



HAL
open science

THE ADDITION OF CYCLOPHOSPHAMIDE TO LENALIDOMIDE AND DEXAMETHASONE IN MULTIPLY RELAPSED/REFRACTORY MYELOMA PATIENTS; A PHASE I/II STUDY

Stephen Schey, Gareth J Morgan, Karthik Ramasamy, Beth Hazel, Sophie Corderoy, Dariusz Ladon, Mathew Jenner, Karen Phekoo, Kevin David Boyd, Faith E Davies

► **To cite this version:**

Stephen Schey, Gareth J Morgan, Karthik Ramasamy, Beth Hazel, Sophie Corderoy, et al.. THE ADDITION OF CYCLOPHOSPHAMIDE TO LENALIDOMIDE AND DEXAMETHASONE IN MULTIPLY RELAPSED/REFRACTORY MYELOMA PATIENTS; A PHASE I/II STUDY. *British Journal of Haematology*, 2010, 150 (3), pp.326. 10.1111/j.1365-2141.2010.08250.x . hal-00552599

HAL Id: hal-00552599

<https://hal.science/hal-00552599>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**THE ADDITION OF CYCLOPHOSPHAMIDE TO LENALIDOMIDE
AND DEXAMETHASONE IN MULTIPLY
RELAPSED/RERACTORY MYELOMA PATIENTS; A PHASE I/II
STUDY**

Journal:	<i>British Journal of Haematology</i>
Manuscript ID:	BJH-2010-00300.R1
Manuscript Type:	Ordinary Papers
Date Submitted by the Author:	07-Apr-2010
Complete List of Authors:	<p>Schey, Stephen; Kings College Hospital Foundation NHS Trust and Kings College London, Haematology morgan, garth; Institute of Cancer Research, Section of Haematology Ramasamy, Karthik; Kings College Hospital, Haematological Medicine; Kings College London Hazel, Beth; Kings College Hospital Foundation NHS Trust, Haematology Corderoy, Sophie; Kings College Hospital Foundation NHS Trust, Haematology Ladon, Dariusz; Kings College Hospital Foundation NHS Trust, Haematology Jenner, Mathew; Institute of Cancer Research, Section of Haematology Phekoo, Karen; Kings College Hospital Foundation NHS Trust, Haematology boyd, kevin; The Royal Marsden Hospital, Haemato-oncology Davies, Faith; Institute of Cancer Research, Section of Haematology</p>
Key Words:	MYELOMA, CORTICOSTEROIDS, THERAPY

1
2
3 **THE ADDITION OF CYCLOPHOSPHAMIDE TO LENALIDOMIDE AND**
4 **DEXAMETHASONE IN MULTIPLY RELAPSED/RERACTORY MYELOMA**
5 **PATIENTS; A PHASE I/II STUDY**
6
7
8
9

10
11
12 SA Schey¹, GJ Morgan², K Ramasamy¹, B Hazel¹, D Ladon¹ S Corderoy¹, M
13 Jenner², K Phekoo¹, K Boyd², FE Davies²
14
15
16
17

- 18
19
20 1. Kings College Hospital Foundation NHS Trust, London, UK
21
22 2. Royal Marsden NHS Foundation Trust, London, UK
23
24
25

26
27 **Corresponding author:**
28

29 Stephen A Schey
30

31 Department of Haematological Medicine
32

33 King's College Hospital
34

35 London
36

37 UK
38

39
40
41 Phone: +44203-299-4607
42

43 Fax: +442032993514
44

45 e-mail: sschey@nhs.net
46
47

48 Running Title: Lenalidomide with cyclophosphamide and dexamethasone in
49 relapsed myeloma
50
51
52
53
54
55
56
57
58
59
60

Summary

Two identical Phase III randomised trials confirmed the significant clinical activity of lenalidomide and dexamethasone in myeloma patients with relapsed disease. We report the results of a Phase I/II dose escalation study, which set out to evaluate the optimal dose of cyclophosphamide when used in combination with a fixed dose of Lenalidomide and dexamethasone in relapsed/refractory myeloma. A total of 31 patients were enrolled in cohorts of 3 patients at 5 dose levels of cyclophosphamide to a maximum dose of 700mg days 1 and 8 of a 28 day cycle. Patients received Lenalidomide 25 mg days 1 through 21 and dexamethasone 20mg orally days 1-4 and 8-11. The maximum tolerated dose (MTD) of this regimen is 600mg cyclophosphamide days 1 and 8 and the regimen is well tolerated with grade 3/4 haematological complications only occurring in 26% of patients, grade 3/4 infection in 3% of patients, both at the 700mg cyclophosphamide dose level with thromboembolic complications in 6% of patients. The **overall** complete remission rate was 29%, very good partial remission rate 7% and partial remission rate 45% giving an overall response rate of 81%. After a median follow-up of 21 months, projected 2 year progression free survival (PFS) is 56% and the overall survival at 30 months is 80%. **10 patients were treated in an extended cohort group at the maximum tolerated dose of cyclophosphamide with a 40% CR rate. No dose reductions for any of the study drugs or deaths was required during cycles 1-9.** The combination of Lenalidomide, cyclophosphamide and dexamethasone is a safe and effective combination in relapsed myeloma inducing a high response rate that are durable and warrants further investigation in the phase 3 setting.

Introduction:

Immunomodulatory (IMiD) drugs are an important set of molecules in the management of myeloma patients. Thalidomide was first shown to be effective in relapsed/refractory myeloma (Singhal, *et al* 1999) with responses of partial response (PR) or greater being seen in >20% of patients (Yakoub-Agha, *et al* 2002). Based on these and subsequent studies, thalidomide is currently used at all disease stages and often in combination with a steroid and alkylating agent. More recently, the role of Lenalidomide (Revlimid), a more potent IMiD, has been explored in patients with relapsed myeloma in two identical phase 3 studies (Dimopoulos, *et al* 2007, Weber, *et al* 2007). These studies compared Lenalidomide/Dexamethasone with Dexamethasone alone and demonstrated the combination improved progression free and overall survival.

Alkylating agents have been the standard of care for myeloma patients for many years with Melphalan and Prednisolone being considered the standard approach for patients not destined for autologous transplantation. A series of clinical trials performed in the UK in the 1980s, demonstrated the equivalent efficiency of cyclophosphamide to melphalan and highlighted its favourable toxicity profile with less profound myelosuppression (Augustson, *et al* 2005), lacking the stem cell toxicity of melphalan, making it safe to use in patients destined for transplant (Child, *et al* 2003). In addition, cyclophosphamide has a large non-renal component of elimination making it a safer drug for patients with renal impairment.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Combination chemotherapy regimen exploiting synergistic affects of the individual components are often highly effective in oncology and there is a need to develop effective combinations for patients with myeloma.

