the combination of Cyclophosphamide/Dexamethasone plus lenalidomide in patients with AL amyloidosis

Secondary study objectives

- To assess the toxicity of Cyclophosphamide/Dexamethasone plus lenalidomide combination in patients with AL amyloidosis

- To assess organ response rate of Cyclophosphamide/Dexamethasone plus lenalidomide combination in patients with AL amyloidosis

Endpoints

Primary Endpoint

- Hematologic and organ progression free survival

Secondary Endpoints

- Overall survival
- Time to Hematologic progression
- Time to Organ progression
- Objective overall response rate
- Time to response
- Time to best response
- Duration of response
- Time to next anti-amyloidosis therapy
- Safety (type, frequency, severity [National Cancer Institute(NCI) Common Terminology Criteria (CTC), and relationship of adverse events to study therapy)

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

This phase 1/2, single-arm, open-label single center study (clinicaltrials.gov NCT00981708, EudraCT 2006-007082-36) included pretreated or previously untreated patients with AL amyloidosis with biopsy confirmed AL amyloidosis, at least one involved organ and adequate renal function, defined as a serum creatinine ≤2.5 mg/dL. Other criteria included absolute neutrophil count ≥1.5x10^9/L, platelet counts ≥100x10^9/L, adequate liver function (AST and ALT ≤2xULN or ≤5xULN if hepatic involvement was present, total bilirubin ≤1.5 mg/dL) and an ECOG Performance Status ≤3. Patients should be >18 years, have evaluable or measurable disease defined by either measurable serum free light chains (≥100 mg/L, kappa or lambda, provided κ/λ ratio is abnormal) or monoclonal protein in the serum≥10 g/L.
The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Lenalidomide was provided by Celgene.

Patients received dexamethasone 20 mg on days 1-4 (80 mg per cycle), oral cyclophosphamide on days 1-10, and lenalidomide on days 1-21 every 28 days for a planned duration of 12 cycles. Table 1 depicts the dose levels in the phase I of the study.

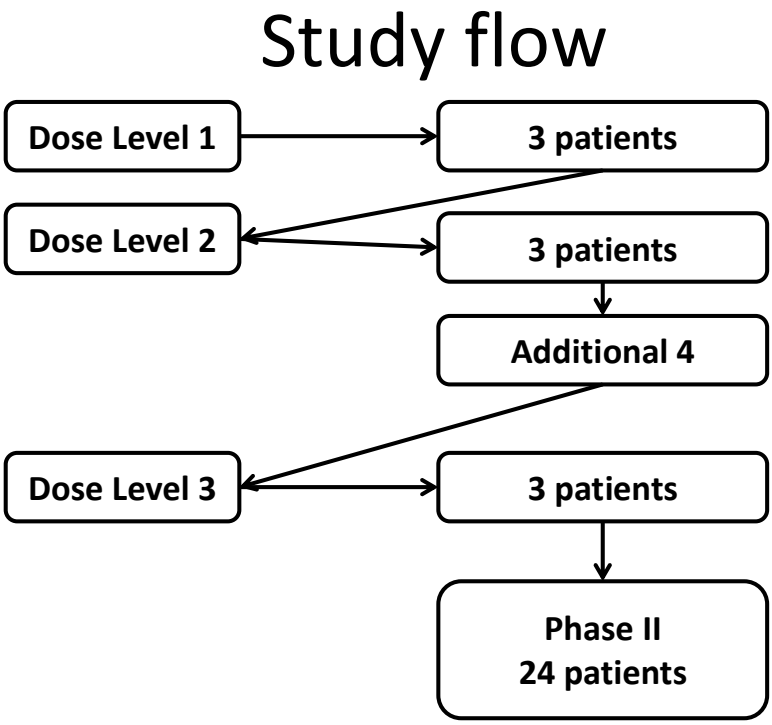
Table 1

Dose level	Lenalidomide dose	Cyclophosphamide dose (mg per day on days 1-10)
0	10 mg	50 mg
1	10 mg	100 mg
2	15 mg	100 mg

The initial design of the study included also lenalidomide at dose levels of 20 mg and 25 mg. However, based on data from other studies (11, 13, 14) that were made available during the phase I of our study and our experience with RdC, we decided to use a maximum dose of 15 mg for lenalidomide.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

In the phase I part of the study, patients were observed for 2 cycles of therapy for determination of dose limiting toxicity (DLT). A standard 3+3 design was followed. If no DLT was encountered in the first 3 patients at a dose level, 3 patients were enrolled at the next dose level. If >1 of 3 patients experienced a DLT, then MTD was considered to have been exceeded. If 1 of 3 patients experienced a DLT, 3 more patients were enrolled at the same dose level (total 6 patients). If no more patients experienced a DLT (1 of 6), 3 patients were enrolled at the next dose level. In case of ≥2 of 6 patients experiencing a DLT then MTD was considered to have been exceeded (study flow).



Patients had to have completed at least two cycles of treatment in the previous dose cohort before enrolling patients at the next higher dose level. In the phase II arm of the study patients received protocol treatment with MTD, as defined in the phase I arm. All patients received low-dose aspirin (100 mg) as prophylactic antithrombotic treatment throughout the treatment course. If low-dose aspirin was contraindicated or was not considered adequate due to other conditions (atrial fibrillation, previous deep vein thrombosis-DVT, heavy proteinuria) then patients received another form of anti-thrombotic therapy according to our institutional guidelines. Standard supportive care also included a PPI, trimethoprim/sulfamethoxazole and valacyclovir. Efficacy was evaluated at the beginning of each cycle or whenever there was a delay >14 days in the beginning of a new cycle. All patients were followed for survival and disease progression. Consensus criteria were used for the definition of organ involvement and assessment of hematologic and organ response (15). Adverse events were recorded throughout the study and until 30 days after the last dose of lenalidomide. Patients who received at least one dose of treatment with lenalidomide were assessable for safety. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Subjects who met the following inclusion criteria were eligible for the study.

1. Understand and voluntarily sign an informed consent form.

2. Age ≥18 years at the time of signing the informed consent form.

3. Able to adhere to the study visit schedule and other protocol requirements.

4. Confirmed diagnosis of AL amyloidosis

5. Need for treatment in the judgment of their treating physician

6. Evaluable or measurable disease defined by any of the following:

I. Measurable serum free light chains ≥ 10 mg/dL, kappa or lambda, provided κ/λ ratio is abnormal (measurable disease)

II. monoclonal protein in the serum≥1 g/dL

7. ECOG Performance Status (PS) 0, 1, 2 or 3

8. Laboratory test results within these ranges:

- Absolute neutrophil count ≥ 1.5 x 109/L
- Platelet count ≥ 100 x 109/L
- Serum creatinine ≤ 2.5 mg/dL
- Total bilirubin ≤ 1.5 mg/dL
- AST (SGOT) and ALT (SGPT) ≤ 2 x ULN or ≤ 5 x ULN if hepatic metastases are present.

9. Women of childbearing potential (WCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL 10 – 14 days prior to therapy and repeated within 24 hours of starting study drug and must begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide. Women must also agree to ongoing pregnancy testing. Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential. (See Appendix 1 Pregnancy Testing Guidelines and Acceptable Birth Control Methods.)

10. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast

11. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation. (patients intolerant to ASA may use low molecular weight heparin).

9.3.2 Exclusion criteria

1. Patients with symptomatic multiple myeloma with asymptomatic biopsy confirmed AL amyloidosis (Appendix 3)

2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).

4. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

5. Use of any other experimental drug or therapy within 28 days of baseline.

6. Known hypersensitivity to thalidomide.

7. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

8. Any prior use of lenalidomide.

9. Concurrent use of other anti-cancer agents or treatments.

10. Known positive for HIV or infectious hepatitis, type A, B or C.

11. □ grade 2 peripheral neuropathy

12. Life expectancy < 3 months

13. Concurrent use of steroids (Patients may receive prednisone up to 20 mg/d, or equivalent corticosteroids for concurrent illness or adrenal replacement therapy

9.3.3 Removal of Patients from Therapy or Assessment

Treatment was continued until 12 cycles of treatment were completed or the occurrence of any of the following events:

- Lack of therapeutic effect
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Major violation of the study protocol.
- Withdrawal of consent

- Lost to follow up
- Death
- Suspected pregnancy

Efficacy was evaluated at the beginning of each cycle or whenever there was a delay >14 days in the beginning of a new cycle. All patients were followed for survival and disease progression. All patients were evaluable for safety assessments.

9.4 TREATMENTS

9.4.1 Treatments Administered

Patients received dexamethasone 20 mg on days 1-4 (80 mg per cycle), oral cyclophosphamide on days 1-10, and lenalidomide on days 1-21 every 28 days for a planned duration of 12 cycles.

9.4.2 Identity of Investigational Product(s)

Investigational Drug : Lenalidomide (Revlimid)

Supplier(s)

Celgene Corporation supplied Revlimid®, lenalidomide

Dosage form

Lenalidomide was supplied as 5 mg and 25 mg capsules for oral administration.

Packaging

Drug was shipped to study site in individual bottles with tear-off labels. Bottles contained 21 capsules.

Labeling

Lenalidomide investigational supplies were dispensed to the patient's in individual bottles of capsules. Each bottle was identified by the contents as study medication and had a protocol number. In addition, the label had, the quantity contained, and all applicable labelling requirements according to European regulations.

Receipt of study drug

The Investigators were responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator verified the accuracy of the information on the form, signed and date it, retained a copy in the study file, and returned a copy to Celgene or its representative.

Storage

At the study site, all investigational study drugs was be stored in a locked, safe area to prevent unauthorized access.

The study drug was stored at room temperature away from direct sunlight and protected from excessive heat and cold

9.4.3 Method of Assigning Patients to Treatment Groups

Consecutive patients in the phase I of the study were allocated to dosing levels according to the design of the protocol as per table 1

In the phase II of the study patients received therapy according to the dose defined in phase I of the study (lenalidomide 15 mg per day on days 1-21 and p.o. cyclophosphamide 100 mg/day days 1-10 and dexamethasone 20 mg per day on days 1-4 every 28 days)

9.4.4 Selection of Doses in the Study

The dose of lenalidomide was based on the clinical experience in patients with solid tumors, myelodysplastic syndromes and multiple myeloma. These data were available at the time of the design of the current study

Clinical experience with lenalidomide in solid tumors

Twenty patients with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in patient dose-escalation design, where patients started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy(16).

Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1(17).

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled. Lenalidomide was administered in daily doses of 5mg (3 patients), 10mg (3 patients) and 20mg (6 patients). Dose limiting toxicity was seen at 20mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients.

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analyses of response rates are pending. The toxicity

profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a lenalidomide dose of 25 mg daily orally for 21 days with a 7-day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favorable and similar to the previous phase III study.

Clinical experience in multiple myeloma with lenalidomide

In two phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg (18). In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled (19).

Anti-myeloma activity was observed in each of these 2 phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25mg and 50mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg.

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone (56) (20).

A recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently reported by the Mayo Clinic. Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, two had minor response (MR) and one

stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Rev/Dex is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma(21).

A phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients is ongoing. The MTD of lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with lenalidomide 15mg on Days 1-21 in combination with DVd was sepsis/septic shock (22). Additional phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in patients with relapsed or refractory multiple myeloma (58). More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg qd, Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25mg qd or placebo, Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg qd, Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. A New Drug Application (NDA) is currently being prepared for the use of lenalidomide in Multiple Myeloma.

Clinical experience in myelodysplastic syndromes (MDS) with lenalidomide

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona (23). Patients received lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All patients had had no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the 3 dose schedules used. Responses were observed in 24 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. Patients with a major response reached a median hemoglobin level of 13.2 grams per deciliter, with a corresponding 5.3 grams per deciliter median increase from baseline. After a median follow-up of 81 weeks, the median duration of major response had not been reached and was more than 48 weeks. Of 20 patients with karyotypic abnormalities, 10 (50%) patients had a complete cytogenetic remission. The response rate was highest in patients with a clonal interstitial deletion involving chromosome 5q31.1 (10 out of 12, 83%). Neutropenia and thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 patients (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10mg on Days 1-21, repeated every 28 days, to 44 patients, and at a dose of 10mg daily to the other 104 patients. Transfusion independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent patients with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable patients. With a median follow-up of 9.3 months, the median response duration had not been

reached. Neutropenia (39%) and thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions(24).

Another Celgene sponsored trial (MDS-002) in patients with low to intermediate-1 risk MDS enrolled 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS. Among the patients with documented low to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion independence was achieved in 54 patients (33%) and 30 patients (18%) achieved a minor response, defined as a 50% or greater decrease in blood transfusion requirement. The median duration of transfusion-independence was 41 weeks. The median baseline hemoglobin level was 8.0g/dl, which increased by 3.2g/dl in responding patients. Among 20 patients evaluable for cytogenetic response, 9 patients (45%) experienced a cytogenetic remission.

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

9.4.5 Selection and Timing of Dose for each Patient

All patients were assigned to receive the drugs according to dosing pre specified in table 1, in the pahse I of the study and lenalidomide 15 mg per day on days 1-21 and p.o. cyclophosphamide 100 mg/day days 1-10 and dexamethasone 20 mg per day on days 1-4 every 28 days in the phase II of the study.

Patients were counseled to receive the drugs at the same hours – Lenalidomide could be administered in the morning or in the evening (but in the same time for each patient) independently of meals. Dexamethasone was given in the morning after a light meal . Cyclophosphamide was given in the morning and in the afternoon with an empty stomach

9.4.5.1 Dose Continuation, Modification and Interruption

Subjects were evaluated for AEs at each visit with the NCI CTCAE v3.0 (Appendix 6: NCI CTCAE v3.0) used as a guide for the grading of severity.

Dose reduction by 1 level occured in the case of grade 4 hematologic toxicity, febrile neutropenia or ≥grade 3 non-hematologic toxicity. If one or more of the above toxicities occur again, dose reduction by 2 levels will take place. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. No dose increase is allowed after the resolution of toxicity.

