A phase I trial to assess the safety, tolerability, PK and PD of CXD101 in patients with advanced cancer expressing the biomarker HR23B

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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 to date) after the MTD was found.
- 39 patients were enrolled, of whom 36 were exposed to CXD101.
- Lymphoma patients were assessed by Cheson 2007, and solid tumour patients by RESIST 1.1.

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 assess 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 30 patients were enrolled in the dose escalation cohort. 29 were evaluable for DLT assessment.

Baseline characteristics

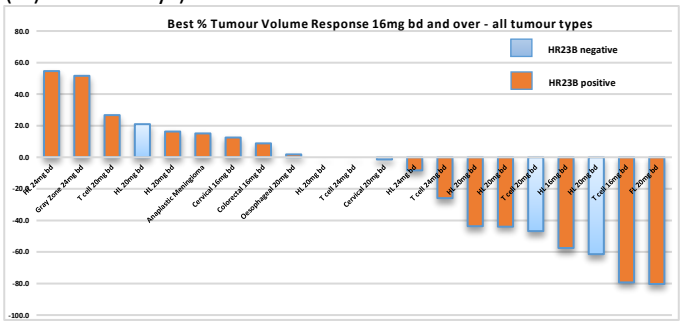
Characteristic	Solid tumour	Haematological tumour	Combined
Histology	Colorectal Ca 3 Lung Ca 2 Cervical Ca 2 Breast Ca 1 Pancreatic Ca 1 Ovarian Ca 1 ENT 1 Other 3	cHL 10 AITL 4 DLBCL 3 PTCL-NOS 2 LPL 1 FL 1 Gray Zone NHL 1	N/A
Gender			
Male	5	13	18
Female	9	9	18
Age (median, range)	58.5 (42-70)	53.5 (21-79)	58 (21-79)
ECOG Performance Status			
0	3	7	10
1	11	15	26
Prior lines of therapy (median, range)	4 (1-17)	4 (1-10)	4 (1-17)
Staging	Stage III 1 IV 13	Ann Arbor* II 3 III 2 IIIS 4 IV 12	
International prognostic index (IPI)	N/A	N/A	N/A
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)	11	14	25
Negative (score 0-5)	2	7	9
Data not available	1	1	2

Dose limiting toxicity (DLT) 1st 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.

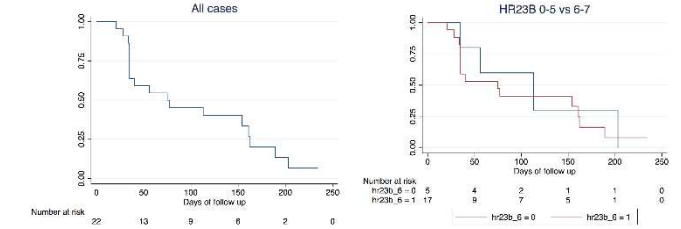
Adverse events (AEs) The most frequent observed were fatigue, nausea and cytopenias. All AEs were manageable.

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 In 22 patients dosed at 16mg b.d. or above, 3 partial responses (2 Hodgkin lymphoma post allogenic stem cell transplantation, 1 refractory angioimmunoblastic T cell lymphoma) and 1 complete response (relapsed follicular lymphoma) were noted (ORR 18%) alongside 9 patients with stable disease. Tumour reductions were predominantly noted in lymphoma patients. The median progression free survival (PFS) in these 22 patients was 76 days (95% confidence interval (CI) 35-161 days).



HR23B No clear statistical correlation was seen where tumour volume reduction and PFS were stratified according to HR23B status. HR23B biomarker nalysis 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. PK and PD work is ongoing.

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