LenD: A study to establish the safety and efficacy of Lenalidomide and Dexamethasone in patients with relapsed or refractory chronic lymphocytic leukaemia.

Gohil SH[1, 2], Maciocia N[2], Patrick P[4], Roberts T[4], Counsell N[4], Smith P[4], Clifton-Hadley L[4], Cwynarski K[2], Pettitt A[5], Nathwani AC[1,2,3§].

Satyen Harish GOHIL

Nicola MACIOCIA

Pip PATRICK

Thomas ROBERTS

Nicholas COUNSELL

Paul SMITH

Laura CLIFTON-HADLEY

Kate CWYNARSKI

Andrew PETTITT

Amit Chunilal NATHWANI

1. Department of Academic Haematology, University College London Cancer Institute, 72 Huntley Street, London, WC1E 6DD, U.K.
2. Department of Haematology, University College London Hospital, University College Hospital, 250 Euston Road, London, NW1 2PG, U.K.
3. National Health Services Blood and Transplant, Oak House, Reeds Crescent, Watford, Hertfordshire, WD24 4QN, U.K.
4. CRUK & UCL Cancer Trials Centre, 90 Tottenham Court Road, London W1T 4TJ, U.K.
5. North West Cancer Research Centre, University of Liverpool, 200 London Road, Liverpool L3 9TA, U.K.

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SG analysed the data and wrote the paper

NM analysed the data and wrote the paper

PP contributed to the research study, analysed the data and reviewed the paper

TR contributed to the research study, analysed the data and reviewed the paper

PS contributed to the research study

LC-H contributed to the research study, analysed the data and reviewed the paper

KC reviewed the paper

AP contributed to the research study and reviewed the paper

AN was chief investigator, analysed the data and wrote the paper

Lenalidomide shows promise in CLL, mediating its anti-leukaemic effect through direct cytotoxicity, modulation of the tumour microenvironment and correction of functional defects in immune cells [1]. Lenalidomide is, however, associated with significant toxicity, especially when doses greater than 10mg/day are used [2-4]. We investigated the safety and tolerability of a relatively low dose of lenalidomide and hypothesised combination with dexamethasone would reduce toxicity, especially tumour lysis syndrome (TLS) and tumour flare reactions (TFR), whilst allowing for dose escalation and thereby improve responses.

LenD was an open label phase II non-randomised multicentre trial conducted in the United Kingdom, approved by the NCRI CLL subgroup and funded by Celgene, who provided drug free of charge (RV-CLL-PI-0569).

Treatment consisted of up to twelve 28-day cycles of oral dexamethasone (20mg/day, days 1-4), and lenalidomide (days 1-28), starting at 5mg/day in cycle 1 and escalating to 10mg/day in the absence of toxicity, if creatinine clearance was ≥ 50ml/min. For those with a creatinine clearance of 30-50 ml/min, lenalidomide was started at 2.5mg/day and escalated to 5mg/day.

Eligible patients, aged 18 years or over, had to have relapsed or refractory CLL requiring treatment as defined by NCI-WG criteria [5], a life expectancy of more than 6 months and a WHO performance status of less than 2. Participants must have received at least one prior line of therapy and deemed unsuitable for fludarabine or alemtuzumab containing regimens. Local or systemic treatment for CLL, investigational therapy and major surgery were not permitted within 4 weeks of starting trial treatment. All participants gave informed consent and agreed to comply with the requirements of the Celgene Revlimid® Pregnancy Prevention Programme.

Patients were reassessed every 4 weeks during treatment, and treatment was discontinued upon disease progression or for unacceptable toxicity. Lenalidomide was interrupted for any grade

3-4 toxicity and recommenced at a dose 2.5mg lower than previously administered once toxicity had resolved to grade 1 or less.

Patients were formally assessed for response 4 weeks after their last cycle of treatment. The primary endpoint was the proportion of patients who achieved an objective response (CR + PR) according to NCI-WG guidelines [5] and the proportion of patients suffering Common Terminology Criteria for Adverse Events (CTCAE v4.03) grade 3/4 toxicities. Secondary endpoints were duration of response and time from study registration to next treatment. All patients who received trial treatment were included in the primary analysis.