Dose Modification for Lenalidomide and Cyclophosphamide (Based on Interval Toxicity Observed on Days 2-28)			
CTCAE Category	**AGENTS**	**Day 2-14 of Cycle**	**Day ≥ 15 of Cycle**
Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever	**Lenalidomide**	• Hold (interrupt dose) lenalidomide. Follow CBC weekly. • If neutropenia resolved to ≤ grade 2 by day 15 and is the only toxicity requiring dose reduction, maintain dose level and add G-GSF at the investigators discretion and	• Omit lenalidomide for reminder of cycle • Maintain same dose level and add G-CSF after day 7 in the next cycle

(temperature ≥ 38.5º C) or Grade 4 neutropenia		continue the cycle until Day 21. If patient already on G-CSF, dose reduce lenalidomide by 1 level. • In the next cycle, maintain same dose level and add G-CSF after day 7. If patient already on G-CSF, dose reduce by 1 level.	• If patient already on G-CSF, dose reduce lenalidomide by 1 level. • If patient on lowest dose lenalidomide, dose reduce cyclophosphamide by 1 level in next cycle.
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm³)	**Lenalidomide**	• Hold (interrupt) lenalidomide dose. Follow CBC weekly. • If thrombocytopenia has resolved to ≤ grade 2, restart lenalidomide at next lower dose level and continue the cycle until Day 21. • Dose reduce lenalidomide by 1 level in next cycle • If patient on lowest dose lenalidomide, dose reduce cyclophosphamide by 1 level in next cycle.	• Omit lenalidomide for remainder of cycle • Dose reduce 1 level in next cycle • If patient on lowest dose lenalidomide, dose reduce cyclophosphamide by 1 level in next cycle.
Grade ≥ 3 Mucositis / Stomatitis	**Cyclophosphamide**	• Reduce cyclophosphamide by 1 levelin the next cycle	• Reduce cyclophosphamide by 1 level in the next cycle
Grade ≥ 3 Hyperbilirubinemia	**Cyclophosphamide**	• Reduce cyclophosphamide by 1 level in the next cycle	• Reduce cyclophosphamide by 1 level in the next cycle
Non-blistering rash Grade 3 Grade 4	**Lenalidomide**	• If Grade 3 hold (interrupt) dose. Follow weekly. • If the toxicity resolves to < grade 2 by Day 15 restart at next lower dose level and continue the cycle until Day 21 • Maintain reduced dose in the next cycle. • Discontinue lenalidomide study drug for grade 4 toxicity.	• Omit lenalidomide for remainder of cycle. • If the toxicity resolves to < grade 2 dose reduce 1 level in next cycle Discontinue lenalidomide study drug.
Desquamating (blistering) rash- any Grade	**Lenalidomide**	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Erythema multiforme ≥ Grade 3	**Lenalidomide**	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.

Dose Modification for Lenalidomide and cyclophosphamide (Based on Interval Toxicity Observed on Days 2-28)			
CTCAE Category	**AGENTS**	**Day 2-14 of Cycle**	**Day ≥ 15 of Cycle**
Neuropathy Grade 3 Grade 4	**Lenalidomide**	• If Grade 3 hold (interrupt) dose. Follow weekly. • If the toxicity resolves to ≤ grade 2 by Day 15 restart at next lower dose level and continue the cycle until Day 21. • Maintain reduced dose in the next cycle • Discontinue lenalidomide study drug.	• Omit lenalidomide for remainder of cycle. • If the toxicity resolves to ≤ grade 2, dose reduce 1 level in next cycle • Discontinue lenalidomide study drug
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade ≥ 3	**Lenalidomide**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21. • Maintain reduced dose in the next cycle Discontinue lenalidomide study drug for grade ≥ 3	• Omit lenalidomide for the reminder of the cycle • If the toxicity resolves to ≤ grade 1, dose reduce 1 level in next cycle • Discontinue lenalidomide study drug
Allergic reaction or Hypersensitivity	**Lenalidomide**	• Hold (interrupt) dose. Follow at least weekly.	• Omit lenalidomide for the remainder of the cycle.

Grade 2-3 Grade 4		• If the toxicity resolves to ≤ grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21. • Maintain reduced dose in next cycle • Discontinue lenalidomide study drug.	• If the toxicity resolves to ≤ grade 1, dose reduce 1 level in next cycle • If toxicity recurs, discontinue therapy • Discontinue lenalidomide study drug
Constipation Grade 1-2 ≥ Grade 3	**Lenalidomide**	• Initiate bowel regimen and maintain dose level. • Interrupt dose. Initiate bowel regimen • If the toxicity resolves to ≤ grade 2 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21. • Maintain reduced dose in next cycle.	• Initiate bowel regimen and maintain dose level. • Omit lenalidomide for the remainder of the cycle. • If the toxicity resolves to ≤ grade 2, dose reduce 1 level in next cycle
Venous Thrombosis/embolism ≥ Grade 3	**Lenalidomide**	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit lenalidomide for remainder of cycle and start anticoagulation. • Maintain dose level in next cycle
Hyperthyroidism or Hypothyroidism	**Lenalidomide**	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle at same dose level	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle at same dose level

Dose Modification for <u>Lenalidomide</u> and <u>cyclophosphamide</u> (Based on Interval Toxicity Observed on Days 2-28)			
CTCAE Category	**AGENTS**	**Day 2-14 of Cycle**	**Day ≥ 15 of Cycle**
Other Non-hematologic toxicity Assessed as lenalidomide-	**Lenalidomide**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 15 restart at next lower	• Omit lenalidomide for remainder of cycle.

Related ≥ Grade 3		dose level and continue the cycle until Day 21.	• If the toxicity resolves to ≤ grade 2 dose reduce 1 level in next cycle
Other Toxicity assessed as Cyclophosphamide Related ≥ Grade 3	**Cyclophosphamide**	• Hold until resolves to baseline or ≤ grade 1, then reduce by 50% in next cycle	• Hold until resolves to baseline or ≤ grade 1, then reduce by 50% in next cycle

Dose Modification for <u>Lenalidomide</u> and <u>cyclophosphamide</u> (Based on Toxicity Observed on Day 1)		
CTCAE Category	**AGENTS**	**Day 2-14 of Cycle**
Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	**Lenalidomide**	• Evaluate patient at least weekly until ANC ≥ 1000.* • Maintain both drug doses as in previous cycle and use G-CSF starting day 7 • If patient received G-CSF in previous cycle, dose reduce lenalidomide by 1 level. • If at lowest dose of lenalidomide in previous cycle, dose reduce cyclophosphamide by 1 dose level
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm³)	**Lenalidomide**	• Evaluate patient at least weekly until platelets ≥ 50,000.* • Dose reduce lenalidomide by 1 level. • If at lowest dose of lenalidomide in previous cycle, dose reduce cyclophosphamide by 1 dose level
Grade <u>≥</u> 1 Mucositis / Stomatitis	**Cyclophosphamide**	• Evaluate patient at least weekly until stomatitis resolved (grade 0)* • Dose reduce cyclophosphamide by 1 dose level

Grade ≥ 2 Hyperbilirubinemia	**Cyclophosphamide**	• Evaluate patient at least weekly until ≤ grade 1* • Dose reduce cyclophosphamide by 1 dose level
Non-blistering rash Grade 3 Grade 4	**Lenalidomide**	• Evaluate patient at least weekly until rash ≤ grade 2 * • Dose reduce by 1 level • Discontinue lenalidomide study drug
Desquamating (blistering) rash- any Grade	**Lenalidomide**	• Discontinue lenalidomide study drug.
Erythema multiforme ≥ Grade 3	**Lenalidomide**	• Discontinue lenalidomide study drug.

Dose Modification for Lenalidomide and cyclophosphamide (Based on Toxicity Observed on Day 1)		
CTCAE Category	**AGENTS**	**Day 2-14 of Cycle**
Neuropathy Grade 3 Grade 4	**Lenalidomide**	• Evaluate patient at least weekly until ≤ grade 2 * • Dose reduce by 1 level • Discontinue lenalidomide study drug.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade ≥ 3	**Lenalidomide**	• Evaluate patient at least weekly until ≤ grade 1 * • Dose reduce by 1 level • Discontinue lenalidomide study drug

Allergic reaction or Hypersensitivity Grade 2-3 Grade 4	**Lenalidomide**	• Discontinue lenalidomide study drug.
Constipation ≥ Grade 3	**Lenalidomide**	• Initiate bowel • Evaluate patient at least weekly until ≤ grade 1 * • Maintain dose level • If problem recurs, dose reduce by 1 level
Venous Thrombosis/embolism ≥ Grade 3	**Lenalidomide**	• Start anticoagulation; restart treatment at investigator's discretion (maintain dose level).
Hyperthyroidism or Hypothyroidism	**Lenalidomide**	• Evaluate etiology, and initiate appropriate therapy. Maintain lenalidomide dose level
Other Non-hematologic toxicity Assessed as lenalidomide- Related ≥ Grade 3	**Lenalidomide**	• Evaluate patient at least weekly until ≤ grade 2 * • Dose reduce by 1 level
Other Toxicity assessed as Cyclophosphamide Related ≥ Grade 3	**Cyclophosphamide**	• Evaluate patient at least weekly until ≤ grade 2 * • Dose reduce by 1 level

* If the start of next cycle is delayed more than 4 weeks, the Principal Investigator and Celgene will be notified and patient removed from the protocol

Dexamethasone

CTCAE Category	Adverse Event	Agent	Dosage Change
Based on interval adverse event			
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis grade 1-2 (requiring medical management)	**Dexamethasone**	Treat with H2 blockers, sucralfate, or PPI. If symptoms persist decrease dose to level –2 permanently
	≥ Grade 3 (requiring hospitalization or surgery)		Hold Dexamethasone until symptoms adequately controlled. Restart at level -2 along with concurrent therapy with H2 blockers, sucralfate, or PPI. If symptoms persist despite these measures, discontinue prednisone permanently
	Acute pancreatitis		Discontinue Dexamethasone permanently
Cardiovascular	Edema ≥ grade 3 (limiting function and unresponsive to therapy or anasarca		Use diuretics as needed, decrease Dexamethasone dose to level -1. If edema persists decrease dose to level –2. Discontinue prednisone permanently if symptoms persist at dose level -2
Musculoskeletal, connective tissue and bone disorders	Muscle weakness ≥ grade 2 (interfering with function ± interfering with activities of daily living)		Decrease Dexamethasone dose to level -1. If symptoms persist decrease dose to level –2. Discontinue prednisone permanently if symptoms persist at dose level -2.
Neurology	Confusion and mood alteration. ≥ grade 2 (interfering with function ± interfering with activities of daily living)		Hold until symptoms resolve, restart at dose level -2. If symptoms persist despite above measures, discontinue Dexamethasone permanently
Metabolism and nutrition	Hyperglycemia ≥ grade 3 (glucose ≥ 250 mg/dL)		Administer insulin or oral hypoglycemics as needed. If hyperglycemia is not controlled despite treatment, decrease Dexamethasone to dose by one level until satisfactory glucose levels are achieved.
Other	≥3 toxicities		Hold until toxicity resolves to baseline or ≤ grade 1 and then restart dose level -2

Dose Reduction Schedule for Dexamethasone

Starting Dose	Level –1	Level -2
20 mg PO daily Days 1 - 4	16 mg PO daily Days 1 - 4	12 mg PO daily Days 1 – 4

9.4.6 Blinding

This was an open label study

9.4.7 Prior and Concomitant Therapy

Recommended concomitant therapy

Subjects received full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

Anticoagulation

- Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, adriamycin) and erythropoeitin the risk of thrombosis is increased. All patients were given aspirin (100 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin or Coumadin was utilized in patients with appropriate indications.

- **Erythropoietin**: Erythropoietin was used to treat anemia at the discretion of the treating physician. Use according to the published ASCO/ASH guidelines is strongly encouraged. (JCO 2002, 20:4083-4107)

- **G/GM-CSF**: Use of G-CSF or GM-CSF could be used in phase II to prevent/treat neutropenia at the discretion of the treating physician according to to ASCO guidelines (Ozer, H et al. J Clin Oncol 1996)

- Patients could not receive additional anticancer therapy (concomitant therapy) while participating in this study. Patients could receive concomitant medication to relieve adverse reactions to the study drugs (i.e., pain medication, antibiotic, or antifungal medication).

- H2 blockers or proton pump inhibitors were given during days of Dexamethasone therapy

Prohibited concomitant therapy

Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents was not permitted while subjects were receiving study drug during the treatment phase of the study.Which drugs or procedures were allowed before and during the study, whether and how their use was recorded, and any other specific rules and procedures related to

permitted or forbidden concomitant therapy should be described. How allowed concomitant therapy might affect the outcome due either to drug-drug interaction or to direct effects on the study endpoints should be discussed, and how the independent effects of concomitant and study therapies could be ascertained should be explained.

9.4.8 Treatment Compliance

At all times, when dispensing study drug, site personnel reviewed the instructions, printed on the packaging, with subjects. Subjects were consulted to maintain a diary to record the drug administration (but was not mandatory). Subjectswere asked to bring any unused study drug to the research center at their next visit. Research personnel counted and recorded the number of used and unused study drug capsules at each visit

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Assessments of safety and efficacy were conducted according to the following schedule

Procedure	Screening **≤ 28days from Baseline (First day study drug administration)**	**Cycle 1**				**Cycle 2-12**		**Discontinuation From Study Drug**	**Follow-Up Phase**
		Day 1	Day 8	Day 15	Day 21	**Day 1**	**Day 15**		**Every 3 months**
Informed Consent	X								
Record prior medications, treatments	X								
Record prior anti-cancer therapies	X								
Physical examination, vital signs, weight	X	X		X		X	X	X	
Toxicity notation, ECOG performance status and NY heart association class	X	X		X		X	X	X	
Chest x-ray	X							X	
X-ray skeletal survey[1]	X								
Toxicity notation, PS, and NY heart association class	X	X		X		X	X	X	X
Bone marrow aspirate and biopsy, PCLI	X [2]								
Amyloid stain of bone marrow and fat aspirate.	X								
ECG	X							X	X
Echocardiogram (LVEF and septal thickness)	X[3]								X
24hour Holter study	X								
Abdominal CT or Ultrasound	X[3]								X
Hematology	X	X*		X		X	X	X	
Serum chemistry [4]	X	X*		X		X	X	X	
Electrophoresis of serum and urine	X					X			
Immunofixation serum and urine	X								
Immunoglobulin free light chain	X					X		X	X

Prothrombin time (PT), Factor X	X					X			X
Cardiac troponin T, and NT-proBNP	X					X			X
Urinalysis / 24 hour urine protein	X					X		X	X
Creatinine clearance (24 hour or iothalomate)	X							X	X
EMG and neurology exam with neurologic inventory of symptoms if clinically significant peripheral neuropathy	X								
Pregnancy test [5]	X [6]	X	X	X	X	X[6]	X[6]	X[6]	
Dispensement of Cycle 1 study drug		X				X			
Record adverse events				X		X	X	X	
Record concomitant therapies/procedures						X	X	X	
Dispense study drug for next cycle		X				X			
Perform drug accountability		X				X		X	
Obtain Follow-Up anti-cancer treatments									X
Obtain Follow-Up survival information									X

* Only if more than 14 days from baseline assessment

[1] Only when symptomatic multiple myeloma is suspected

[2] Only to be repeated in the case of hematologic CR.