The addition of an alkylating agent to standard chemotherapy (CVAMP), thalidomide (CTD or MTP) or bortezomib (MPV or CVD) has been shown to increase response rates and possibly to prolong survival(Berenson, *et al* 2006, Kropff, *et al* 2007, Palumbo, *et al* 2006, Raje, *et al* 1997, Sidra, *et al* 2006). However, the optimal dose of cyclophosphamide in combination with lenalidomide, which is known to cause myelosuppression, has not yet been defined. The aims of this study were to develop a safe alkylating agent, Lenalidomide, and steroid combination suitable for clinical use and evaluation in subsequent randomised clinical trials. To this end, the maximum tolerated dose and toxicity profile of cyclophosphamide when used in combination with Lenalidomide and dexamethasone for patients with relapsed refractory disease was determined.

METHODS

This was an open label, dose escalation phase I/II study designed to determine the maximum tolerated dose (MTD) of the combination of cyclophosphamide, Lenalidomide and dexamethasone. Research was approved by the King's College Hospital institutional review board and Cambridgeshire ethics committee and all participants gave written informed consent. Cyclophosphamide was given to 5 cohorts of 3 patients each at increasing doses from 300 mg po up to a maximum of 700 mg cyclophosphamide on days 1 and 8 of a 28 day cycle in combination with dexamethasone 20mg po, daily on days 1-4 and 8-11; **Lenalidomide was given at a dose of 25mg po, daily on days 1-21 in line** with the MM009 and MM010 phase 3 clinical trial protocols. **The scheduling of cyclophosphamide on day 1 and 8 was chosen to minimise the haematological toxicity that was observed when it was given in addition on days 15 and 22 in our previously reported study.** A total of 9 induction courses were administered and patients were then maintained on Lenalidomide at the maximum tolerated dose until disease progression or unacceptable toxicity. A further 10 patients were treated at the MTD dose of cyclophosphamide to gain experience of the regimen at this dose level. All subjects received low dose aspirin (e.g. 75mg) as thromboprophylaxis. Erythropoietin was not given routinely in this study nor was prophylactic anti-viral or anti-fungal treatment. Growth factor support was allowed if the neutrophil count dropped below $1.0 \times 10^9/l$ prior to initiating the next course of treatment and was then given for each successive course.

1
2
3 Patients diagnosed as relapsed myeloma, at first or subsequent relapse, were
4 eligible for the study but were excluded if they had received chemotherapy,
5 including corticosteroids, within 28 days of the start of treatment. Local
6 radiotherapy for symptom relief for previously recognised myeloma deposits
7 was allowed before starting treatment but not to new sites of disease if they
8 developed during the study which was classified as disease progression.
9 Patients were eligible if they had adequate renal function (serum creatinine <2
10 mg//dl) and bone marrow reserve (baseline platelet count >20 x 10⁹/l or
11 absolute neutrophil count >1.0 x 10⁹/l). In addition, patients with grade 3
12 peripheral neuropathy or a history of other malignancy within 3 years were
13 excluded.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32

Dose limiting Toxicity

33
34 Dose limiting toxicity (DLT) was defined as; Grade 4 haematological toxicity
35 occurring during cycle 1, febrile neutropenia during cycle 1, grade 3/4 non-
36 haematological toxicity during cycle 1 (excluding alopecia), or failure to start
37 cycle 2 within 7 days of scheduled day due to treatment related toxicity.
38 Providing no patient within a cohort experienced DLT, the subsequent cohort
39 received an increased dose of cyclophosphamide. If one patient in a dose
40 cohort experienced DLT, another three patients were enrolled at the same
41 dose. If 2 or more of all 6 patients at that dose experienced DLT, the MTD
42 would be determined as one cohort dose level below. If 1 or fewer of the 6
43 patients experienced DLT, three more patients were recruited into the
44 subsequent, higher dose cohort, up to a maximum of 700mg. .
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Dose modification and withdrawal

1
2
3 During the extended phase of the study, Lenalidomide was discontinued if the
4 patient developed a desquamating rash or erythema multiforme any grade or
5
6 sinus bradycardia or other cardiac arrhythmias \geq grade 3 within a treatment
7
8 cycle. Cyclophosphamide was withheld if patients developed cystitis grade ≤ 2
9
10 and all therapy was withheld if other Grade ≥ 3 non-haematological toxicity or
11
12 grade 4 haematological toxicity occurred. If myelosuppression occurred
13
14 following the second or subsequent course of treatment, Lenalidomide was
15
16 discontinued until the neutrophil level was $>1.0 \times 10^9/l$. A new course of
17
18 treatment began on the scheduled day 1 of a new cycle if the ANC is \geq
19
20 1,000/ μ L, the platelet count is $\geq 50,000/\mu$ L, and any lenalidomide-related
21
22 allergic reaction/ hypersensitivity or sinus bradycardia/ other cardiac
23
24 arrhythmia adverse event that may have occurred has resolved to \leq grade 1
25
26 severity, or any other lenalidomide related adverse event that may have
27
28 occurred had resolved to \leq grade 2 severity. If these conditions were not met
29
30 on day 1 of a new cycle, the subject was evaluated weekly and a new cycle of
31
32 therapy initiated when the adverse event had resolved. If subjects could not
33
34 initiate a new cycle of therapy within 28 days of the scheduled day 1, the
35
36 patient was withdrawn from therapy. The dose of Lenalidomide was reduced
37
38 in subsequent courses by 5mg decrements and the patients' response
39
40 assessed at weekly intervals whilst being continued on the initial dose of
41
42 cyclophosphamide. Treatment was discontinued if there was evidence of
43
44 disease progression or the patient developed unacceptable toxicity. Patients
45
46 who discontinued treatment due to an adverse event were followed up to
47
48 documented resolution or stabilisation of the event. In the event of a
49
50 haematological DLT, patients were allowed to reduce the dose of
51
52 Lenalidomide or cyclophosphamide and continue on treatment at the next
53
54
55
56
57
58
59
60

1
2
3 reduced dose level, provided haematological recovery occurred within 4
4 weeks. Patients with stable disease were allowed to continue on study as long
5
6 as clinical benefit was obtained. Subjects who discontinued treatment for any
7
8 reason underwent a safety assessment 30 days post the last dose of study
9
10 drug. At completion of cycle 9, subjects who had stable disease or better with
11
12 an acceptable toxicity profile were able to continue on Lenalidomide as single
13
14 agent maintenance therapy.
15
16
17
18