Twelve patients were recruited from 2 UK sites (University College London and Royal Liverpool University Hospitals) between November 2012 and May 2014. Despite initial enrolment in line with expectations, the trial was closed prematurely in December 2014 due to poor recruitment (target =24), which was impacted by the availability of new B cell receptor inhibitors (BCRi). All 12 patients were male, with a median age of 61.5 years (range 33-82) and had received a median of 5 prior lines of therapy (range 2-9) (Table 1).

In total 62 cycles of lenalidomide and dexamethasone were delivered across the 12 patients. The median number of cycles completed per patient was 3.5, and only 3 patients managed to complete the full 12 cycles of trial treatment. The median daily dose of lenalidomide achieved across the entire cohort was 5mg. Only 5 patients reached 10mg/day, 4 of whom had subsequent dose reductions or omissions due to toxicity.

Four patients (33.3%) stopped trial treatment early due to adverse events: the first due to renal toxicity likely related to lenalidomide but not TLS, the second due to febrile neutropenia, the third due to grade 3 and 4 neutropenia and thrombocytopenia respectively, and the fourth due to multiple side effects. Four (33.3%) patients stopped treatment due to evidence of disease progression. An additional patient showed evidence of progressive disease at the time of formal

response assessment 13.7 months after registration. Of these patients the median time to next treatment was 6.6 months (range 0.9-15.2 months).

Eleven patients (91.7%) experienced a grade 3 or higher adverse event during trial treatment (Table 2). The most common grade 3 or higher toxicities were thrombocytopenia (n=7, 58.3%) and neutropenia (n=6, 50.0%), with sepsis reported in 2 patients (16.7%). One patient (8.3%) developed thromboembolic disease. No patients developed TLS or TFR. There was one early death, within 50 days of enrolment, due to a perforated sigmoid colon, possibly related to lenalidomide and dexamethasone.

Three patients achieved a partial response, giving an overall response rate (ORR) of 25.0% (95% CI: 5.5-57.2%). A further two patients had stable disease. The three patients who achieved a partial response achieved median daily lenalidomide doses of 3.8mg, 2.5mg and 5.0mg. Two patients completed 12 cycles of treatment and were still alive and progression-free 18.5 and 16.4 months post-registration. The first was 66 years old, WHO performance status 0, with unmutated IgVH and del 13q14.3, who had three prior lines of therapy (FCR, Chlorambucil and Rituximab/Bendamustine). The second was 57 years old, WHO performance status 0, with unmutated IgVH and complex cytogenetics including del 17p and 11q, who had 5 prior lines of therapy (FC, Rituximab/Dexamethasone, Allogeneic stem cell transplant (ASCT) with Donor Lymphocyte Infusion (DLI), Rituximab/Dexamethasone, Rituximab/Bendamustine/Mitoxantrone). The third patient who had previously received 7 lines of prior therapy (Chlorambucil, Fludarabine, R-CHOP, radiotherapy, ESHAP, ASCT and Rituximab) achieved a partial response but completed only 3 cycles of treatment before stopping due to clinician discretion. He progressed and died 4.8 months and 16.0 months post-registration respectively. The only other patient who completed 12 cycles of treatment is alive 19.4 months post-registration having progressed after 13.7 months. This patient was 69 years old, with unmutated IgVH and Del 17p13.1, WHO performance status 0, who had undergone five previous lines of therapy (FC, splenectomy, Rituximab and Dexamethasone, ASCT and

Bendamustine/Mitoxantrone). There was no clear clinical or biochemical predictors of response in these 3 patients although low β_2-microglobulin and presence of trisomy 12 have been shown to associate with long term response [6].

After a median follow-up of 18.5 months, 4 (33.3%) patients are alive without progression and 1 (8.3%) patient alive with progression. 7 (58.3%) patients have died, due to disease progression (n=5), infection (n=1) or perforated sigmoid colon (n=1).

To our knowledge, this is the first study to report on the use of a combination lenalidomide and dexamethasone in relapsed/refractory CLL patients. Despite limited numbers of patients, it adds to the growing body of evidence on the use of lenalidomide in CLL. We hypothesised combination of low dose lenalidomide and dexamethasone would establish safety and efficacy of this regimen and did not observe a single incidence of TLS or TFR. However, despite the relatively low doses of lenalidomide used, a high rate of both haematological and non-haematological toxicity was observed, in keeping with other studies. .