[3]To be repeated to asses organ response or progression

[4] To include Thyroid Stimulating Hormone (TSH) at Screening, end of Cycle 3 and every three months thereafter.

[5] For women of child-bearing potential only. (see Appendix XX)

[6] Must occur 10 – 14 days and again within 24 hours prior to initiation of lenalidomide, weekly for the first 4 weeks, then monthly while on therapy and 30 days post the last dose of lenalidomide. Women with irregular menstruation, must have a pregnancy test every 2 weeks while on therapy.

- The investigator were responsible for the evaluation of clinical outcomes
- Efficacy was assessed according to the criteria published by Gertz et al (Am J Hematol 2005)
- Safety was assessed in every visit
- Toxicity was assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE). The NCI CTCAE V3.0 can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html. If a specific

event was not included in the NCI CTCAE toxicity scale, the following scale was used to grade the event

Grade	Definition
1	**Mild** Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2	**Moderate** Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3	**Severe** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4	**Life-threatening** Immediate risk of death; requires hospitalization and clinical intervention.
5	**Death**

9.5.2 Appropriateness of Measurements

Efficacy and safety assessments were performed by standard criteria

9.5.3 Primary Efficacy Variable(s)

A. Hematologic response

I. Terms and definitions

- M-protein: synonyms include M-spike, monoclonal protein and myeloma protein, monoclonal paraprotein, M-component
- Response terms: The following response terms will be used: complete response (CR), , partial response (PR), stable disease or no response (NR), plateau, and progression or relapse (PD).
- Measurable disease: Patients who have a measurable serum or urine M-protein, or serum free light chains. A "measurable" serum M-protein is > 0.5 g/dL a "measurable" urine M-spike is > 200 mg/24 hours and a "measurable" serum free light chain is > 10 mg/dL with abnormal □/□ ratio. The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients with amyloidosis When using this assay, it is important to note that the FLC levels vary considerably

with changes in renal function and do not solely represent monoclonal elevations. Thus both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. The serum FLC assay should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" by traditional criteria (serum M protein 0.5 gm/dL and/or urine M protein 200 mg/24), and the baseline level of the involved FLC is 10mg/dL and clonal (abnormal ratio). Patients included on the study on the basis of FLC alone (ie no measurable serum/urine) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC assay.

- Confirmed response: In order to be classified as a response, confirmation of serum and urine monoclonal protein results must be made by verification on two consecutive determinations
- Bone marrow aspirate and biopsy are not required to document or confirm PR or progression

II. Clarification of test indications

- Immunofixation studies of both serum and urine and FLC values are required to document CR regardless of registration values

III. Monoclonal protein considerations

- Serum and urine M-protein levels should be determined by electrophoresis rather than by quantitative immunoglobulin (Ig) measurement. Exceptions are made in cases in which the M-spike value may be deemed to be unreliable (see bullets below). In these cases, quantitative immunoglobulin should be used. To assess response and progression, however, SPEP values should only be compared to SPEP values and quantitative Ig values only to quantitative Ig values.

- Small -migrating M-proteins (usually IgA M-proteins) are contaminated by normal globulins that are often greater in quantity that the M spike itself

- Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel

Hematologic (Immunochemical) Response Criteria (Getz et al Am J Hematol 2005)

Complete response

- Serum and urine negative for a monoclonal protein by immunofixation
- Free light chain ratio normal
- Marrow<5% plasma cells

Partial response

- If serum M component>0.5 g/dL, a 50%reduction
- If light chain in the urine with a visible peak and>100 mg/day and 50% reduction
- If free light chain>10 mg/dL (100 mg/L)and 50% reduction

Progression

- From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double
- From PR or stable response, 50% increase in serum M protein to>0.5 g/dL or 50% increase in urine M protein to>200 mg/day; a visible peak must be present
- Free light chain increase of 50% to>10 mg/dL (100 mg/L)

Stable No CR, no PR, no progression

B. Organ response

I. Organ response will be evaluated on the basis of improvement of one or more affected organs as defined below. Only 1 parameter is required to satisfy the organ response criteria, and the response must be maintained for a minimum of one month to be considered a valid response. These response criteria and their ability to predict prolonged survival have previously been reported.

Improvement of one or more affected organ(s) as defined by

- Kidney: 50% reduction in 24-hour urine protein excretion (at least 0.5 g/day). Creatinine and creatinine clearance must not worsen by 25% over baseline (minimum change of creatinine 0.5 mg/dL and of creatinine clearance 15 ml/min).

- Heart (any of below):

Type A. ?2 mm reduction in the interventricular septal (IVS) thickness by echocardiogram (echocardiogram must be performed at the same institution).

Type B. Improvement of ejection fraction by ?20% (echocardiogram must be performed at the same institutionand baseline ejection fraction must be less than or equal to 45%).

Type C. Improvement by 2 New York Heart Association classes without an increase in diuretic use or improvement by 1 New York Heart Association class associated with a 50% reduction in diuretic requirements without Type A or B deterioration

- Liver (either of the below):

Type A. ?50% decrease in (or normalization of) an initially elevated alkaline phosphatase level

Type B. Reduction in the size of the liver by at least 2 cm (radiographic determination) .

- Neuropathy (either of the below):

Type A. Reduction in the Neuropathy Impairment Score (NIS) by 10 points. The NIS is based on the neurologic examination, and the items provide a measure of severity of muscle weakness (scored as 0= normal, 1= 25% , 2= 50%, 3= 75% weak, 4= paralyzed); loss of deep tendon reflexes scored as normal (0), decreased (1), or absent (2) and sensory loss graded as normal (0), diminished (1), or absent (2).

Type B. Improvement in the summated compound muscle action potential (CMAP) amplitude by 2 mv. This value is derived from summated value of compound muscle action potential amplitudes of the tibial, peroneal and ulnar nerves from the nerve conduction studies .

- GI tract: normalization of a low serum carotene level or reduction of diarrhea to less than 50% of previous movements/day or decrease in fecal fat excretion by 50%.

Organ progression is defined by fulfillment of at least one of the major criteria

- Kidney: 50% increase in urinary protein loss (at least 1 g/24 hours), or 25% worsening of creatinine or creatinine clearance (minimum change of 0.5 mg/dL and 15 ml/min, respectively).

- Heart (either of the below):

Type A. Increase in cardiac wall thickness by ≥2 mm (2-D ECHO)
Type B. An increase in New York Heart Association class by 1 grade with a decreasing ejection fraction of ≥10%.

- Liver (either of the below):

Type A. ≥50% increase of alkaline phosphatase above lowest confirmed level
Type B. Increase in liver size by at least 2 cm (radiographic determination).

- Neuropathy (either of the below):

Type A. Increase in the Neuropathy Impairment Score (NIS) by 10 points.
Type B. Worsening in the summated compound muscle action potential (CMAP) amplitude by 2 mv. This value is derived from summated value of compound muscle action potential amplitudes of the tibial, peroneal and ulnar nerves from the nerve conduction studies.

- GI Tract: reduction of serum carotene level below normal limit; worsening of diarrhea with increase > than 50% of previous movements/day or fecal fat by 50%.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

1. Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2. Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

3. Time to Progression

Time to progression will be measured as the time from when the patient started treatment to the time the patient is first recorded as having disease progression, or the date of death if the patient dies due to causes other than disease progression.

4. Time to Treatment Failure

Time to treatment failure will be measured as the time from when the patient started treatment to the time the patient is withdrawn due to: adverse events, progressive disease/insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. The date of last dose of treatment will be used as the date of event in the case that PD was not recorded earlier.

5. Survival

Survival will be measured as the time from start of treatment to the date of death or the last date the patient was known to be alive.

6. Time to Response

For patients who achieve a major objective response (CR or PR of measurable disease), the time to response will be assessed as the time from start of treatment to the date of response.

9.6 DATA QUALITY ASSURANCE

Investigators entered study data onto CRFs.

The Investigator were available for study-related monitoring visits and audits by Celgene or it's representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP) and provided direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, were available during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification.

The data collection was completed prior to each visit and was made available to the sponsors' representative so that the accuracy and completeness could be checked.

Periodic monitoring visits were performed by the sponsor's designated associate

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

Statistical considerations- Sample size

In the phase I of this study, a maximum of 30 patients will be recruited (maximum 6 patients per 5 dosing levels), in order to determine the maximum tolerated dose.

According to the minimax two stage Simon's design, in the phase II study 24 patients are required in order to test at α=0.05 the null hypothesis that the rate of heamatologic response is less than 5% versus the alternative hypothesis that the rate of heamatologic tesponse is at least 25%. Following this design, this phase II trial will have a power of 90%. Taking into account a 2% dropout rate, 31 patients are needed to be accrued.

Based on the above considerations, the maximum total number of patients for both phase I and II studies was estimated to be 55

In the phase I of the study, 13 patients entered the 3 dose cohorts and, according to the design of the study, 24 patients entered the phase II of the study

Overview

1. Primary endpoint: Proportion of confirmed responses
2. Patient evaluability: All patients meeting the eligibility criteria who have signed a consent form and begun treatment will be considered evaluable for estimation of the response probability. Those who die will be considered to have had disease progression unless documented evidence clearly indicates no progression has occurred. In the event that such evidence is obtained, or in the case of major treatment violation, the patient's response data will be considered censored at the date the patient was withdrawn from treatment.
3. Response probability: The true confirmed response proportion will be estimated by dividing the number of successes by the total number of evaluable patients. A ninety-five percent confidence

interval for the true success proportion will be calculated according to the approach of Duffy and Santner.

4. Definitions and Analyses of Secondary Endpoints:

- Time to progression: The time to progression is defined as the time from registration to disease progression. Those who die will be considered to have had disease progression at the time of death unless documented evidence clearly indicates no progression has occurred. The distribution of time to progression will be estimated using the method of Kaplan-Meier.
- Overall Survival: Overall survival time is defined as the time from registration to death due to any cause. The distribution of overall survival time estimated using the method of Kaplan-Meier.
- Duration of response: Duration of response will be calculated from the documentation of response until the date of progression in the subset of patients that respond.
- Time to Hematologic progression: Time to Hematologic progression will be calculated from the date of hematologic response until the date of hematologic progression according to predefined criteria
- Time to Organ progression: Time to Organ progression will be calculated from the date of a confirmed organ response until confirmed organ progression according to predefined criteria
- Objective overall hematologic response rate: Objective overall hematologic response rate will include all partial and complete hematologic responses according to predefined criteria
- Time to Hematologic response: Time to hematologic response will be calculated from the date of initiation of treatment (day 1, cycle 1) until the date of hematologic response according to predefined criteria
- Time to Organ response: Time to organ response will be calculated from the date of initiation of treatment (day 1, cycle 1) until the date of organ response according to predefined criteria
- Time to best hematologic response: Time to hematologic best response will be calculated from the time of initiation of treatment (day 1, cycle 1) until the date of best hematologic response.
- Time to best organ response: Time to organ best response will be calculated from the time of initiation of treatment (day 1, cycle 1) until the date of best organ response.
- Duration of response: will be calculated from the date of response (hematologic or organ, whichever occurs first) until the date of hematologic or organ progression (whichever occurs first)
- Time to next anti-amyloidosis therapy: Time to next anti-amyloidosis therapy will be calculated from the date of last protocol treatment until the date of first next anti-amyloidosis treatment
- Toxicity: As per NCI CTCAE 3.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either unrelated or unlikely related to study treatment in the event of an actual relationship developing

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES
N/A

10. STUDY PATIENTS

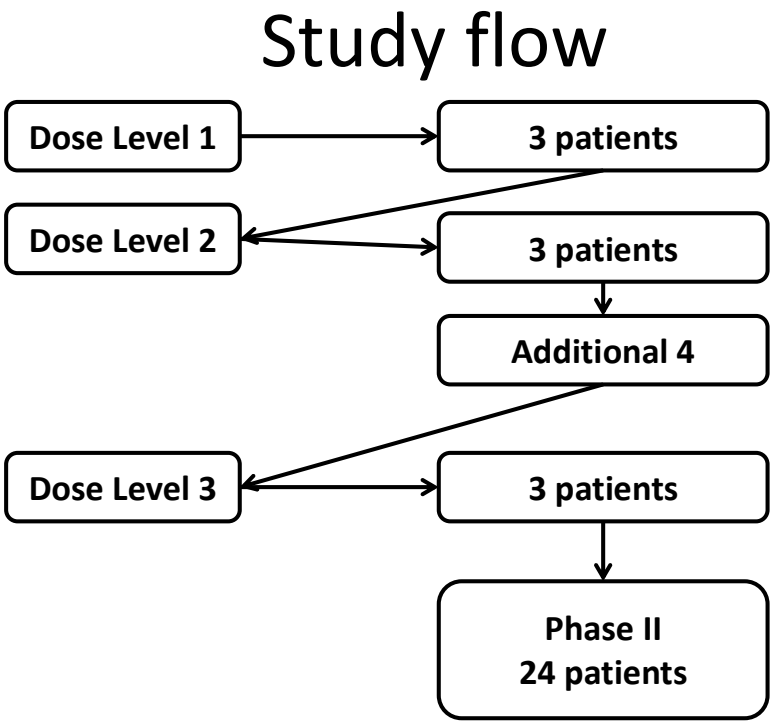
10.1 DISPOSITION OF PATIENTS

Table 2: Disposition of patients in the phase I of the study and results of the phase I of the study

Dose level	Lenalidomide dose	Cyclophosphamide dose (mg per day on days 1-10)	N		CR	PR	NR
0	10 mg	50 mg	3	No DLT	-	2	1
1	10 mg	100 mg	7	1 DLT (DVT)	1	2	4
2	15 mg	100 mg	3	No DLT	-	2	1

Phase II of the study

Lenalidomide dose	Cyclophosphamide dose (mg per day on days 1-10)	N
15 mg	100 mg	24



10.2 PROTOCOL DEVIATIONS

No protocol deviation were recorded

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

All patients were included in safety analysis

All patients, except one who withdrew consent were included in efficacy analysis

Analysis was performed on intent to treat

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 3: Patients Characteristics (n=37)

