Results of a Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CXD101: Preliminary Safety and Activity in Relapsed or Refractory Hodgkin and Non-Hodgkin Lymphoma Patients

T. A. Eyre[1, 2], G.P. Collins[2], A. Gupta[1], S. Sheikh[2,3], V. Woodcock[1], J. Whittaker[4], L.M. Wang[5], E. Soilleux[5], F. Tysoe[1], R. Cousins[1], N. La Thangue[3, 4], D. Kerr[4,6] & M. R. Middleton[1, 7]

1. Early Phase Clinical Trials Unit, The Oxford Cancer Centre, Churchill Hospital, Oxford, OX3 7LE 2. Department of Clinical Haematology, The Oxford Cancer Centre, Churchill Hospital, Oxford, OX3 7LE 3. Laboratory of Cancer Biology, Department of Oncology, University of Oxford, Old Road Campus Research Building, Oxford, OX3 7DQ 4. Celleron Therapeutics Ltd, 25 Milton Park, Oxfordshire, OX14 4SH 5.Department of Cellular Pathology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, OX3 9DU. 6. Nuffield Division of Clinical and Laboratory Sciences, Level 4, Academic Block, John Radcliffe Infirmary, Headington, Oxford, OX3 9DU. 7 NIHR Oxford Biomedical Research Centre, Oxford, UK.

Background

- Histone deacetylase inhibitors (HDACi) are associated with responses in a range of tumours and have therapeutic potential as monotherapy [1] and in combination. There remains a lack of predictive biomarkers
- CXD101 is a Class I-selective HDACi that induces histone acetylation in a time- and dose-dependent manner in a variety of cell lines in-vitro and human leucocytes treated ex-vivo.
- CXD101 is an active single agent in xenograft studies and exhibits dose-dependent pharmacodynamic effects.

Methods

- We sought to determine the maximal tolerated dose (MTD) of CXD101 in a dose escalation study in advanced solid and haematological cancer. The dose was escalated from 1 mg bd for 5 days in a 21 day cycle, following a 3 + 3 design. Eligible patients had advanced solid tumours or relapsed, refractory lymphoma.
- A preliminary assessment of efficacy was performed in a dose expansion cohort (n = 6) after the MTD was found.
- 39 patients were enrolled, of whom 36 were exposed to CXD101. Lymphoma patients were assessed by Cheson 2007. We present the data, focusing on the 22 lymphoma patients treated.

HR23B A genome-wide loss-of-function screen identified HR23B, a protein that shuttles ubiquitinated cargo proteins to the proteasome, as a sensitivity determinant for HDAC inhibitor-induced cell apoptosis [2]. HR23B status was assessed on all cases with available tissue. High HR23B expression in relapsed CTCL in-situ correlates with response to HDACi [3]; suggesting de-regulated proteasome activity is key contributor to anti-cancer activity. HDAC6 regulates HR23B activity [4]

Results 22 lymphoma patients were enrolled in the dose escalation and expansion cohort to date.

Dose limiting toxicity (DLT) The first DLT was noted at 16mg bd in cohort 5. Subsequent DLTs were seen at 20mg b.d. (1 of 6), and at the non-tolerated dose of 24/25mg b.d. (2 of 5; both neutropenic infection). A formal MTD and recommended phase II dose was established at 20 mg bd.