21 22 **Safety and Efficacy Assessment**

23
24 Patients were assessed weekly during the first month of treatment and 4
25
26 weekly thereafter. Response was assessed prior to each course of treatment,
27
28 using the international uniform response criteria (Durie, *et al* 2006). Bone
29
30 marrow aspirate/biopsy evaluations were carried out at trial entry and at
31
32 discontinuation of treatment to confirm response. Adverse events were graded
33
34 according to NCI common toxicity criteria (Version 3.0, Bethesda, MD, USA
35
36 [http:// ctep.cancer.gov/forms/ CTCv20_4-30-992.pdf](http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf)). All patients who
37
38 developed grade 4 haematological toxicity underwent bone marrow
39
40 examination.
41
42
43
44
45
46
47
48

49 **Statistical Analysis:**

50
51 The primary outcome measures were toxicity and safety. The secondary
52
53 endpoints were response, progression free and overall survival. **The MTD**
54
55 **was identified using arithmetic (or fixed) dose escalation.** Response rates
56
57 together with two-sided 95% confidence intervals were provided for all study
58
59 endpoints based on categorised responses. Data from all subjects who
60
received any study drug were included in the safety analyses. **Overall**

1
2
3 survival (OS) was measured from day 1 of trial entry to death from any
4 cause or last known follow-up; progression-free survival (PFS) from day
5 1 of trial entry to the first indicator of disease progression, death of any
6 cause, or last known follow-up; Survival curves were estimated using
7 Kaplan-Meier methodology, and log-rank test was used to assess
8 differences between groups. Differences were considered significant if
9 the p value was $<.01$.

20 21 22 ***Fluorescent in situ hybridisation***

23
24 FISH was performed on CD138+ve cells using standard approaches. At least
25 100 cells were analysed with a cut-off level of 20%. The panel consisted of
26 probes for 1q21/1p36/CEP 1 (Stretton Scientific), CEP12/13q14.3/13q34, IGH
27 break-apart, IGH/FGFR3, IGH/CCND1, IGH/MAF., CEP 5/9/15 (Vysis), p53
28 (Cytocell Ltd)

35 36 37 38 **RESULTS**

39 40 ***Patient Characteristics:***

41
42 A total of 31 patients were enrolled into the study of whom 28 (90%) had
43 previously received thalidomide, 8 (26%) bortezomib and 20 (65%) prior
44 autologous stem cell transplant (Table 1). The median age at enrolment was
45 65 years (range 42 – 79), median time since the last therapy 7 months (range
46 1 – 84) and the median ISS 1 (range 1 – 3). Five cohorts were enrolled at
47 increasing doses of cyclophosphamide; Cohort 1 (300mg (n=3)), cohort 2
48 (400mg, (n=6)), cohort 3 (500mg (n=3)), cohort 4 (600mg (n=3)) and cohort 5
49 (700mg (n=6)). Median follow-up at time of analysis is 21 months.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 31 patients (80%) had samples taken for cytogenetics and fluorescent *in-situ*
4 hybridization (FISH) analysis. 10 (33%) patients failed and 14/31(45%) were
5
6 classified as good risk. 7/14 good risk patients had normal cytogenetics. 7/31
7
8 (22%) patients were shown to be in a cytogenetically poor risk category; 4
9
10 patients had del13, 2 had t(4:14), 5 had t(14:16) and 1 patient had a del17p.
11
12
13
14
15

16 17 **Toxicity:**

18
19 All patients were evaluable for toxicity during cycle 1 (Figure 1, Table 2). Two
20 patients developed grade 4 haematological toxicity in the cohort of patients
21 receiving 700mg of cyclophosphamide (1 neutropenia and the other
22 pancytopenia) and 3 other patients developed grade 3 neutropenia at a dose
23 of 300, 400 and 600 mg. Two further patients developed grade 2 neutropenia
24 at 600 and 700 mg and one other grade 2 neutropenia and anaemia at
25 400mg. One patient receiving 700mg developed grade 3 syncope, chest pain
26 and pneumonia and was withdrawn from study. Haematological toxicity was
27 therefore established as the dose limiting toxicity (DLT). The maximum
28 tolerated dose of cyclophosphamide in combination with Lenalidomide and
29 dexamethasone was, established at 600mg daily on days 1 and 8 of a 28 day
30 cycle. A total of 10 more patients were enrolled into the phase 2 part of the
31 study at the 600mg dose level, and, of these, none experienced a dose
32 limiting toxicity.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53

54
55 During the extended access phase of the study 10 patients (32%) developed
56 grade 3 cytopenia in the absence of progressive disease; during cycle 2-5.
57
58 Two patients in CR developed transient grade 3 neutropenia during cycles 9
59 and 15 of maintenance both of whom restarted after a 1 week delay. A further
60

1
2
3 patient in PR also developed transient grade 3 neutropenia but was able to
4 restart after a delay of 1 week. No non-haematological grade 3 or 4 toxicity
5 was reported. 3(10%) patients were withdrawn due to metabolic disturbance;
6
7
8 1 patient developed hyperglycaemia during cycle 2 requiring hospital
9 admission and a second developed recurrent hypocalcaemia necessitating
10 withdrawal from study during cycle 10. A third patient developed a raised
11 serum creatinine and hypotension in association with grade 3
12 thrombocytopenia necessitating a 4 week delay during cycle 3 and was
13 subsequently withdrawn. 2 patients (6%) developed a deep vein thrombosis
14 during cycle 5 necessitating a delay in treatment and warfarinisation. Further
15 investigations identified evidence of a pulmonary embolus on CT scan and the
16 other had a low level of possibility on a VQ scan. Two patients (6%)
17 developed infection; 1 patient died of meningitis during cycle 2 and another
18 patient developed shingles during cycle 16 requiring treatment with acyclovir
19 before restarting lenalidomide maintenance 2 weeks later. 2 patients (6%)
20 developed grade 3 cardiac arrhythmias, 1 a bradycardia during cycle 5
21 necessitating withdrawal from the study and another developed atrial
22 fibrillation during cycle 3 necessitating discontinuation of treatment before
23 being able to restart at the same dose level. No grade 3-4 neurological toxicity
24 was reported but 2 patients (6%) reported emergent grade 1-2 peripheral
25 neuropathy. Treatment was not discontinued and both patients reported no
26 progression with continuing treatment.