	Phase I	Phase II	All patients
	N(%)	**N(%)**	**N (%)**
Male / Female	6 (46%) / 7 (54%)	13 (54%)/11 (46%)	19 (51%)/ 18 (49%)
Age (median / range)	68 (45-78)	65 (48-82)	68 (45-82)
Age >65 years	9 (69%)	12 (50%)	21 (57%)
Untreated / Pretreated	7 (54%) / 6 (46%)	17 (71%)/7 (29%)	24 (65%) / 13 (35%)
Previous Therapies			
Thalidomide	1 ((8%)	3 (13%)	4 (11%)
Bortezomib	4 (31%)	1 (4%)	5 (14%)
High Dose Melphalan	1 (8%)	3 (13%)	4 (11%)
Organ Involvement			
Heart	8 (62%)	13 (54%)	21 (57%)
Kidney	8 (62%)	16 (67%)	24 (65%)
Liver	2 (15%)	1 (4%)	3 (8%)
Nerve	2 (15%)	6 (25%)	8 (22%)
Soft Tissue	4(31%)	6 (25%)	10 (27%)
Number of involved organs			
(Median/range)	2 (1-4)	2 (1-3)	2 (1-4)
≥2 organs	7 (54%)	13 (54%)	20 (54%)
NTproBNP (median/ range)	2325 (36-9197)	448 (59-9047)	1046 (46-9197)
NTproBNP≥ 332 ng/L	9 (69%)	14 (58%)	23 (62%)
TroponinT≥ 0.035 ng/L	6 (46%)	7 (29%)	13 (35%)
Mayo stage			
I	4 (31%)	10 (42%)	14 (38%)
II	3 (23%)	7 (29%)	10 (27%)
III	6 (46%)	7 (29%)	13 (35%)
IVS (mm) (median / range)	12 (9-23)	13 (8-20)	13 (8-23)
IVS ≥15 mm	5 (38%)	6 (25%)	11 (30%)
Symptoms of CHF	7 (54%)	12 (50%)	19 (51%)
NYHA ≥2	6 (46%)	10 (42%)	16 (43%)
ECOG performance status	**6 (46%)**	**9 (38%)**	**15 (40%)**
Proteinuria (mg/24h) (Median / Range)	1525 (100-17000)	4530 (0-21000)	2208 (0-21000)
Serum Albumin (gr/dl) (median / range)	3.8 (1-6.4)	3.45 (1.8-4.4)	3.6 (1-6.4)
Serum creatinine (mg/dl) (median / range)	0.9 (0.6-2.2)	0.82 (0.45-1.99)	0.9 (0.45-2.2)
eGFR* (ml/min/1.73m^2) (median / range)	75.9 (29-139)	82.14 (26-210)	81.6 (26-210)
eGFR < 30 ml/min/1.73m^2)	1 (8%)	1 (4%)	2 (5%)
Light Chain type (κ / λ)	1 (8%) / 12 (92%)	7 (29%)/17 (71%)	8 (22%) / 29 (78%)
Involved FLC (mg/L)	103 (26-3220)	191 (15.8-6070)	166 (15.8-6070)

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

A total of 242 cycles of RdC have been given, 89 in the phase I and 153 in the phase II of the study. The median number of cycles that was given in the phase II of the study was 5, while 47% of patients received at least 6 cycles and 24% received the planned 12 cycles of RdC. Treatment was discontinued before cycle 12 due to disease progression or death in 19 patients, toxicity in 3 patients and patient's refusal to continue therapy due to reasons other than toxicity in 5 patients. Ten (71%) patients with stage I completed at least 6 cycles and 6 patients (43%) completed 12 cycles of RdC. The respective figures for patients with stage II disease were 30% (3 of 10) and 20% (2 out of 10 patients) and for stage–III were 31% (4 out of 13) and (2 of 13) 15%. A dose reduction for lenalidomide was required in 9 (27%) patients. Only one patient required reduction of the dose of dexamethasone and two of cyclophosphamide.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

Thirty seven patients (13 in the phase I and 24 in the phase II) received at least one dose of RdC. One patient withdrew consent after she had received RdC for a few days and was excluded from efficacy analysis but was included in safety analysis. Table 1 presents patients' characteristics: 65% were previously untreated, 57% had cardiac and 65% had renal involvement, 64% had at least two organs involved and 38% had ECOG performance status ≥2. Concerning cardiac function, 51% had symptoms of congestive heart failure (CHF), and 64% were Mayo stage II or III according to their cardiobiomarkers .

Phase I results

Table 2 presents the results of the phase I of the study. A DLT was recorded at dose level 1 (an episode of DVT in a patient receiving aspirin as thromboprophylaxis). No DLT was recorded at dose level 2, and this dose (lenalidomide 15 mg per day and p.o. cyclophosphamide 100 mg/day) was further evaluated in the phase II of the study.

Hematologic and organ responses

Hematologic responses were recorded in all three dose cohorts (Table 2). Table 3 depicts hematologic and organ responses. On intent to treat, a hematologic response was achieved by 20 (55%) patients, including 3 (8%) with hematologic CR. In addition, according to recently proposed criteria, 4 additional patients (rated as PR by the standard criteria(15)) could be rated as a VGPR (i.e. dFLC <40 mg/L)(18). Hematologic responses were observed in 40% of patients with stage II and 54% of patients with stage III disease compared to 64% of stage-I patients (p=0.505). Among patients who received at least 2 cycles of RdC, hematologic responses were seen in 58% and for patients who received at least 6 cycles of RdC hematologic responses were 88% and in all patients who completed the planned 12 cycles of RdC. The median time to hematologic response for all patients was 2.54 months (95% CI: 1-4.1) and for patients treated at the maximum tolerated dose was 1.9 months (2 cycles of RdC).

The response rates were similar for previously treated or previously untreated patients (58% and 54% respectively). Among 4 patients who had previously received thalidomide, 1 achieved a response and among 5 patients who had previously received bortezomib, 4 achieved a response.

Fourteen patients (38%) received further therapy after failure to respond to RdC or after relapse: 11 (79%) were given bortezomib with dexamethasone and 6 (43%) achieved a hematologic response (exclusively patients who were treated with bortezomib).

An organ response was recorded in 8 (22%) patients, including 1 cardiac and 8 renal responses (one patient achieved both cardiac and renal response). Organ responses were recorded in both pretreated and previously untreated patients (Table 3). Because significant improvement in organ function may need several months to occur, organ responses were recorded only in patients who survived enough to achieve a response, thus, 8 of 20 patients (40%) that survived at least 6 months had an organ response.

Table 4 : Hematologic and organ responses

	N	≥ PR	CR	Organ response
All patients*	36**	20 (55%)	3 (8%)	8 (22%)
Phase II	23**	11 (48%)	2 (9%)	6 (26%)
Evaluable for response (at least 2 cycles of RdC)	32	20 (63%)	3 (9%)	8 (25%)
At DLT (lenalidomide 15 mg/day)	26**	13 (50%)	2 (8%)	5 (19%)
Previously Untreated	24	13 (54%)	2 (8%)	3 (13%)
Pretreated	12**	7 (58%)	1 (8%)	5 (42%)

*Intention to treat

** One patients withdrew consent after a few days of RdC and was not included in efficacy analysis

Cardiac biomarkers and renal function

An increase in NTproBNP ≥30% and ≥300 ng/L after the 1st cycle of RdC was observed in 21 (69.5%) of evaluable patients (N=30) patients but only one patient had also a concomitant increase of troponin-T levels (Figure 1). These increases were observed in 5 stage I patients (of 12 evaluable), 7 stage II patients (of 8 evaluable) and 9 stage III patients (of 10 evaluable). However a reduction of NTproBNP towards the baseline levels was observed after the 3rd cycle (Figure 1A & B). Transient increase of

NTproBNP was observed both in patients with no overt cardiac involvement and in patients with cardiac involvement. The increase in NTproBNP was not associated with fluctuations of eGFR (Figure 1) and was in discordance with FLC levels, which were either dropping or stable (Figure S3-5). The increase in NTproBNP was associated with inferior survival (p=0.02) with a hazard ratio of 1.013 (95%CI 1.0029-1.023) per 100 pg/mL of increase over baseline. No patient had a decrease of eGFR above 50% during treatment with RdC. However a transient decrease ≥25% was recorded in 15 (42%) patients; in 2 patients this reduction was associated with increase of proteinuria followed by progression of their renal diseases. Decrease in eGFR was associated with the use of diuretics and in most patients eGFR returned near or above baseline levels. Furthermore, one patient with renal and cardiac involvement who achieved a cardiac and renal response had a significant increase of eGFR >50%.

Progression and survival

After a median follow up of 13 months (range 0.3-43 months) for all patients, 26 (72%) patients have progressed (hematologic or organ progression or death) and 22 (60%) patients have died (Figure 2); most of them due to progressive cardiac amyloidosis. Median follow up for surviving patients is 29 months (range 8-43). No patients were lost to follow-up. The median time to progression for all patients was 10 months (95% CI: 1.8-18) and the median survival was 17 months (95% CI: 6-28), with 1-year survival rate of 58% and 2-year survival rate of 41%. Early deaths (within the first 3 months after initiation of therapy) occurred in 7 (19%) patients; all patients who died early had significant cardiac involvement (median NTproBNP 6315 ng/L, range 2023-9197 ng/L). The median PFS for previously untreated patients is 3 months and for previously treated patients 17 months. The respective median OS is 6.5 vs 29 months. Early deaths (< 2 months from the initiation of therapy) occurred in 4 previously untreated and in none of previously treated patients. These differences may be explained by the "preselection" of previously treated patients (i.e. they survived long enough to receive a second chance because their organ dysfunction was less severe).

Patients with cardiac involvement had a median survival of 6.4 months while it has not been reached for those without cardiac amyloidosis (2-year survival of 68% vs. 24% for those with cardiac involvement, p=0.001)(Figure 3A). According to Mayo Clinic risk stratification by cardiobiomarkers, median survival for stage I has not been reached (2-year estimate was 73%) and it was 6.5 months for both stage II and III respectively (p=0.004) (Figure 3B). However, stage II patients had quite unfavorable characteristic (median NTproBNP for stage II patients was 2167 ng/L, 50% had performance status ≥2 and 40% were NYHA stage 2-3).

11.4.2 Statistical/Analytical Issues

Progression free survival (PFS) was defined form the date of initiation of RdC until the date of hematologic or organ progression or death by any cause. Overall survival was calculated from the date of 1st dose of RdC until the date of death by any cause or the date of last contact. Survival curves were plotted with the method of Kaplan-Meier and compared by the use of the log-rank test.

11.4.2.1 Adjustments for Covariates

N/A

11.4.2.2 Handling of Dropouts or Missing Data

N/A

11.4.2.3 Interim Analyses and Data Monitoring

N/A

11.4.2.4 Multicentre Studies

N/A

11.4.2.5 Multiple Comparison/Multiplicity

N/A

11.4.2.6 Use of an "Efficacy Subset" of Patients

N/A

11.4.2.7 Active-Control Studies Intended to Show Equivalence

N/A

11.4.2.8 Examination of Subgroups

N/A

11.4.3 Tabulation of Individual Response Data

Table 5: Individual response and efficacy data

Patient#	Date of 1st dose	Date of Last Dose	Number_ of RdC Cycles	PFS (Months)	Survival (Months)	Best Hematologic Response	Organ Response	Type of Therapy at PD	Status	Time to response (Months)
1	05-02-08	01-04-08	2.00	2.7	2.7	NR	NO		Dead	
2	06-02-08	16-03-09	12.00	19.9	42.7	PR	N/E	VelDex	Alive	2.0
3	07-02-08	07-11-08	10.00	9.7	9.7	PR	NO		Dead	4.8
4	04-04-08	11-05-09	10.00	15.2	32.6	NR	NO	MelDex	Dead	
5	11-04-08	10-02-09	11.00	13.9	17.0	PR	NO	MelDex	Dead	4.7
6	14-04-08	21-10-08	5.00	9.8	21.2	PR	NO		Dead	2.2
7	12-06-08	28-04-09	12.00	38.5	38.5	CR	YES		Alive	17.0
8	23-06-08	06-04-09	11.00	38.2	38.2	PR	YES		Alive	4.8
9	31-07-08	26-11-08	4.00	3.9	3.9	PR	NO		Dead	1.1
10	15-08-08	08-10-08	2.00	1.8	4.0	NR	NO	VelDex	Dead	
11	17-09-08	03-12-08	3.00	3.2	3.2	PR	NO		Dead	1.0
12	19-09-08	23-10-08	2.00	1.3	1.3	PR	NO		Dead	0.9
13	04-10-08	14-09-09	12.00	34.8	34.8	PR	N/E		Alive	1.0
14	16-10-08	13-03-09	5.00	4.9	10.9	NR	NO	VelDex	Dead	
15	06-11-08		1.00	33.7	33.7	NE	N/E	VelDex	Alive	
16	05-11-08	20-11-09	12.00	18.7	33.7	PR	YES	VelDex	Alive	2.9
17	04-12-08	20-02-09	3.00	2.4	6.5	NR	NO	VelDex	Dead	
18	19-12-08	08-01-10	12.00	23.7	28.8	PR	YES	Endoxan -Dexa	Dead	2.9
19	24-02-09	28-01-10	12.00	30.1	30.1	PR	NO		Alive	1.9
20	13-03-09	15-02-10	12.00	29.5	29.5	CR	YES		Alive	0.9
21	22-04-09	30-03-10	12.00	12.2	28.2	PR	N/E		Alive	7.8
22	20-05-09	14-08-09	3.00	2.9	2.9	NR	NO		Dead	
23	01-06-09	18-06-09	1.00	0.6	0.6	NE	N/E		Dead	
24	27-05-09	17-07-09	2.00	1.7	3.8	PR	N/E	VelDex	Dead	1.0
25	08-09-09	30-09-09	1.00	2.4	2.4	NR	N/E		Dead	
26	25-09-09	03-02-10	5.00	1.8	12.5	NR	NO	VelDex	Dead	
27	15-10-09	20-09-10	12.00	17.4	17.4	PR	YES		Dead	3.8
28	18-11-09	28-04-10	6.00	21.3	21.3	CR	NO		Alive	5.5

29	02-12-09	10-10-10	11.00	20.9	20.9	NR	N/E		Alive	
30	04-01-10	10-06-10	5.00	7.8	14.3	NR	NO	VelDex	Dead	
31	28-01-10		10.00	19.0	19.0	PR	YES		Alive	0.9
32	21-08-10	26-01-11	6.00	6.4	6.4	PR	NO		Dead	4.5
33	13-10-10	24-01-11	4.00	10.6	10.6	NR	NO	VelDex	Alive	
34	22-10-10	07-01-11	3.00	2.7	10.3	NR	NO	VelDex	Alive	
35	10-12-10	16-11-11	2.00	1.9	1.9	NR	N/E		Dead	
36	28-12-10	04-01-11	1.00	0.2	0.2		N/E		Dead	
37	11-01-11	07-06-11	5.00	7.6	7.6	NR	YES		Alive	

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Hematologic responses were recorded in all three dose cohorts (Table 5). There was no relationship between Lenalidomide or cyclophosphamide dose and hematologic or organ response

11.4.5 Drug-Drug and Drug-Disease Interactions

N/A

11.4.6 By-Patient Displays

N/A

11.4.7 Efficacy Conclusions

- Oral RdC regimen has manageable and predictable toxicity with significant activity.
- patients with AL amyloidosis can benefit from a lower dose of lenalidomide without the risk of excessive toxicity associated with standard doses of lenalidomide (25, 26).
- Patients with AL amyloidosis are also very sensitive to toxicities associated with high dose steroids (27) and the use of low dose dexamethasone in RdC regimen was associated with improved tolerance as reflected by the requirement for dexamethasone dose reduction in only one patient.
- The use of low dose oral cyclophosphamide was accompanied by very low hematologic toxicity.
- Fatigue was the most common reason to reduce the dose of lenalidomide but in patients with AL amyloidosis fatigue may also be related to the multisystem involvement, CHF, diuretics or significant hypoalbuminemia.
- Rash was also common in our patients but was mostly mild, probably due to the lower doses of lenalidomide.