The ORR of 25% in LenD is comparable with the 11-44% reported in other studies [2,3,7], although Chanan-Khan *et al* and Ferrajoli *et al* both used a higher starting dose of lenalidomide and achieved higher median doses. Our cohort of patients were heavily pre-treated (median 5 prior lines of therapy) and had high risk features such as 17p deletion, which is in keeping with other trials in the relapsed/refractory setting.

Interestingly, four patients enrolled into LenD had received a prior ASCT, of whom 2 achieved a PR and 1 maintaining stable disease. Lenalidomide has been associated with graft versus leukaemia effect [8], although we saw no evidence of corresponding graft versus host disease, likely due to a long interval between ASCT and lenalidomide administration unlike other trials [9].

High rates of toxicity prevented planned dose escalations and resulted in a relatively low median daily dose of lenalidomide, which may have limited efficacy, but it is unclear whether

dexamethasone contributed to the toxicity profile. Chen *et al* reported a superior ORR of 74% with lenalidomide and dexamethasone [10], but this was in untreated patients, who generally have higher response rates, even with single agent lenalidomide [11-14]. However, when compared to chlorambucil in the front line setting, lenalidomide has lower response rates and higher toxicity and mortality (Chanan-Khan*, et al* 2017).

In summary, our pilot study demonstrates lenalidomide combined with dexamethasone can provide some patients with durable responses, including following ASCT. However in this extensively pre-treated cohort, lenalidomide is associated with significant toxicity, even at low starting doses. Dexamethasone appears to reduce the risk of TLS and TFR but did not minimise overall toxicity or allow for dose escalation.

Combination therapy with lenalidomide, including with anti-CD20 antibodies have reported higher ORR [15,16] and given the potential synergistic mode of action of lenalidomide and BCRi, novel combinations are warranted and currently under investigation (NCT01886859).(

Although small molecule inhibitors such as Ibrutinib and Venetoclax have drastically altered management and improved outcomes in CLL, they are not curative. Lenalidomide may have a role for this high risk group of patients with refractory disease, especially as we are entering an era of not having been previously exposed to multiple cytotoxic and immunosuppressive regimens. .

High levels of toxicity with lenalidomide necessitates stringent medical supervision, cautious dose escalation and further research to identify the most suitable patient cohort.

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Table 1: Baseline patient characteristics

	N = 12
	Median (range)
Age, years	61.5 (33 – 82)
Sex	**n (%)**
Female	0 (0.0)
Male	12 (100.0)
WHO performance status	
0	6 (50.0)
1	4 (33.3)
2	2 (16.7)
IgVH mutational analysis	
Mutated	0 (0.0)
Unmutated	9 (75)
Missing	3 (25)
Chromosomal abnormalities	
Trisomy 12	2 (16.7)
Del 13q14.3	5 (41.7)
Del 11q22.3	3 (25.0)
Del 17p13.1	7 (58.3)
	Median (range)
Previous lines of treatment	5 (2 – 9)
Haematology	
Haemoglobin, g/dl	11.9 (9.6 – 17.6)
Neutrophils, $x10^9$/l	5.9 (0.1 – 18.4)
WBC, $x10^9$/l	42.6 (2.4 – 167.3)
Lymphocytes, $x10^9$/l	33.4 (1.8 – 155.6)
Platelets, $x10^9$/l	117.5 (12.0 – 225.0)
Monocytes, $x10^9$/l	0.8 (0.0 – 3.9)

Table 2: CTCAE Grade 3-4 adverse events by frequency

Event Term	Any grade 3+ (%), N=12
Haematological	
Thrombocytopenia	7 (58.3)
Neutropenia	6 (50.0)
Anaemia	2 (16.7)
Febrile neutropenia	2 (16.7)
Non-haematological	
Gastrointestinal disorders	
Diarrhoea	1 (8.3)
Colonic perforation	1 (8.3)
Infections and infestations	
Bladder infection	1 (8.3)
Lung infection	1 (8.3)
Sepsis	2 (16.7)
Upper respiratory infection	1 (8.3)
Investigations	
Alanine aminotransferase increased	1 (8.3)
Blood bilirubin increased	1 (8.3)
Metabolism and nutrition disorders	
Hypernatremia	1 (8.3)
Respiratory, thoracic & mediastinal disorders	
Dyspnoea	2 (16.7)
Hiccups	1 (8.3)
Renal & Urinary Disorders	
Renal & urinary disorder NOS	1 (8.3)
Vascular disorders	
Thromboembolic event	1 (8.3)