27
28
29 To date, a total of 13 patients have been withdrawn from study, 8 were
30 withdrawn during the induction phase; 3 because of disease progression, 1
31 with infection; 1 with diabetes mellitus; 1 with an arrhythmia and 2 developed
32 cytopenias. A further 5 patients were withdrawn during the maintenance

1
2
3 phase; 3 with disease progression, 1 with thrombocytopenia and 1 with
4 hypocalcaemia during cycle 11. At the beginning of cycle 5, 66% of patients
5 continued on 25mg daily of Lenalidomide and 64% of patients completed 9
6 courses of induction treatment. At the end of the planned 9 cycles of treatment
7 13 (40%) patients continued on Lenalidomide 25mg, 2 (6.5%) on 20mg and 4
8 (12%) on 15 mg of daily (Figure 2). The most common reason for dose delay
9 and reduction during the first month of treatment was grade 3 neutropenia.
10 There were 9 infectious events reported; 7 grade 1, 1 grade 2, and 1 grade 3
11 occurring at the maximum dose of 700mg cyclophosphamide (fig 2). The most
12 commonly observed adverse events were; neutropenia (grade 1-3), cramps
13 (grade 1-2), somnolence (grade 1-2), constipation/diarrhoea (grade 1-2),
14 minor infections (grade 1-2), and musculo-skeletal aches and pains (grade 1).
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

34 **Determination of MTD:**

35
36 During the first 28 days of the study, 2 patients developed a dose limiting
37 toxicity, both of whom were in the 700mg cyclophosphamide cohort. One had
38 an episode of febrile neutropenia, pneumonia and syncope (all grade 3), and
39 the other grade 4 pancytopenia. The maximum tolerated dose of
40 cyclophosphamide in combination with lenalidomide and dexamethasone was,
41 therefore, established at 600mg daily on days 1 and 8 of a 28 day cycle.
42
43
44
45
46
47
48
49
50
51
52

53 **Clinical Response:**

54
55 All patients were evaluable for response. At cycle 1 day 28, 4 patients (13%)
56 had stable disease (SD), 10 (33%) had a minimal response (MR), 16 (53%)
57 had a PR and 1 patient (3%) achieved a CR. After 9 courses of treatment, the
58 maximum responses seen were CR 29%, VGPR 7%, PR 45%, MR 3%, SD
59
60

1
2
3 13% and PD 3% (fig 3). By the end of course 6 a maximum response was
4 achieved by 27 patients (90%), (Figure 3). All patients achieved their
5 maximum response by this time point and no patients had a further
6 improvement in their response following commencement of maintenance
7 therapy. Thus, on an intention to treat basis, 81% of patients achieved a
8 maximum response of PR **or greater and 36% >VGPR.**
9
10
11
12
13
14
15
16
17

18 **Of the ten patients entered into the maximum tolerated dose cohort, 6**
19 **achieved PR, and 4 achieved CR. One patient was withdrawn due to**
20 **progressive disease at cycle 11 of maintenance. There were no deaths**
21 **and no dose reduction of any study drugs was performed during cycles**
22 **1-9.**
23
24
25
26
27
28
29
30
31

32 There was no difference in response rates between those patients with
33 cytogenetic abnormalities and those without ($p=0.73$) and similarly, the
34 response for those patients with serum beta 2 microglobulin <2.5 were not
35 statistically different from those with levels of 2.5 or higher ($p=0.03$). There
36 were a total of 12 patients who received cyclophosphamide at a dose of less
37 than 600 mg and 19 patients who received a dose of 600mg or more. No
38 significant differences in response rates were seen between these 2 groups.
39
40
41
42
43
44
45
46
47
48
49

50
51 After a median follow-up of 21 months, the actuarial median progression free
52 survival (PFS) for the whole group was not reached (Fig 4). At 2 years the
53 PFS is estimated to be 56%. Median actuarial overall survival has also not
54 been reached but was 80% at 30 months (Fig 5). The 1 patient with deletion
55 of 17p53 achieved a PR after 2 courses of treatment and has a progression
56 free interval of 17 months.
57
58
59
60

DISCUSSION

This is the first study to establish the maximum tolerated dose of cyclophosphamide in combination with a fixed dose of Lenalidomide and dexamethasone. The combination was well tolerated and the haematological toxicity was not significantly increased despite the advanced age of the patients and heavy pre-treatment, compared to the use of Lenalidomide and dexamethasone alone where >30% of patients had only 1 prior treatment and dexamethasone resistance was an exclusion criteria. Importantly, myelotoxicity was easily managed by withholding cyclophosphamide and restarting at a reduced dose. The non-haematological toxicity was low and managed with simple medical intervention that did not require interruption or delay in treatment for the vast majority of subjects. **Cardiac arrhythmias is a well known complication of treatment with IMiDs and chemotherapy. 2 of our patients developed grade 3 arrhythmias that necessitated temporary discontinuation of treatment in one and withdrawal from the study in another. In elderly patients receiving this agent it would be prudent therefore to regularly monitor their cardiac status.**

The major dose limiting toxicity was haematological with neutropenia developing in 41% of patients, although grade 3-4 toxicity was only seen in 19%. Non-haematological grade 3-4 toxicity occurred in less than 5% of patients with thrombosis occurring in only 2 patients, both of whom restarted treatment after warfarinisation. **Higher haematological toxicity has been reported recently with combination of cyclo/ Pred/ Lenalidomide, but at higher doses of cyclophosphamide (Attaya Suvannasankha 2009, Donna E. Reece 2009).** Importantly, toxicity figures in our study are similar to those

1
2
3 seen in MM009 and MM010 studies, suggesting that cyclophosphamide does
4 not add significantly to haematological toxicity. The toxicity profile also seems
5 to differ from the combination of melphalan and prednisolone with
6 Lenalidomide where Grade 3-4 haematological toxicity at a level of 52.4% was
7 seen at the maximum tolerated dose level (Palumbo, *et al* 2007). The
8 difference in myelosuppression with cyclophosphamide compared to
9 melphalan is consistent with the CRD combination being a safer and more
10 tolerable regimen than MPR.
11
12
13
14
15
16
17
18
19
20
21
22
23