- Of concern are the significant rates of infections, which were with the cause of two deaths despite the use of prophylactic antibiotics.
- The absence of neurotoxicity should also be acknowledged.
- Organ responses were recorded in 22% of our patients, a figure which is similar to those reported by other investigators for lenalidomide-based therapies. Organ responses may take several months to occur, even more than one year after a hematologic response has been achieved. Furthermore, patients with severe cardiac dysfunction may die early due to complications of heart disease before any organ response could be achieved. Thus, organ response rate in patients who survived at least 6 months was 40%, which is significant.
- Our data also indicate that RdC is not able to change the fate of patients with severe cardiac dysfunction. However, even among patients with elevated cardiobiomarkers, there is a subset that may benefit from effective treatment.

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Table 6: Individual doses of RdC

Patient#	Initial dose of Lenalidomide (mg/day)	Initial dose of Cyclophosphamide (mg/day)	Initial Dose of Dexamethasone (mg/day)	Dose reduction of lenalidomide
1	10	100	20	No
2	10	50	20	No
3	10	100	20	No
4	10	100	20	Yes
5	10	100	20	No
6	10	100	20	No
7	10	100	20	No
8	10	100	20	No
9	10	100	20	No
10	10	100	20	No

11	15	100	20	No
12	15	100	20	No
13	15	100	20	No
14	15	100	20	No
15	15	100	20	No
16	15	100	20	Yes
17	15	100	20	No
18	15	100	20	Yes
19	15	100	20	No
20	15	100	20	Yes
21	15	100	20	No
22	15	100	50	No
23	15	100	20	No
24	15	100	20	No
25	15	100	20	No
26	15	100	20	No
27	15	100	20	Yes
28	15	100	20	Yes
29	15	100	20	No
30	15	100	20	Yes
31	15	100	20	Yes
32	15	100	20	No
33	15	100	20	No
34	15	100	20	No
35	15	100	20	No

36	15	100	20	No
37	15	100	20	Yes

Table 7: Duration of exposure

Patient#	Gender	Age	Number of RdC Cycles
1	Female	70	2
2	Male	48	12
3	Male	68	10
4	Female	61	10
5	Male	78	11
6	Female	68	5
7	Female	67	12
8	Male	45	11
9	Male	68	4
10	Male	76	2
11	Female	76	3
12	Female	74	2
13	Male	53	12
14	Female	50	5
15	Female	59	1
16	Male	59	12
17	Male	64	3
18	Male	68	12
19	Female	67	12
20	Female	77	12

21	Male	51	12
22	Male	75	3
23	Female	78	1
24	Male	61	2
25	Female	48	1
26	Male	78	5
27	Male	69	12
28	Female	74	6
29	Male	68	11
30	Female	69	5
31	Female	62	10
32	Male	57	6
33	Female	63	4
34	Male	75	3
35	Female	59	2
36	Male	55	1
37	Female	82	5

12.2 ADVERSE EVENTS (AEs)

12.2.1 Brief Summary of Adverse Events

A total of 242 cycles of RdC have been given, 89 in the phase I and 153 in the phase II of the study. The median number of cycles that was given in the phase II of the study was 5, while 47% of patients received at least 6 cycles and 24% received the planned 12 cycles of RdC. Treatment was discontinued before cycle 12 due to disease progression or death in 19 patients, toxicity in 3 patients and patient's refusal to continue therapy due to reasons other than toxicity in 5 patients. Ten (71%) patients with stage I completed at least 6 cycles and 6 patients (43%) completed 12 cycles of RdC. The respective figures for patients with stage II disease were 30% (3 of 10) and 20% (2 out of 10 patients) and for stage–III were 31% (4 out of 13) and (2 of 13) 15%. A dose reduction for lenalidomide was required in 9 (27%) patients. Only one patient required reduction of the dose of dexamethasone and two of cyclophosphamide.

The most common hematologic toxicities included neutropenia and anemia - no platelet or RBCs transfusions were required. G-CSF support was required only in one patient – after a reduction of the dose of lenalidomide no G-CSF was required again. Fatigue, non-neutropenic infections, and rash were the most common non-hematologic toxicities. No significant neurotoxicity was recorded. Fatigue was the most common reason for dose reductions of lenalidomide. Infections were also common; however no neutropenic infections were recorded. Most of the febrile episodes were associated with symptoms of upper respiratory tract infection and were treated on outpatient basis with oral antibiotics. Two patients in the phase II of the study, both of whom had severe nephrotic syndrome, died due to non-neutropenic sepsis. Rash was common (33% of patients), but required dose reduction in only 2 patients. No patient discontinued therapy due to a skin rash.

Most patients (83%) received low-dose aspirin and the rest received either LMWH (14%) or coumadin (3%). Two episodes of DVT were recorded, the first occurred in the phase I of the study, and the second in a patient with heavy proteinuria receiving LMWH. One patient died due to complications that followed an acute MI, while on treatment with RdC. A coronary angiography showed a 2 vessel disease. Another patient with cardiac involvement and 3-vessel coronary artery disease died suddenly 7 days after the initiation of therapy with RdC. Finally, a patient suffered a stroke after the 11th cycle of RdC. In all the above episodes, patients were receiving aspirin.

12.2.2 Display of Adverse Events

Table 8 : Toxicity attributable to RdC (N=37)

	Any grade[+]	Grade 3 / 4[+]	Grade 5
Neutropenia	9 (24%)	9 (24%)	
Thrombocytopenia	5 (14%)	3 (8%)	
Anemia	6 (16%)	4 (11%)	
Cardiovascular	23 (85%)	1 (3%)	2 1 (55%)
Fever /Infections	9 (24%)	5 (14%)	
Fatigue	19 (52%)	5 (14%)	
Rash	13 (35%)	2 (5%)	
DVT	2 (5%)	2 (5%)	
Diarrhea	5 (15%)	2 (5%)	
Peripheral edema	8 (22%)	-	
Increased Creatinine	6 (17%)	-	
Constipation	6 (17%)	-	
Hypotension/Orthorstasis	6 (17%)	-	
Hyponatremia	6 (17%)	-	
Myalgia	3 (8%)	-	
Peripheral Neuropathy*	4 (11%)	-	
Myalgia	1 (3%)	-	

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Hypocalcemia	1 (3%)	-

[+]According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0

* Grade 1 in all cases

12.2.3 Analysis of Adverse Events & Listing of Adverse Events by Patient

Table 9: AEs per patient (grading according to NCI CTC 3.0)

Patient#	Neuropathy	Neuropathic pain	Hypotension Orthostasis	Hyponatremia	Hypocalcemia	Creatinine	Fever	Constipation	Diarrhea	Peripoheral Edema	Rash	DVT	Fatigue	Neutropenia	Thrombocytopenia	Anemia
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	1	1	0	0	0	3	0	2	0	0	0	1	3	0	3
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	2	0	0	0	0	2	1	2	0	2	1	0	3	3	3	3
5	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
6	0	0	2	0	0	0	0	0	0	0	1	0	3	3	0	0	0
7	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
8	0	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0
9	0	0	0	0	0	2	5	1	1	1	0	0	1	0	0	0
10	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
11	0	0	0	1	0	0	3	1	2	0	1	0	2	0	0	0
12	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0
13	0	0	0	0	0	0	1	0	0	0	0	0	1	3	2	3
14	0	0	2	0	0	1	3	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0
16	0	0	2	0	0	0	0	0	0	2	0	0	0	4	3	3
17	0	0	2	0		2	0	0	0	0	0	0	2	0	0	0
18	1	0	0	0	1	0	3	0	0	0	0	0	3	0	0	0
19	0	0	0	0	0	0	1	0	0	0	1	0	1	0	0	0
20	0	0	0	0	0	0	0	0	3	0	3	0	2	0	0	0
21	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
22	0	0	0	0	0	2	0	0	0	0	0	0	0	3	0	0

23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0
24	0	0	0	0	0	0	0	0	0	0	1	0	2	0	0	0
25	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0
27	0	0	0	0	0	0	0	3	0	0	0	0	2	3	0	0
28	0	0	0	0	0	0	0	1	0	0	1	0	3	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
30	0	0		0	0	0	0	0	0	1	3	0	2	0	0	0
31	0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
32	0	0	0	0	0	0	0	2	0	0	1	0	0	0	2	0
33	0	0	0	0	0	0	0	0	0	2	0	0	0	3	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	3	3	3	0	0

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

Table 10: List of deaths in patients treated with RdC

Patient#	Gender	Age	WEIGHT	Date of Last Dose	Date of Death	Days since last dose	SAE possible/probable Relation to RdC
1	Female	70	70	26-03-08	26-04-08	31	NO
3	Male	68	82	07-11-08	29-11-08	22	YES
4	Female	61	54	11-05-09	24-12-10	592	NO
5	Male	78	77	10-02-09	12-09-09	214	NO
6	Female	68	55	21-10-08	20-01-10	456	NO
9	Male	68	70	26-11-08	26-11-08	1	YES
10	Male	76	73	08-10-08	15-12-08	68	NO
11	Female	76	66	03-12-08	23-12-08	20	NO
12	Female	74	54	23-10-08	28-10-08	5	YES

14	Female	50	61	13-03-09	14-09-09	185	NO
17	Male	64	82	20-02-09	20-06-09	120	NO
18	Male	68	98	08-01-10	15-05-11	492	NO
22	Male	75	63	14-08-09	17-08-09	3	YES
23	Female	78	44	18-06-09	20-06-09	2	YES
24	Male	61	80	17-07-09	20-09-09	65	NO
25	Female	48	71	30-09-09	20-11-09	51	NO
26	Male	78	72	03-02-10	10-10-10	249	NO
27	Male	69	64	20-09-10	31-03-11	192	NO
30	Female	69	75	10-06-10	17-03-11	280	NO
32	Male	57	86	26-01-11	04-03-11	37	NO
35	Female	59	64	16-01-11	06-02-11	21	YES
36	Male	55	84	04-01-11	04-01-11	1	YES

12.3.1.2 Other Serious Adverse Events

Table 11: List of serious adverse events

Patient#		Age	WEIGHT	Date of Last Dose	Date of Death or SAE	Days since last dose	Possible or probable Relation to RdC	Narrative	grade	outcome	SAE Criterion	Treatment
2	Male	48	90	14-11-08	15-11-08	1.00	YES	Dyspnoea	3	Recovered	Involved or Prolonged Hospitalization	Restarted
3	Male	68	82	06-11-08	07-11-08	1	YES	Hemorrhage	3	Recovered	Involved or Prolonged Hospitalization	Discontinued
3	Male	68	82	06-11-08	29-11-08	23	YES	Cardiac Infraction	5	Not Recovered	Death	Discontinued
5	Male	78	77	10-02-09	11-02-09	1	YES	Stroke	4	Recovery with sequelae	Involved persistence of significant disability or incapacity	Discontinued
9	Male	68	70	25-11-08	26-11-08	1	YES	Septic Shock	5	Death	Involved or Prolonged Hospitalization	Discontinued
11	Female	76	66	02-12-08	03-12-08	1	YES	Dyspnoea	3	Recovered	Involved or Prolonged Hospitalization	Discontinued

11	Female	76	66	03-12-08	23-12-08	20	YES	Death	5	Not Recovered	Death	Discontinued
12	Female	74	40	23-10-08	23-10-08	0	YES	Diarrhea	3	Recovered	Involved or Prolonged Hospitalization	Discontinued
12	Female	74	40	23-10-08	28-10-08	5	YES	Sudden death	5	Not Recovered	Death	Discontinued
14	Female	50	61	24-12-08	25-12-08	1	YES	Pneumonia	3	Recovered	Involved or Prolonged Hospitalization	Restarted
17	Male	64	82	20-02-09	25-02-09	5	YES	Fatigue	3	Not Recovered	Involved or Prolonged Hospitalization	Discontinued
17	Male	64	82	20-02-09	25-02-09	5	YES	Hypotension	2	Recovered	Involved or Prolonged Hospitalization	Discontinued
22	Male	75	63	14-08-09	17-08-09	3	YES	Pulmonary Edema	5	Death	Death	Discontinued
23	Female	78	44	18-06-09	20-06-09	2	YES	Infection	5	Death	Death	Discontinued
23	Female	78	44	18-06-09	20-06-09	2	YES	Pulmonary Edema	5	Death	Death	Discontinued
25	Female	48	71	30-09-09	05-10-09	5	YES	Cholecystitis	2	Recovered	Involved or Prolonged Hospitalization	Discontinued
35	Female	59	64	16-01-11	17-01-11	1	YES	Septic Shock	5	Death	Involved or Prolonged Hospitalization	Discontinued
36	Male	55	84	04-01-11	04-01-11	0	YES	Sudden death	5	Not Recovered	Death	Discontinued

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Patients Initials **O-L**	Patient Number **11**	Sex **Female**	Date of birth **15-01-1932**	Age (years) **76**
Weight: **66 kgr**	Height: **168 cm**			
Event Onset Date **02-12-2008**	Investigator awareness date **03-12-2008**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Not Recovered**
Date of last dose of lenalidomide **02-12-2008**	Date of last dose of cyclophosphamide **22-11-2008**	Date of last dose of dexamethasone **16-11-2008**	Concomitant medication **Furosemide Carvedilol**	Was the event related to study therapy **Possible**

Dose of Lenalidomide **15 mg**	Dose of cyclophosphamide **100 mg**	Dose of dexamethasone **20 mg**	**Pantoprazole** **Spironolactone** **Citalopram** **Amiodarone** **Valacyclovir** **T4** **Aspirin** **Allopourinol**	Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Dyspnea Grade 3**	Description of event **The patient was admitted to hospital due to dyspnea, cough and hypoxemia. The patient had no fever and was not neutropenic. She was hemodynamically stable and with diuresis. Chest x-ray revealed bilateral infiltrates and vascular congestion.**	Description of management **The patient was given diuretics and antiarrhythmics due to deterioration of her preexisting congestive heart failure**	Outcome **The patient continued to be symptomatic despite increased dose of diuretics. She died of complete atrioventricular block**	Comment **Deterioration of the underlying disease (AL amyloidosis with cardiac involvement)**
Patients Initials **O-L**	Patient Number **11**	Sex **Female**	Date of birth **15-01-1932**	Age (years) **76**
Weight: **66 kgr**	Height: **168 cm**			
Event Onset Date **23-12-2008**	Investigator awareness date **23-12-2008**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Death**
Adverse event Term **Dyspnea Grade 3**	Description of event	Description of management	Outcome	Comment **Death due to progression of**