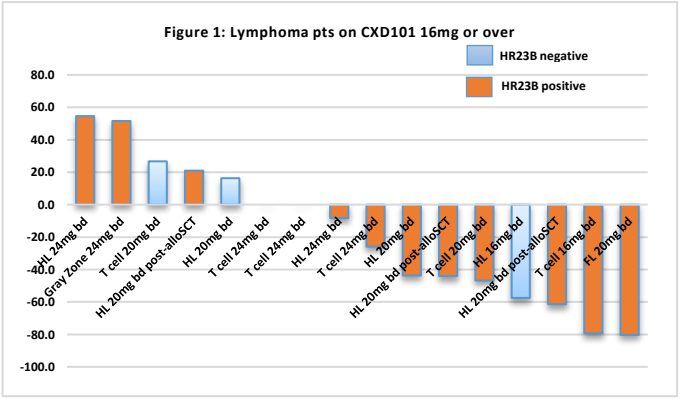
Baseline characteristics

Characteristic	Haematological tumour
Histology	Classical Hodgkin lymphoma (cHL) 10 Angioimmunoblastic T cell lymphoma (AITL) 4 Diffuse large B cell lymphoma (DLBCL) 3 Peripheral T cell lymphoma-NOS (PTCL-NOS) 2 Lymphoplasmacytic lymphoma (LPL) 1 Follicular lymphoma (FL) 1 Gray Zone non-Hodgkin lymphoma 1
Gender	
Male	13
Female	9
Age (median, range in years)	53.5 (21-79)
ECOG Performance Status	
0	7
1	15
Prior lines of therapy (median, range)	4 (1-10)
Staging	Ann Arbor II 3 III 2 IIIS 4 IV 12 N/A 1
International prognostic index (IPI)	
Low 0-1	3
Low/Intermediate 2	8
High/Intermediate 3	9
High 4-5	1
Data not available	1 (LPL)
HR23B status	
Positive (score 6-7)	14
Negative (score 0-5)	7
Data not available	1

Adverse events (AEs) The most frequent observed were fatigue, nausea and cytopenias. All AEs were manageable.

Total (possibly / probably / definitely related)	All Grades	%	G1-2	%	G3-4	%	SAEs
Haematology							
Thrombocytopenia	48	38%	35	28%	13	10%	
Neutropenia	46	36%	26	20%	20	16%	
Anaemia	16	13%	13	10%	3	2%	
Leucopenia	16	13%	9	7%	7	6%	
Neutropenic Fever	4	3%	1	1%	3	2%	4
Gastrointestinal							
Nausea	24	19%	24	19%	0	0%	
Diarrhoea	15	12%	14	11%	1	1%	
Vomiting	14	11%	14	11%	0	0%	1*
Anorexia	13	10%	13	10%	0	0%	1*
Infections							
Bronchial Infection	6	5%	5	4%	1	1%	
General/Constitutional							
Fatigue	34	27%	32	25%	2	2%	1*
Flu-like Symptoms	4	3%	4	3%	0	0%	
Cardiovascular							
QTc prolongation	24	19%	22	17%	2	2%	

Overall response rate (ORR) In 17 lymphoma patients dosed at 16mg b.d. or above, 3 partial responses (PR) (2 cHL post allogenic stem cell transplantation, 1 refractory AITL) and 1 complete response (CR) (relapsed FL) (ORR 23.5%) alongside 7 patients gaining clinical benefit with stable disease. Tumor volume reduction was seen in 56% of lymphoma cases (Fig 1). The median progression free survival (Fig 2) in these 17 patients was 113 days (95% confidence interval (CI) 35-162 days). In those with PR (n=3) and CR (n=1), the duration of response: 203 days, 161 days, 141 days (ongoing), and 176 days (ongoing) respectively. Results on the solid tumor patients are reported separately (ESMO, 2016).



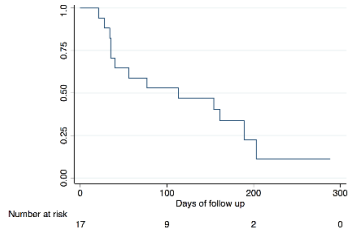


Figure 2 Progression free survival

HR23B No clear statistical correlation was seen where tumour volume reduction and PFS were stratified according to HR23B status. HR23B biomarker analysis at this time point is limited by variable tumour type, CXD101 dose, and biopsy time-lag.

Conclusions MTD observed was 20 mg bd for 5 days in a 3-weekly cycle. Disease activity was seen in T cell, follicular and Hodgkin lymphoma. PD and PK data are ongoing.

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