24 The addition of cyclophosphamide in this study has increased the overall
25 response rate [CR + VGPR + PR] to 81% which is superior to that reported for
26 Lenalidomide alone (17%–23%) (Armoiry, *et al* 2008) or in combination with
27 dexamethasone (48%–51%) (Wang, *et al* 2008). **These responses were**
28 **observed despite the number of median lines of prior therapy of 3 (range**
29 **1-6), used in this study compared to that seen in the MM009 and MM010**
30 **trials where up to one third of patients were treated at first relapse.**
31
32 These responses are also higher than our previously reported CR+PR
33 response rates of 65% in a retrospective audit of patients receiving a
34 combination of Lenalidomide, cyclophosphamide and dexamethasone
35 (Morgan, *et al* 2007), all of whom had end-stage disease.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 Responses after relapse from first line treatment for myeloma are generally
54 short-lived, with outcomes being determined by the presence of adverse co-
55 morbidities, cytogenetic abnormalities and the adverse side-effects profile of
56 re-induction treatment. In both first and subsequent relapses, increasing drug
57 resistance and accumulated myelo- and nephrotoxicity restrict the intensity of
58
59
60

1
2
3 drug that can safely be delivered. There are few studies examining the
4 survival of patients after first relapse. A retrospective analysis of 2528 patients
5 entered into the non-intensive MRC Myeloma IV, V, VI and VII trials between
6 1980 and 1997, who achieved a stable plateau phase (Augustson, *et al* 2005)
7 showed that the median OS of the 1372 patients who achieved plateau was
8 3.9 years. At relapse, for those with 1 prior therapy it was 16.1 months and 9.2
9 for ≥ 2 prior therapies. If duration of response is taken into account in those
10 whose duration of plateau phase was < 1 yr, 1-3 yrs and > 3 yrs, the median
11 survivals from relapse were 11, 17 and 21 months, respectively. The mean
12 duration of survival at first, second and third plateau were 4.8, 2.0 and 1.0
13 years respectively. In a more recent study of patients with relapsed/refractory
14 disease (Quach, *et al* 2009), progression free survival beyond 2 years was
15 seen in only 27/141 (19%). The predicted two year PFS of 56% within the
16 CRD combination would support the hypothesis that Revlimid adds
17 significantly to the effects of cyclophosphamide and dexamethasone alone
18 and represents a significant step forward.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 It has been suggested (Stewart, *et al* 2007) that the presence of t(4;14),
44 t(14;16), t(14;20) and del17p13 on FISH and del 13 on metaphase
45 cytogenetics are associated with high risk disease. Although the numbers are
46 too small to draw firm conclusions, a quarter of patients in this study were
47 classified as high risk, but there was no difference seen in response to
48 treatment compared to standard risk patients (93% versus 85%; data not
49 shown). Similar results have been reported by the Canadian group (Reece, *et*
50 *al* 2009). **Our results support these findings they need to be confirmed in**
51
52
53
54
55
56
57
58
59
60

1
2
3 **a larger study before the CRD regimen can be recommended as a good**
4 **therapeutic option for patients with poor cytogenetic features.**
5
6
7
8
9

10 The responses seen with the CRD regimen compared well with the results of
11 other phase I/II studies of Lenalidomide combinations. The combination of
12 Lenalidomide, dexamethasone with liposomal doxorubicin and vincristine, was
13 associated with a response rate of 75% and CR/nCR rate of 29% but the
14 maximum tolerated dose of Lenalidomide was only 10mg /day(Baz, *et al*
15 2006). More recently, a Phase I/II study by the German Myeloma Study
16 Group, DSMM(Knop, *et al* 2009), using Lenalidomide in combination with
17 dexamethasone, conventional doxorubicin and pegfilgrastim support, was
18 associated with an ORR of 69% (CR+VGPR+PR). They further reported, at a
19 median follow-up of 14.6 months a median time to disease progression of 45
20 weeks and the one year survival probability was 88%. In our study, the overall
21 survival of 80% at 30 months is encouraging. The German Group further
22 report a higher percentage of grade 3/4 neutropenia (48%) and
23 thrombocytopenia (38%) compared to what we observed here in combination
24 with cyclophosphamide. The thromboembolic complication rate we report is
25 similar to the DSMM study, but grade 3/4 infections were less common (3% vs
26 10%).
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52
53 The optimal combination of novel agents and chemotherapy drugs will vary
54 between individual patients according to their prior responses, suitability for
55 stem cell transplant and co-morbidities. The response rate in this study is high
56 and the PFS and OS are impressive and they need to be substantiated in a
57 larger phase II study. As new agents become available we need to identify
58
59
60

1
2
3 how best to use them in combination to optimise response rate and duration
4
5 of responses by conducting well designed clinical trials. At relapse the
6
7 combination of Lenalidomide with cyclophosphamide and dexamethasone
8
9 appears to be well tolerated with encouraging responses and outcomes and
10
11 these findings should be confirmed in larger randomised trials in the future.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 **Acknowledgements:** *The authors acknowledge financial support from the*
28 *Department of Health via the National Institute for Health Research (NIHR)*
29 *comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS*
30 *Foundation Trust in partnership with King's College London and King's College*
31 *Hospital NHS Foundation Trust. Cancer Research UK and the Celgene Corporation*
32 *also provided financial support for the trial administration*
33
34
35
36
37
38
39
40
41
42
43