	The patient was admitted to hospital due to dyspnea, cough and hypoxemia. The patient had no fever and was not neutropenic. She was hemodynamically stable and with diuresis. Chest x-ray revealed bilateral infiltrates and vascular congestion.	**The patient was given diuretics and antiarrhythmics due to deterioration of her preexisting congestive heart failure**	**The patient continued to be symptomatic despite increased dose of diuretics. She died of complete atrioventricular block**	**the underlying disease (AL amyloidosis with cardiac involvement)**
Date of last dose of lenalidomide **02-12-2008** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **22-11-2008** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **16-11-2008** Dose of dexamethasone **20 mg**	Concomitant medication **Furosemide** **Carvedilol** **Pantoprazole** **Spironolactone** **Citalopram** **Amiodarone** **Valacyclovir** **T4** **Aspirin** **Allopourinol**	Was the event related to study therapy **Not Related** Did the event abate after stopping therapy **Not Applicable** Did the event reappear after reintroduction of study therapy **Not Applicable**

Patients Initials **S-K**	Patient Number **9**	Sex **Male**	Date of birth **14-08-1940**	Age (years) **68**
Weight: **70 kgr**	Height: **175 cm**			
Event Onset Date **26-11-2008**	Investigator awareness date **11-12-2008**	Seriousness Criteria **Death** **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered** **Death**

Date of last dose of lenalidomide **25-11-2008** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **22-11-2008** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **16-11-2008** Dose of dexamethasone **20 mg**	Concomitant medication **Furosemide** **omeprazole** **Eplerene** **Valacyclovir** **Aspirin** **Allopourinol**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Fever/ Infection / Septic Shock**	Description of event **The patient was admitted to hospital due to fever ≥40 °C. The fever did not abate despite antibiotics and the patient developed multiorgan insufficiency, hypotension and septic shock.**	Description of management **The patient was given IV Antibiotics and hydration – He was managed to another hospital Study staff became aware after contacted patient's family because the patient he did not come to his appointment**	Outcome **Death**	Comment

Patients Initials **A-P**	Patient Number **3**	Sex **Male**	Date of birth **19-03-1940**	Age (years) **68**
Weight: **78 kgr**	Height: **165 cm**			
Event Onset Date **07-11-2008**	Investigator awareness date **10-11-2008**	Seriousness Criteria	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Recovered**

		Involved or prolonged hospitalization		
Date of last dose of lenalidomide **06-11-2008** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **03-11-2008** Dose of cyclophosphamide **50 mg**	Date of last dose of dexamethasone **25-10-2008** Dose of dexamethasone **20 mg**	Concomitant medication **omeprazole** **Valacyclovir** **Aspirin** **Allopourinol** **Ezetimib** **Atorvastatin** **Ciprofloxacin** **Dutasteride**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Melena / upper GI hemorrhage**	Description of event **The patient was admitted to hospital due upper GI hemorrhage. He was hemodinamically stable and endoscopy showed a duodenal ulcer .**	Description of management **The patient was given blood transfusions and IV fluids plus IV PPIs– Aspirin was discontinued.**	Outcome **Death**	Comment **Aspirin was given as per protocol as prophylaxis along with PPI (omeprazole)**

Patients Initials **A-P**	Patient Number **3**	Sex **Male**	Date of birth **19-03-1940**	Age (years) **68**
Weight: **78 kgr**	Height: **165 cm**			
Event Onset Date **29-11-2008**	Investigator awareness date **29-11-2008**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered Death**

		Involved or prolonged hospitalization		
Date of last dose of lenalidomide **06-11-2008** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **03-11-2008** Dose of cyclophosphamide **50 mg**	Date of last dose of dexamethasone **25-10-2008** Dose of dexamethasone **20 mg**	Concomitant medication **omeprazole** **Valacyclovir** **Allopourinol** **Ezetimib** **Atorvastatin** **Dutasteride**	Was the event related to study therapy **Not related** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Acute Myocardial Infraction**	Description of event **The patient was admitted to hospital due upper GI hemorrhage. Endoscopy showed a duodenal ulcer and aspirin was discontinued. The patients suffered an acute MI while in hospital. Coronary angiography showed two vessel disease.**	Description of management **The patient was given blood transfusions and IV fluids plus IV PPIs– Aspirin was discontinued.**	Outcome **Death**	Comment **Aspirin was discontinued after GI hemorrhage. Coronary artery disease probably preexisted**

Patients Initials **D-F**	Patient Number **36**	Sex **Male**	Date of birth **16-03-1955**	Age (years) **56**
Weight: **83.5 kgr**	Height: **178 cm**			

Event Onset Date **05-01-2011**	Investigator awareness date **10-01-2011**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered Death**
Date of last dose of lenalidomide **04-01-2011** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **31-12-2010** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **04-01-2011** Dose of dexamethasone **20 mg**	Concomitant medication **omeprazole** **Valacyclovir** **Olmesatran** **Bisoprolol** **Aspirin** **simvastatin** **TMP/SMX**	Was the event related to study therapy **Possibly** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Sudden Death**	Description of event **We were informed by a family member that he patient died suddenly, at home. No further information was provided. No autopsy was performed.**	Description of management **The patient was found dead at home**	Outcome **Death**	Comment **Sudden death – the patients had a known history of 3-vessel CAD but refused surgery**

Patients Initials **A-K**	Patient Number **35**	Sex **Female**	Date of birth **15-06-1951**	Age (years) **59**
Weight: **64 kgr**	Height: **162 cm**			
Event Onset Date **17-01-2011**	Investigator awareness date **17-01-2011**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered Death**

Date of last dose of lenalidomide **16-01-2011** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **16-01-2011** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **11-01-2011** Dose of dexamethasone **20 mg**	Concomitant medication **omeprazole** **Valacyclovir** **Bisoprolol** **Aspirin** **Folic acid** **TMP/SMX** **Thyroxin** **Calcium** **Supplement**	Was the event related to study therapy **Possibly** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Lower Respiratory Tract Infection / septic shock / Respiratory Insufficiency**	Description of event **The patient was admitted to hospital due to symptoms of lower respiratory tract infection, dyspnea, cough without fever. A lower respiratory tract infection was diagnosed based on clinical and radiographic criteria. Due to hypoxemia was admitted to the ICU and received ventilator support**	Description of management **The patients was intubated and received ventilatory support** **IV antibiotics included Meropenem, vancomycin, azithromycin, oseltamivir, cefepime, gentamycin, colimycine, voriconazole, tygecycline, TMP/SMX, aztreonam.** **Other drugs included midazolame, cisastracurium, remifentanyl, propofol,**	Outcome **Death**	Comment **The patient died due to multiorgan failure as a result of the infection**

		norepinephrine, hydrocortisone, IV human albumin, IV gamma-globulin		

Patients Initials **G-G**	Patient Number **12**	Sex **Female**	Date of birth **15-06-1934**	Age (years) **74**
Weight: **40 kgr**	Height: **157 cm**			
Event Onset Date **23-10-2008**	Investigator awareness date **29-10-2008**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Completely Recovered**
Date of last dose of lenalidomide **22-10-2008** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **22-10-2008** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **19-10-2008** Dose of dexamethasone **20 mg**	Concomitant medication **Furosemide** **Amiodarone** **omeprazole** **Spironolactone** **Valacyclovir** **Aspirin**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Diarrhea Grade 3**	Description of event **The patient was admitted to another hospital due to diarrhea and signs of dehydration.**	Description of management **The patient was given IV fluids**	Outcome **Completeley recovered from diarrhea**	Comment **The patient had GI involvement by amyloid**

Patients Initials **G-G**	Patient Number **12**	Sex **Female**	Date of birth **15-06-1934**	Age (years) **74**
Weight: **40 kgr**	Height: **157 cm**			
Event Onset Date **28-10-2008**	Investigator awareness date **29-10-2008**	Seriousness Criteria **Death** **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Death**
Date of last dose of lenalidomide **22-10-2008** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **22-10-2008** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **19-10-2008** Dose of dexamethasone **20 mg**	Concomitant medication **Furosemide** **Amiodarone** **omeprazole** **Spironolactone** **Valacyclovir**	Was the event related to study therapy **Not Related** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Sudden Death**	Description of event **The patient was hospitalized to another hospital due to diarrhea which had recovered and died suddenly. No Autopsy was performed**	Description of management	Outcome **Death**	Comment **Death probably related to underlying disease (AL amyloidosis with cardiac involevement)**

Patients Initials **M -K**	Patient Number **14**	Sex **Female**	Date of birth **15-06-1958**	Age (years) **50**

Weight: **61 kgr**	Height: **167 cm**			
Event Onset Date **25-12-2008**	Investigator awareness date **30-12-2008**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Completely Recovered**
Date of last dose of lenalidomide **24-12-2008** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **20-10-2008** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **11-12-2008** Dose of dexamethasone **20 mg**	Concomitant medication **Gabapentine** **Fluorocortisone** **Midodrine** **Fluvastatin** **LMWH** **Ciprofloxacin** **Valacyclovir** **omeprazole**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **No**
Adverse event Term **Lower respiratory tract infection / Pneumonia Grade 3**	Description of event **The patient was admitted to another hospital due to pleurodynia. A chest x-ray on the following day revealed right lung pneumonia with pleuritic fluid.**	Description of management **The patient was given IV fluids and IV antibiotics (Azithromycin, cefepime)**	Outcome **Completely recovered from the infection**	Comment **She continued therapy with RdC after discharge from hospital**

Patients Initials **S-S**	Patient Number **2**	Sex **Male**	Date of birth **31-05-1960**	Age (years) **48**
Weight: **92 kgr**	Height: **177 cm**			

Event Onset Date **15-11-2008**	Investigator awareness date **17-11-2008**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Completely Recovered**
Date of last dose of lenalidomide **14-11-2008** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **14-11-2008** Dose of cyclophosphamide **50 mg**	Date of last dose of dexamethasone **14-11-2008** Dose of dexamethasone **20 mg**	Concomitant medication **atorvastatin** **Acenocoumarol** **Carvedilol** **Valacyclovir** **Omeprazole** **Aspirin** **Thyroxine**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **No**
Adverse event Term **Lower respiratory tract infection / Pneumonia Grade 3** **Dyspnea Grade 3**	Description of event **The patient was admitted to another hospital due to cough, dyspnea and dark sputum. Radiology revealed infiltrates on both lung fields**	Description of management **The patient was given IV fluids and IV antibiotics (Meropenem, Teicoplanin, Azithromycin)**	Outcome **Completely recovered from the infection**	Comment **He continued therapy with RdC after discharge from hospital**
Patients Initials **S-S**	Patient Number **2**	Sex **Male**	Date of birth **31-05-1960**	Age (years) **48**
Weight: **92 kgr**	Height: **177 cm**			
Event Onset Date **24-12-2008**	Investigator awareness date **05-01-2009**	Seriousness Criteria	Severity assessment (CTC AE 3.0) **Grade 2**	Outcome **Completely Recovered**

		Involved or prolonged hospitalization		
Date of last dose of lenalidomide **23-12-2008** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **23-12-2008** Dose of cyclophosphamide **50 mg**	Date of last dose of dexamethasone **23-12-2008** Dose of dexamethasone **20 mg**	Concomitant medication **atorvastatin** **Acenocoumarol** **Carvedilol** **Valacyclovir** **Omeprazole** **Aspirin** **Ciprofloxacin** **Folic acid** **Thyroxine**	Was the event related to study therapy **Possible** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **No**
Adverse event Term **Dyspnea Grade 2**	Description of event **The patient was admitted to another hospital due to dyspnea without cough, fever or other signs of infection. On lab test anemia grade 2 was found and received blood transfusion. An acute blood loss from the GI tract was not proved by endoscopy**	Description of management **The patient was given Blood transfusion**	Outcome **Completely recovered**	Comment **He continued therapy with RdC after discharge from hospital**

Patients Initials **A-A**	Patient Number **23**	Sex **Female**	Date of birth **17-06-1931**	Age (years) **78**
Weight: **46 kgr**	Height: **140 cm**			

Event Onset Date **20-06-2009**	Investigator awareness date **22-06-2009**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered** **Death**
Date of last dose of lenalidomide **13-06-2009** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **04-06-2009** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **10-06-2009** Dose of dexamethasone **20 mg**	Concomitant medication **Perindopril** **Valasrtan** **Atorvastatin** **omeprazole** **Valacyclovir** **Furosemide** **Aspirin** **TMP/SMX**	Was the event related to study therapy **Possibly** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Pulmonary edema**	Description of event **The patient was admitted to another hospital due to dyspnea. A diagnosis of congestion/pulmonary edema and renal failure was made.**	Description of management **No detailed description of the management is available**	Outcome **Death**	Comment **The patient died due to pulmonary edema / acute decompensation of CHF. She had cardiac involvement by amyloidosis. she had discontinued a week before the event due to fever , which resolved**

Patients Initials	Patient Number	Sex	Date of birth	Age (years)

K-K	**22**	**Male**	**18-06-1934**	**75**
Weight: **63 kgr**	Height: **170 cm**			
Event Onset Date **15-08-2009**	Investigator awareness date **25-08-2009**	Seriousness Criteria **Death**	Severity assessment (CTC AE 3.0) **Grade 5**	Outcome **Not Recovered Death**
Date of last dose of lenalidomide **10-08-2009** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **10-08-2009** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **10-08-2009** Dose of dexamethasone **20 mg**	Concomitant medication **Carvedilol** **omeprazole** **Valacyclovir** **Furosemide** **Aspirin**	Was the event related to study therapy **Possibly** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Pulmonary edema**	Description of event **The patient was developed dyspnea. A physician who examined the patient at home diagnosed pulmonary congestion/ edema but the patient refused to go to a hospital and died 2 days later at his home.**	Description of management **No detailed description of the management is available**	Outcome **Death**	Comment **The patient died due to pulmonary edema / acute decompensation of CHF. He had cardiac involvement by amyloidosis and the death is probably due to progression of his underlying disease**

Patients Initials	Patient Number	Sex	Date of birth	Age (years)

K-K	**25**	**Female**	**31-07-1961**	**48**
Weight: **65 kgr**	Height: **165 cm**			
Event Onset Date **05-10-2009**	Investigator awareness date **08-10-2009**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 2**	Outcome **Completely Recovered**
Date of last dose of lenalidomide **28-09-2009** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **17-09-2009** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **11-09-2009** Dose of dexamethasone **20 mg**	Concomitant medication **Ladose** **Lexotanil** **omeprazole** **Valacyclovir** **Furosemide** **LMWH**	Was the event related to study therapy **Not related** Did the event abate after stopping therapy **Not Applicable** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Cholecystitis**	Description of event **The patient was admitted to another hospital due to symptoms of acute cholecystitis.**	Description of management **She received IV antibiotics but no details are available**	Outcome **Completely recovered**	Comment **The patient died due to pulmonary edema / acute decompensation of CHF. He had cardiac involvement by amyloidosis and the death is probably due to progression of his underlying disease**

Patients Initials **I-A**	Patient Number **17**	Sex **Male**	Date of birth **23-12-1944**	Age (years) **65**
Weight: **85 kgr**	Height: **177 cm**			
Event Onset Date **25-02-2009**	Investigator awareness date **25-02-2009**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 3**	Outcome **Not Recovered**
Date of last dose of lenalidomide **23-02-2009** Dose of Lenalidomide **15 mg**	Date of last dose of cyclophosphamide **12-02-2009** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **06-02-2009** Dose of dexamethasone **20 mg**	Concomitant medication **Clopidogrel** **allopourinol** **Carvedilol** **omeprazole** **Valacyclovir** **Furosemide** **Aspirin** **Solosa** **Metformin**	Was the event related to study therapy **Possibly** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Fatigue** **Hypotension**	Description of event **The patient was developed admitted to hospital due to fatigue grade 3 and hypotension on standing position.**	Description of management **Midodrine**	Outcome **Not recovered**	Comment **The patient had disease progression based on the criteria used in the study and he was withdrawn from the study**

Patients Initials **I-M**	Patient Number **5**	Sex **Male**	Date of birth **22-01-1928**	Age (years) **81**
Weight: 77 **kgr**	Height: **165 cm**			

Event Onset Date **11-02-2009**	Investigator awareness date **16-02-2009**	Seriousness Criteria **Involved or prolonged hospitalization**	Severity assessment (CTC AE 3.0) **Grade 4**	Outcome **Recovery with sequelae**
Date of last dose of lenalidomide **11-02-2009** Dose of Lenalidomide **10 mg**	Date of last dose of cyclophosphamide **29-01-2009** Dose of cyclophosphamide **100 mg**	Date of last dose of dexamethasone **23-01-2009** Dose of dexamethasone **20 mg**	Concomitant medication **rabeprazole** **Valacyclovir** **Furosemide** **Aspirin** **Amiodarone** **TMP/SMX**	Was the event related to study therapy **Probable** Did the event abate after stopping therapy **No** Did the event reappear after reintroduction of study therapy **Not Applicable**
Adverse event Term **Stroke**	Description of event **The patient was admitted to another hospital due to aphasia and right hemiplegia**	Description of management **No details are available**	Outcome **Recovered with sequelae (right hemiplegia)**	Comment

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

- Deaths related to deterioration of cardiac dysfunction occurred in 8 patients – A causal relationship to RdC is possible, however unlikely. These patients had clinically significant cardiac amyloidosis

- One patient died due to complications that followed an acute MI, while on treatment with RdC. A coronary angiography showed a 2 vessel disease. Another patient with cardiac involvement and 3-vessel coronary artery disease died suddenly 7 days after the initiation of therapy with RdC. Finally, a patient suffered a stroke after the 11th cycle of RdC. In all the above episodes, patients were receiving aspirin.

- Three patients died due to infectious complications while on treatment with RdC – none of the patients was neutropenic, all three had significant cardiac involvement with nephrotic range proteinuria and were receiving prophylactic antibiotics

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal

Laboratory Value (14.3.4)

We observed an increase of NTproBNP in our patients after the first cycle of RdC; this has been well described in patients with AL treated with IMiDs, including thalidomide, at a similar frequency (28-30). The increase in the levels of NTproBNP was not associated with poor survival and also it did not seem to be related to deterioration of renal function(30). In our study, we observed that an increase in NTproBNP was associated with shorter survival in univariate analysis but the small number of patients did not allow for further analysis. Since we did not observe an increase of cardiac troponins it is difficult to consider this increase of NTproBNP as a result of a direct cardiotoxic effect of lenalidomide, with or without cyclophosphamide. We have also observed that even patients without evidence of cardiac involvement (i.e. patients with Mayo stage I disease) had significant increases in NTproBNP, which returned to baseline after a few cycles of RdC, while they were receiving RdC. These patients did not have any signs of cardiac involvement during or after therapy with RdC and we did not observe an increase in cardiac troponins. We cannot rule out that this increase was not due to fluid retention. Whether the addition of cyclophosphamide may amplify a putative cardiotoxicity of lenalidomide needs further investigation. Thus, we cannot consider these increases innocuous and physicians should be careful when they use lenalidomide with cyclophosphamide in AL amyloidosis, and follow patients closely for signs of deterioration of cardiac function. In contrast to a previous report (31), we did not observe any major decrease of eGFR during treatment with RdC, despite fluctuations in eGFR probably related with factors such as the use of diuretics and the hydration status.

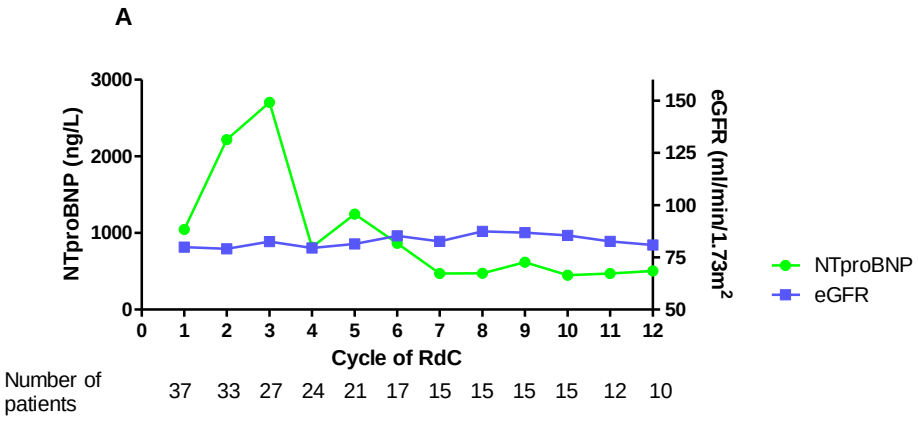
12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Table 12 : Serum Creatinine per patient per cycle

Number#	Gender	Age	Weight	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
1	Female	70	70	0.70	0.60										
2	Male	48	90	0.80	0.90	0.80	0.90	0.80	0.90	0.80	0.80	0.65	0.78	1.10	0.79
3	Male	68	82	0.80	0.60	0.70	0.60	0.70	0.70	0.65	0.80	0.70	0.82		
4	Female	61	54	1.90	1.90	2.80	1.80	1.90	1.75	2.00	2.31	2.00	1.95		
5	Male	78	77	0.60	0.70	0.60	0.80	0.80	0.80	0.66	0.72	0.71	0.61	0.79	
6	Female	68	55	0.80	0.80	0.60	0.70	0.70							
7	Female	67	55	0.50	0.50	0.50	0.50	0.45	0.61	0.66	0.56	0.63	0.65	0.64	0.65
8	Male	45	84	0.90	1.00	1.00	0.70	0.87	0.90	1.03	0.82	0.82	0.77	0.82	
9	Male	68	70	2.20	2.80	2.83	3.18								
10	Male	76	73	1.50	2.10										
11	Female	76	66	0.90	1.06	0.88									
12	Female	74	54	1.00	1.17										
13	Male	53	71	0.71	0.79	0.58	0.65	0.63	0.69	0.74	0.67	0.94	0.90	0.84	0.75
14	Female	50	61	0.68	0.59	0.69	0.75	0.98							
15	Female	59	61	1.46											
16	Male	59	81	1.63	1.65	1.49	1.45	1.01	1.06	1.04	1.24	1.12	1.09	1.20	1.11
17	Male	64	82	1.00	1.41	1.40									
18	Male	68	98	1.16	1.45	1.10	1.12	1.25	1.31	1.33	1.14	1.34	1.92	1.54	1.45
19	Female	67	65	0.61	0.65	0.80	0.85	0.86		0.75	0.73	0.80	0.76	0.77	0.90
20	Female	77	76	0.95	0.93	0.87	1.12	0.89	0.94	0.89	0.89	0.85	0.96	0.87	0.86
21	Male	51	70	0.45	0.55	0.65	0.64	0.74	0.87	0.73	0.77	0.74	0.67	0.71	0.70
22	Male	75	63	1.07	1.70	1.99									
23	Female	78	44	1.99											
24	Male	61	80	0.98	0.96										
25	Female	48	71	0.60											
26	Male	78	72	1.09	0.97	0.85	1.28	0.91							
27	Male	69	64	1.12	1.33	1.17	1.28	0.93	1.36	1.16	1.14	1.14	1.18	1.34	1.25
28	Female	74	93	0.74	0.76	0.67	1.03	0.86	1.07						
29	Male	68	70	0.60	0.74	0.74	0.67		0.61	0.75	0.80	0.72	0.72	0.67	0.69
30	Female	69	75	0.65		0.67	0.82	0.74							
31	Female	62	73	0.51	0.48	0.44	0.50	0.54	0.58	0.49	0.56	0.51	0.48		
32	Male	57	86	0.85	1.14	1.25	1.43	1.15	1.35	1.81					
33	Female	63	78	0.54	0.53	0.61	0.69								
34	Male	75	80	1.09	1.53	1.91									
35	Female	59	64	0.54	0.53										
36	Male	55	84	1.06											
37	Female	82	58	1.10	1.09	1.35	1.20	1.50							

Figure 1: Median NTproBNP and eGFR per cycle



12.4.2.2 Individual Patient Changes

12.4.2.3 Individual Clinically Significant Abnormalities

Table 13: NTproBNP values per cycle per patient

							NTproBNP (ng/L)											
Patient#	Gender	Age	WEIGHT	Lenalidomide	Cyclophosphamide	Dexametashone	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
1	Female	70	70	10	100	20	304	441										
2	Male	48	90	10	50	20	241	276	433	250		215	200		316	193	338	407
3	Male	68	82	10	100	20	371	1510	463	437	507	431	531	570	299	455		
4	Female	61	54	10	100	20	5180	8005	8303	11024		5096	13855	6500	10733	10151		
5	Male	78	77	10	100	20	1122	2261			1557	1193	1562	1590	2144	1643	2144	
6	Female	68	55	10	100	20	2532		5430	4185	3963							
7	Female	67	55	10	100	20	312	247	238	123	215	403	321	376	554	440	410	422
8	Male	45	84	10	100	20	36	47	40	41			66	52	78	69	54	
9	Male	68	70	10	100	20	7981	23377	13434									
10	Male	76	73	10	100	20	2325	795										
11	Female	76	66	15	100	20	5011	8217	5648									
12	Female	74	54	15	100	20	9197											

13	Male	53	71	15	100	20	675	2219	2261	1513	1247	865	1110	1274	683	580		533
14	Female	50	61	15	100	20	1418	2367	3216	6418	13479							
15	Female	59	61	15	100	20	2857											
16	Male	59	81	15	100	20	3648	5099	3145	4028	3575	3887	2547	2144	3528	3860	3077	2993
17	Male	64	82	15	100	20	2808	7605	7800									
18	Male	68	98	15	100	20	335	334	288	532	805	541	409	338	938	254	629	505
19	Female	67	65	15	100	20	120	241	223		121		294					
20	Female	77	76	15	100	20	251	687	246	235	477			344	394		470	
21	Male	51	70	15	100	20	181			78				36		74		
22	Male	75	63	15	100	50	9047	16003	22296									
23	Female	78	44	15	100	20	6315											
24	Male	61	80	15	100	20	12051	14254										
25	Female	48	71	15	100	20	3071											
26	Male	78	72	15	100	20	170											
27	Male	69	64	15	100	20	77											
28	Female	74	93	15	100	20												
29	Male	68	70	15	100	20	66											
30	Female	69	75	15	100	20	448		400									
31	Female	62	73	15	100	20	59											
32	Male	57	86	15	100	20	2312	4483	5477	6259	7415	7899						
33	Female	63	78	15	100	20	91	80		684								
34	Male	75	80	15	100	20	99	191		2133								
35	Female	59	64	15	100	20	2023	4702										
36	Male	55	84	15	100	20	7600											
37	Female	82	58	15	100	20	347			945								

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Thirteen patients developed a skin rash , which was mild in 11 patients while in 2 patients was grade 3 and required dose reduction

12.6 SAFETY CONCLUSIONS

The study combination has predictable toxicity. There were no unexpected AEs. The rates if AEs were not increased compared to previous reports of lenalidomide based regimens in patients with AL amyloidosis and probably was better tolerated than in studies in which full dose (25 mg) of lenalidomide was used

The rates of infections and the deaths due to infections is of concern. It must be noted that all patients received some form of antibiotic prophylaxis (either TMP/SMX or ciprofloxacin), however the population of the study was very frail due to multisystem involvement.

Two deaths in patients with multivessel coronary artery disease indicate that special caution is needed for the use of RdC in patients with CAD (confirmed or suspected).

13. DISCUSSION AND OVERALL CONCLUSIONS

The management of patients with AL amyloidosis requires therapies that effectively target the plasma cell clone but also have a favorable toxicity profile due to the frailty of many patients who often have severe organ dysfunction. Within this context we aimed at the development of an effective oral regimen with acceptable toxicity. We found that the oral RdC regimen has manageable and predictable toxicity with significant activity. We also confirmed that patients with AL amyloidosis can benefit from a lower dose of lenalidomide without the risk of excessive toxicity associated with standard doses of lenalidomide (8, 9). Patients with AL amyloidosis are also very sensitive to toxicities associated with high dose steroids (27) and the use of low dose dexamethasone in RdC regimen was associated with improved tolerance as reflected by the requirement for dexamethasone dose reduction in only one patient. Furthermore, the use of low dose oral cyclophosphamide was accompanied by very low hematologic toxicity. Fatigue was the most common reason to reduce the dose of lenalidomide but in patients with AL amyloidosis fatigue may also be related to the multisystem involvement, CHF, diuretics or significant hypoalbuminemia. Rash was also common in our patients but was mostly mild, probably due to the lower doses of lenalidomide. Of concern are the significant rates of infections, which were with the cause of two deaths despite the use of prophylactic antibiotics. The absence of neurotoxicity should also be acknowledged.