44 **Authorship contributions:**

45
46 Designed research: SS, GM, FD and KP

47
48 Performed research: SS, GM, FD, KR, MJ and KB

49
50 Collected data, analyzed and interpreted data: SC, BH and DL

51
52 Wrote the manuscript: SS, GM, FD and KR
53
54
55
56
57
58
59
60

No conflicts of interest to disclose

REFERENCES

- Armoiry, X., Aulagner, G. & Facon, T. (2008) Lenalidomide in the treatment of multiple myeloma: a review. *J Clin Pharm Ther*, **33**, 219-226.
- Attaya Suvannasankha, S.F., Robin A O'Bryant, Lisa L Wood, and Rafat Abonour (2009) Phase 2 Clinical Trial of Oral Lenalidomide, Cyclophosphamide, and Prednisone (RCP) for Newly Diagnosed Multiple Myeloma Patients. *Blood*, **114**, 2882.**
- Augustson, B.M., Begum, G., Dunn, J.A., Barth, N.J., Davies, F., Morgan, G., Behrens, J., Smith, A., Child, J.A. & Drayson, M.T. (2005) Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*, **23**, 9219-9226.
- Baz, R., Walker, E., Karam, M.A., Choueiri, T.K., Jawde, R.A., Bruening, K., Reed, J., Faiman, B., Ellis, Y., Brand, C., Srkalovic, G., Andresen, S., Knight, R., Zeldis, J. & Hussein, M.A. (2006) Lenalidomide and pegylated liposomal doxorubicin-based chemotherapy for relapsed or refractory multiple myeloma: safety and efficacy. *Ann Oncol*, **17**, 1766-1771.
- Berenson, J.R., Yang, H.H., Sadler, K., Jarutirasarn, S.G., Vescio, R.A., Mapes, R., Purner, M., Lee, S.P., Wilson, J., Morrison, B., Adams, J., Schenkein, D. & Swift, R. (2006) Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. *J Clin Oncol*, **24**, 937-944.
- Child, J.A., Morgan, G.J., Davies, F.E., Owen, R.G., Bell, S.E., Hawkins, K., Brown, J., Drayson, M.T. & Selby, P.J. (2003) High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*, **348**, 1875-1883.
- Dimopoulos, M., Spencer, A., Attal, M., Prince, H.M., Harousseau, J.L., Dmoszynska, A., San Miguel, J., Hellmann, A., Facon, T., Foa, R., Corso, A., Masliak, Z., Olesnyckyj, M., Yu, Z., Patin, J., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*, **357**, 2123-2132.
- Donna E. Reece, E.M.-K., Arooj Khan, Saima Dean, Peter Anglin, Christine Chen, Vishal Kukreti, Joseph R. Mikhael, and Suzanne Trudel (2009) Phase I-II Trial of Oral Cyclophosphamide, Prednisone and Lenalidomide (Revlimid®) (CPR) for the Treatment of Patients with Relapsed and Refractory Multiple Myeloma. *Blood*, **114**.**
- Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. (2006) International uniform response criteria for multiple myeloma. *Leukemia*, **20**, 1467-1473.
- Knop, S., Gerecke, C., Liebisch, P., Topp, M.S., Platzbecker, U., Sezer, O., Vollmuth, C., Falk, K., Glasmacher, A., Maeder, U., Einsele, H. & Bargou, R.C. (2009) Lenalidomide (Revlimid(R)), adriamycin and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: A report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom). *Blood*.
- Kropff, M., Bisping, G., Schuck, E., Liebisch, P., Lang, N., Hentrich, M., Dechow, T., Kroger, N., Salwender, H., Metzner, B., Sezer, O., Engelhardt, M., Wolf, H.H., Einsele, H., Volpert, S., Heinecke, A., Berdel, W.E. & Kienast, J. (2007) Bortezomib

1
2
3
4 in combination with intermediate-dose dexamethasone and continuous low-dose oral
5 cyclophosphamide for relapsed multiple myeloma. *Br J Haematol*, **138**, 330-337.
6 Morgan, G.J., Schey, S.A., Wu, P., Srikanth, M., Phekoo, K.J., Jenner, M. & Davies,
7 F.E. (2007) Lenalidomide (Revlimid), in combination with cyclophosphamide and
8 dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. *Br*
9 *J Haematol*, **137**, 268-269.
10 Palumbo, A., Bringhen, S., Caravita, T., Merla, E., Capparella, V., Callea, V.,
11 Cangialosi, C., Grasso, M., Rossini, F., Galli, M., Catalano, L., Zamagni, E., Petrucci,
12 M.T., De Stefano, V., Ceccarelli, M., Ambrosini, M.T., Avonto, I., Falco, P., Ciccone,
13 G., Liberati, A.M., Musto, P. & Boccadoro, M. (2006) Oral melphalan and prednisone
14 chemotherapy plus thalidomide compared with melphalan and prednisone alone in
15 elderly patients with multiple myeloma: randomised controlled trial. *Lancet*, **367**, 825-
16 831.
17 Palumbo, A., Falco, P., Corradini, P., Falcone, A., Di Raimondo, F., Giuliani, N.,
18 Crippa, C., Ciccone, G., Omede, P., Ambrosini, M.T., Gay, F., Bringhen, S., Musto,
19 P., Foa, R., Knight, R., Zeldis, J.B., Boccadoro, M. & Petrucci, M.T. (2007)
20 Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a
21 report from the GIMEMA--Italian Multiple Myeloma Network. *J Clin Oncol*, **25**,
22 4459-4465.
23 Quach, H., Mileskin, L., Seymour, J.F., Milner, A., Ritchie, D., Harrison, S.,
24 Westerman, D. & Prince, H.M. (2009) Predicting durable remissions following
25 thalidomide therapy for relapsed myeloma. *Leuk Lymphoma*, **50**, 223-229.
26 Raje, N., Powles, R., Kulkarni, S., Milan, S., Middleton, G., Singhal, S., Mehta, J.,
27 Millar, B., Viner, C., Raymond, J., Treleaven, J., Cunningham, D. & Gore, M. (1997)
28 A comparison of vincristine and doxorubicin infusional chemotherapy with
29 methylprednisolone (VAMP) with the addition of weekly cyclophosphamide (C-
30 VAMP) as induction treatment followed by autografting in previously untreated
31 myeloma. *Br J Haematol*, **97**, 153-160.
32 Reece, D., Song, K.W., Fu, T., Roland, B., Chang, H., Horsman, D.E., Mansoor, A.,
33 Chen, C., Masih-Khan, E., Trieu, Y., Bruyere, H., Stewart, D.A. & Bahlis, N.J. (2009)
34 Influence of cytogenetics in patients with relapsed or refractory multiple myeloma
35 treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13.
36 *Blood*.
37 Sidra, G., Williams, C.D., Russell, N.H., Zaman, S., Myers, B. & Byrne, J.L. (2006)
38 Combination chemotherapy with cyclophosphamide, thalidomide and dexamethasone
39 for patients with refractory, newly diagnosed or relapsed myeloma. *Haematologica*,
40 **91**, 862-863.
41 Singhal, S., Mehta, J., Desikan, R., Ayers, D., Roberson, P., Eddlemon, P., Munshi,
42 N., Anaissie, E., Wilson, C., Dhodapkar, M., Zeldis, J. & Barlogie, B. (1999)
43 Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med*, **341**,
44 1565-1571.
45 Stewart, A.K., Bergsagel, P.L., Greipp, P.R., Dispenzieri, A., Gertz, M.A., Hayman,
46 S.R., Kumar, S., Lacy, M.Q., Lust, J.A., Russell, S.J., Witzig, T.E., Zeldenrust, S.R.,
47 Dingli, D., Reeder, C.B., Roy, V., Kyle, R.A., Rajkumar, S.V. & Fonseca, R. (2007)
48 A practical guide to defining high-risk myeloma for clinical trials, patient counseling
49 and choice of therapy. *Leukemia*, **21**, 529-534.
50 Wang, M., Dimopoulos, M.A., Chen, C., Cibeira, M.T., Attal, M., Spencer, A.,
51 Rajkumar, S.V., Yu, Z., Olesnykyj, M., Zeldis, J.B., Knight, R.D. & Weber, D.M.
52 (2008) Lenalidomide plus dexamethasone is more effective than dexamethasone alone
53 in patients with relapsed or refractory multiple myeloma regardless of prior
54 thalidomide exposure. *Blood*, **112**, 4445-4451.
55
56
57
58
59
60

Weber, D.M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmauer, E.A., Siegel, D., Borrello, I., Rajkumar, S.V., Chanan-Khan, A.A., Lonial, S., Yu, Z., Patin, J., Olesnyckyj, M., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*, **357**, 2133-2142.