Importantly, the response rates with RdC were similar to those in the phase II studies which used higher doses of lenalidomide (8, 9) or lenalidomide with cyclophosphamide and dexamethasone (13, 32) and were also rapid, within the first 3 cycles of RdC. The use of lower doses of dexamethasone, and the lack of a maintenance phase for lenalidomide, since the treatment was given for a maximum of 12 months, may explain these low rates of CRs. We should also acknowledge that our patients had characteristics (age, organ dysfunction, cardiobiomarkers, performance status) that are typical of non-selected patients with AL amyloidosis. These characteristics may also explain to a certain extent the lower response rates that were observed with RdC compared regimens such as the recently published MLD (lenalidomide, melphalan and dexamethasone) (14) which enrolled patients with a performance status 0-1 and the 2-year survival is 80% while in our study the median survival of patients with performance 0-1 is 60% but, 40% of our patients had an ECOG performance status >1. It is also difficult to compare RdC to Mel/Dex, which has been used widely and is still the standard therapy for AL amyloidosis. In patients with high risk features (cardiac involvement, elevated cardiobiomarkers) response rates are similar for oral Mel/Dex(33), Mel/Dex plus Thalidomide(34) or , more intensive, IV Melphalan plus dexamethasone(35). Bortezomib-based therapy has also shown significant activity in standard risk AL amyloidosis but in high risk patients the results were less favorable (36, 37) . However, we believe that the two therapies cannot be compared based only on the results of phase I or II studies in populations with significantly different characteristics. Nevertheless, an interesting finding of our study was the fact that most patients who had been pretreated with bortezomib achieved a response with RdC. This was not the case for thalidomide pretreated patients, but due to the small numbers these results should be interpreted cautiously. Thus, RdC may be a treatment option for patients who relapse after bortezomib, an increasingly used therapy for patients with AL amyloidosis. Furthermore, RdC may be an option for AL patients who are not eligible for bortezomib-based regimens due to peripheral autonomic neuropathy or other reasons.

Organ responses were recorded in 22% of our patients, a figure which is similar to those reported by other investigators for lenalidomide-based therapies (8, 9). Organ responses may take several months to occur, even more than one year after a hematologic response has been achieved. Furthermore, patients with severe cardiac dysfunction may die early due to complications of heart disease before any organ

response could be achieved. Thus, organ response rate in patients who survived at least 6 months was 40%, which is significant. The major prognostic impact of elevated cardiobiomarkers (38) was also seen in our patients. The outcome of patients with Mayo stage II and III was poor while those with Mayo stage I disease had significantly better outcome. Of note, the median survival of our patients with stage II and III disease was similar; however, the numbers are small for meaningful comparisons. Furthermore, stage II patients had high risk features (poor performance status in 50%, median levels of NTproBNP was 2167 ng/L and 40% were NYHA stage 2-3). These facts indicate what has been considered as a "predetermined fate" for patients with AL amyloidosis with severe organ dysfunction. The management of patients with severe cardiac amyloidosis is very challenging and both conventional (33, 35) and novel therapies (34, 37) have been associated with poor results. Our data also indicate that RdC is not able to change the fate of patients with severe cardiac dysfunction. However, even among patients with elevated cardiobiomarkers, there is a subset that may benefit from effective treatment.

We observed an increase of NTproBNP in our patients after the first cycle of RdC; this has been well described in patients with AL treated with IMiDs, including thalidomide, at a similar frequency (28-30). The increase in the levels of NTproBNP was not associated with poor survival and also it did not seem to be related to deterioration of renal function(30). In our study, we observed that an increase in NTproBNP was associated with shorter survival in univariate analysis but the small number of patients did not allow for further analysis. Since we did not observe an increase of cardiac troponins it is difficult to consider this increase of NTproBNP as a result of a direct cardiotoxic effect of lenalidomide, with or without cyclophosphamide. We have also observed that even patients without evidence of cardiac involvement (i.e. patients with Mayo stage I disease) had significant increases in NTproBNP, which returned to baseline after a few cycles of RdC, while they were receiving RdC. These patients did not have any signs of cardiac involvement during or after therapy with RdC and we did not observe an increase in cardiac troponins. We cannot rule out that this increase was not due to fluid retention. Whether the addition of cyclophosphamide may amplify a putative cardiotoxicity of lenalidomide needs further investigation. Thus, we cannot consider these increases innocuous and physicians should be careful when they use lenalidomide with cyclophosphamide in AL amyloidosis, and follow patients closely for signs of deterioration of cardiac function. In contrast to a previous report (31), we did not observe any major decrease of eGFR during treatment with RdC, despite fluctuations in eGFR probably related with factors such as the use of diuretics and the hydration status.

In conclusion, the oral combination of lenalidomide with low dose steroids and low dose cyclophosphamide is feasible and results in significant response rates with a manageable toxicity profile. RdC could be an additional option especially for patients with preserved organ function and low levels of cardiobiomarkers who relapse after bortezomib or ASCT or Melphalan with dexamethasone. For patients at moderate or high risk RdC may not be able to alter their outcome.

14. TABLES, FIGURES AND GRAPHS

14.1 DEMOGRAPHIC DATA

Table 14: Patients Characteristics (n=37)

	Phase I	Phase II	All patients
	N(%)	N(%)	N (%)
Male / Female	6 (46%) / 7 (54%)	13 (54%)/11 (46%)	19 (51%)/ 18 (49%)
Age (median / range)	68 (45-78)	65 (48-82)	68 (45-82)
Age >65 years	9 (69%)	12 (50%)	21 (57%)
Untreated / Pretreated	7 (54%) / 6 (46%)	17 (71%)/7 (29%)	24 (65%) / 13 (35%)
Previous Therapies			
Thalidomide	1 ((8%)	3 (13%)	4 (11%)
Bortezomib	4 (31%)	1 (4%)	5 (14%)
High Dose Melphalan	1 (8%)	3 (13%)	4 (11%)
Organ Involvement			
Heart	8 (62%)	13 (54%)	21 (57%)
Kidney	8 (62%)	16 (67%)	24 (65%)
Liver	2 (15%)	1 (4%)	3 (8%)
Nerve	2 (15%)	6 (25%)	8 (22%)
Soft Tissue	4(31%)	6 (25%)	10 (27%)
Number of involved organs (Median/range)			
≥2 organs	2 (1-4)	2 (1-3)	2 (1-4)
	7 (54%)	13 (54%)	20 (54%)
NTproBNP (median/ range)	2325 (36-9197)	448 (59-9047)	1046 (46-9197)
NTproBNP≥ 332 ng/L	9 (69%)	14 (58%)	23 (62%)
TroponinT≥ 0.035 ng/L	6 (46%)	7 (29%)	13 (35%)
Mayo stage			
I	4 (31%)	10 (42%)	14 (38%)
II	3 (23%)	7 (29%)	10 (27%)
III	6 (46%)	7 (29%)	13 (35%)
IVS (mm) (median / range)	12 (9-23)	13 (8-20)	13 (8-23)
IVS ≥15 mm	5 (38%)	6 (25%)	11 (30%)
Symptoms of CHF	7 (54%)	12 (50%)	19 (51%)
NYHA ≥2	6 (46%)	10 (42%)	16 (43%)
ECOG performance status	**6 (46%)**	**9 (38%)**	**15 (40%)**
Proteinuria (mg/24h) (Median / Range)	1525 (100-17000)	4530 (0-21000)	2208 (0-21000)
Serum Albumin (gr/dl) (median / range)	3.8 (1-6.4)	3.45 (1.8-4.4)	3.6 (1-6.4)
Serum creatinine (mg/dl) (median / range)	0.9 (0.6-2.2)	0.82 (0.45-1.99)	0.9 (0.45-2.2)
eGFR* (ml/min/1.73m^2) (median / range)	75.9 (29-139)	82.14 (26-210)	81.6 (26-210)
eGFR < 30 ml/min/1.73m^2)	1 (8%)	1 (4%)	2 (5%)
Light Chain type (κ / λ)	1 (8%) / 12 (92%)	7 (29%)/17 (71%)	8 (22%) / 29 (78%)
Involved FLC (mg/L)	103 (26-3220)	191 (15.8-6070)	166 (15.8-6070)

14.2 EFFICACY DATA

Table 15: Hematologic and organ responses

	N	≥ PR	CR	Organ response
All patients*	36**	20 (55%)	3 (8%)	8 (22%)
Phase II	23**	11 (48%)	2 (9%)	6 (26%)
Evaluable for response (at least 2 cycles of RdC)	32	20 (63%)	3 (9%)	8 (25%)
At DLT (lenalidomide 15 mg/day)	26**	13 (50%)	2 (8%)	5 (19%)
Previously Untreated	24	13 (54%)	2 (8%)	3 (13%)
Pretreated	12**	7 (58%)	1 (8%)	5 (42%)

*Intention to treat

** One patients withdrew consent after a few days of RdC and was not included in efficacy analysis

Figure 2: Progression free and overall survival for all patients

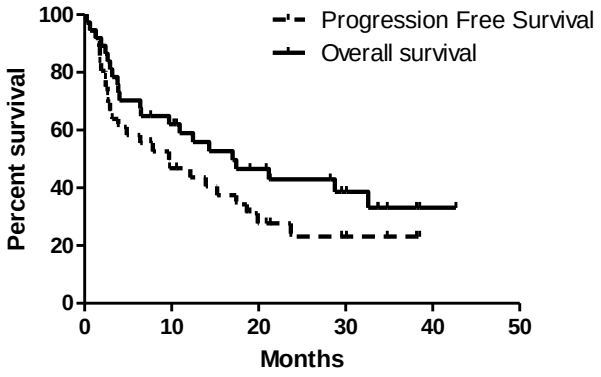
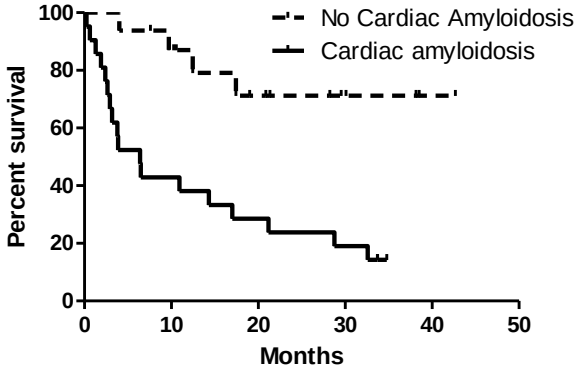
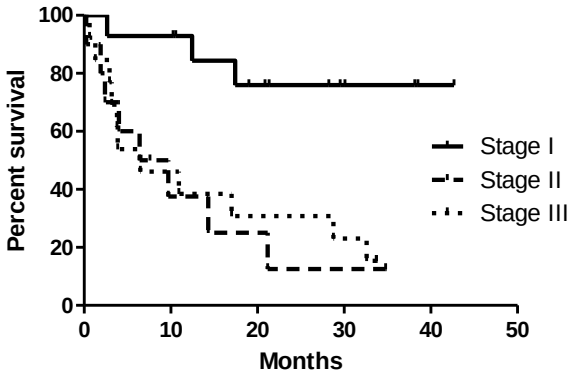


Figure 3: Survival according to (A) cardiac involvement, (B) Mayo stage

A



B


100
80
60
40
20
0
Percent survival
0
10
20
30
40
50
Months
Stage I
Stage II
Stage III

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

Table 16 : Summary of AEs

	Any grade[+]	Grade 3 / 4[+]	Grade 5
Neutropenia	9 (24%)	9 (24%)	
Thrombocytopenia	5 (14%)	3 (8%)	
Anemia	6 (16%)	4 (11%)	
Cardiovascular	3 (8%)	1 (3%)	2 (5%)
Fever /Infections	9 (24%)	5 (14%)	
Fatigue	19 (52%)	5 (14%)	
Rash	13 (35%)	2 (5%)	
DVT	2 (5%)	2 (5%)	
Diarrhea	5 (15%)	2 (5%)	
Peripheral edema	8 (22%)	-	
Increased Creatinine	6 (17%)	-	
Constipation	6 (17%)	-	
Hypotension/Orthorstasis	6 (17%)	-	
Hyponatremia	6 (17%)	-	
Myalgia	3 (8%)	-	
Peripheral Neuropathy*	4 (11%)	-	
Myalgia	1 (3%)	-	
Hypocalcemia	1 (3%)	-	

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 17: List of deaths in patients treated with RdC Within 30 dasy after the last dose of the drug

Patient#	Gender	Age	WEIGHT	Date of Last Dose	Date of Death	Days since last dose	SAE possible/probable Relation to RdC
3	Male	68	82	07-11-08	29-11-08	22	YES
9	Male	68	70	26-11-08	26-11-08	1	YES
11	Female	76	66	03-12-08	23-12-08	20	NO
12	Female	74	54	23-10-08	28-10-08	5	YES
22	Male	75	63	14-08-09	17-08-09	3	YES
23	Female	78	44	18-06-09	20-06-09	2	YES
35	Female	59	64	16-01-11	06-02-11	21	YES
36	Male	55	84	04-01-11	04-01-11	1	YES

Table 18: List of deaths in patients treated with RdC, due to progression of the disease or other unrelated reasons

Patient#	Gender	Age	WEIGHT	Date of Last Dose	Date of Death	Days since last dose	SAE possible/probable Relation to RdC
1	Female	70	70	26-03-08	26-04-08	31	NO
4	Female	61	54	11-05-09	24-12-10	592	NO
5	Male	78	77	10-02-09	12-09-09	214	NO
6	Female	68	55	21-10-08	20-01-10	456	NO
10	Male	76	73	08-10-08	15-12-08	68	NO
14	Female	50	61	13-03-09	14-09-09	185	NO
17	Male	64	82	20-02-09	20-06-09	120	NO
18	Male	68	98	08-01-10	15-05-11	492	NO
24	Male	61	80	17-07-09	20-09-09	65	NO
25	Female	48	71	30-09-09	20-11-09	51	NO
26	Male	78	72	03-02-10	10-10-10	249	NO
27	Male	69	64	20-09-10	31-03-11	192	NO
30	Female	69	75	10-06-10	17-03-11	280	NO
32	Male	57	86	26-01-11	04-03-11	37	NO

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

See section 12.3.2

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

See section 12.4.2

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16. APPENDICES

16.1 Protocol and protocol amendments

See attached file RV0178_Protocol_english.docx

Field Code Changed

16.2 CASE REPORT FORMS

See attached file CRF RV178.docx

Field Code Changed

16.3 Informed Consent

See attached file INFORMED_CONSENT_GREEK_FINAL_RV178.doc

Field Code Changed

16.4 Principal Invetsigator's & co/Sub-investigators CVs

See attached files A. Prof. M.A Dimopoulos (M.A.DIMOPOULOS_SHORT_CURRICUL_NOV_2011.docx) &

Field Code Changed

B. Dr. E. Kastritis (E.Kastritis_short_CV_2011_Sept.docx)

Field Code Changed