Yakoub-Agha, I., Attal, M., Dumontet, C., Delannoy, V., Moreau, P., Berthou, C., Lamy, T., Grosbois, B., Dauriac, C., Dorvaux, V., Bay, J.O., Monconduit, M., Harousseau, J.L., Duguet, C., Duhamel, A. & Facon, T. (2002) Thalidomide in patients with advanced multiple myeloma: a study of 83 patients--report of the Intergroupe Francophone du Myelome (IFM). *Hematol J*, **3**, 185-192.

Table 1 Patient Characteristics

			No (%)
Age:	Median 65	Range (42 – 79)	
Sex:	Male		21 (67)
	Female		10 (33)
M-Component:			
IgG			20 (65)
IgA			9 (29)
LCD			2 (6)
Relapsed			2 (6%)
Refractory			29 (94%)
Previous lines of treatment:			
	Median 3.0	Range (1 – 6)	
Prior therapy:			
ASCT			20 (65)
Thalidomide			8 (90)
Bortezomib			8 (26)
Serum albumin:			
	Median 39	Range (21- 45)	
Serum β_2 m:			
	Median 2.5	Range (1.1 – 12.9)	
Adverse FISH			n (%)
Total assessable			21 (67)
del 13q			4 (13)
t(4:14)			2 (6)
t(14:16)			5 (16)
del 17p53			1 (3)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Peer Review

Table 2. Haematological Toxicity. The number of adverse haematological events (all grades) occurring at each cyclophosphamide dose level.

Haematological Toxicity

Dose(mgs)	No of Patients	Number of patients			
		G1	G2	G3	G4
300		0	0	1	0
400		1	1	1	0
500		0	0	0	0
600		0	1	1	0
700		0	1	0	2
Total		1	3	3	2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Figure 1. Non Haematological Toxicity. Frequency of non-haematological toxicity during the initial 4 weeks of treatment (all grades)

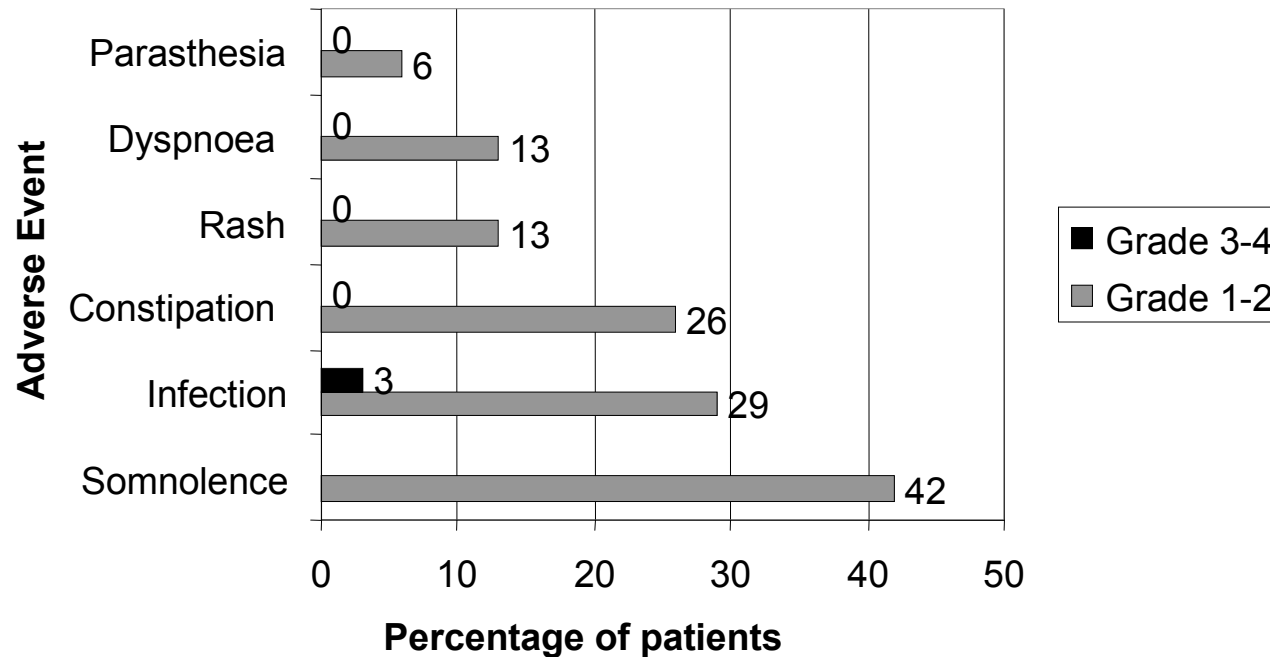
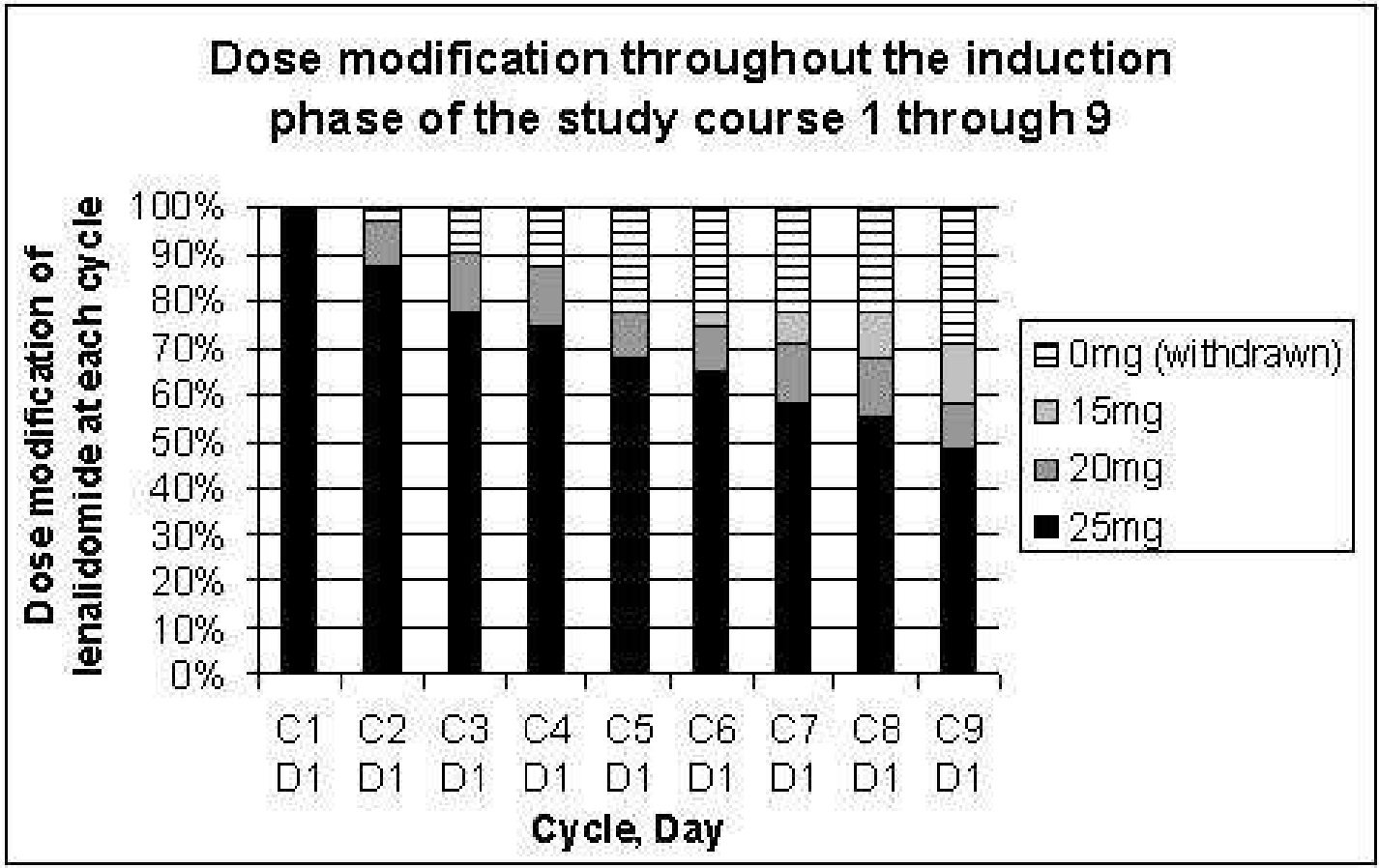


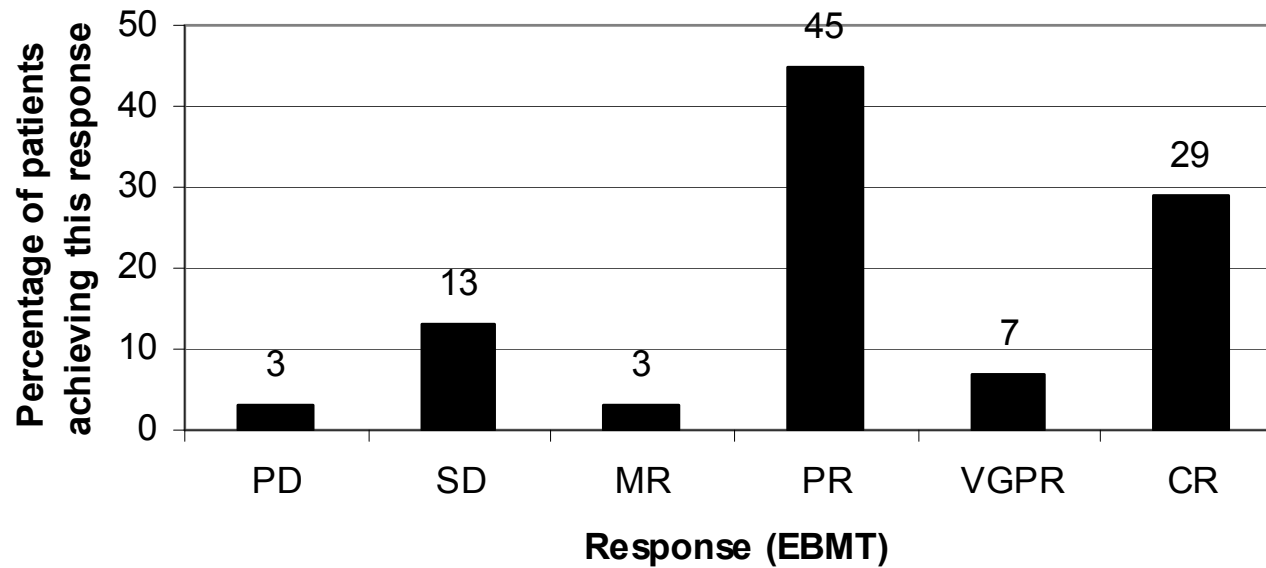
Figure 2: Dose modification throughout the induction phase of the study course 1 through 9



C1 is course 1 and D1 is day 1 of treatment cycle

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

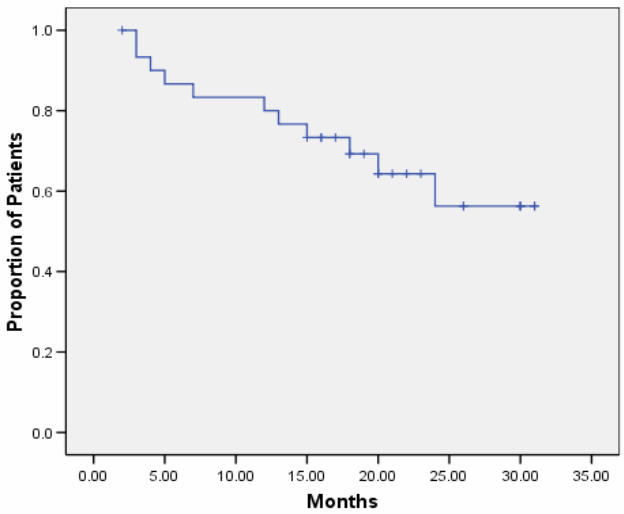
Figure 3: Overall response rate. Percentage of patients achieving maximum response to treatment.



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Figure 4

Progression Free survival - CRD Phase III Study



Overall Survival - CRD Phase III Study

