A Phase 1 Trial of CUDC-907, an Oral, First-in-Class, Dual Inhibitor of HDAC and PI3K, in Patients with Refractory or Relapsed Lymphoma and Multiple Myeloma

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Introduction

- Histone deacetylases (HDACs) and phosphatidylinositol 3-kinase (PI3K) pathways are validated therapeutic targets, as demonstrated by regulatory approvals of various agents for the treatment of certain lymphomas (HDACi or PI3Ki) and multiple myeloma (HDACi).
- CUDC-907 is an orally bioavailable small molecule designed to target HDACs and PI3Ks in a single chemical entity. In preclinical studies, CUDC-907 potently inhibits tumor growth by inducing apoptosis and cell cycle arrest and also modulates the tumor microenvironment.
- Safety and efficacy data from the completed dose escalation and ongoing expansion stages of the Phase 1 trial (CUDC-907-101) are presented showing the therapeutic potential of CUDC-907 administered as monotherapy in subjects with refractory or relapsed lymphoma and multiple myeloma (MM).

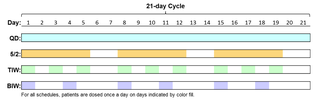
Enzymatic Inhibition

Enzyme	HDAC					PI3K			
Isotype	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

Study Design

Phase 1 open-label study in patients with relapsed/refractory lymphoma or MM

- **Primary Objective:** To determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) of oral CUDC-907
- **Secondary Objectives:** To assess the safety, tolerability, PK, biomarkers of activity, and preliminary anti-cancer activity of CUDC-907
- **Ongoing dose escalation: 3+3 design testing 3 schedules of once daily dosing (QD, "5/2" & intermittent BIW or TIW) (completed)**
  - QD – 30 mg and 60 mg
  - "5/2" (5 days on, 2 days off) – 60 mg
  - Intermittent: BIW - 60, 90, 120 &150 mg; TIW - 60, 90, 120 &150 mg
- **Dose Expansion: 60 mg 5/2 and 120 mg TIW dose levels**
- **Dose limiting toxicity (DLT) defined as**
  - Non-hematological Grade 3 AE, other than Grade 3 nausea or vomiting in subjects treated with less than optimal antiemetic therapy
  - Any AE resulting in a dose delay ≥7 days
  - Grade 4 neutropenia lasting ≥7 days, or ≥Grade 3 with fever >101.3°F (38.5°C) or infection
  - Grade 4 thrombocytopenia ≥7 days, or ≥Grade 3 with significant bleeding
- **Study Population**
  - Histopathologically confirmed diagnosis of lymphoma or multiple myeloma that is refractory to or relapsed after ≥2 prior regimens
  - Measurable or evaluable disease
  - Age ≥ 18 years
  - ECOG performance status ≤2
- **Assessments**
  - AEs were assessed until 30 days after the last dose of CUDC-907 & graded per NCI CTCAE v4.03
  - Antitumor activity was assessed per Revised Response Criteria for Malignant Lymphoma, International Uniform Response Criteria for Multiple Myeloma
  - Pharmacokinetic blood sampling occurred in Cycle 1 pre-dose & on Days 1, 8 & 15, as well as in Cycles 2–4 Day 1 & end of treatment. Additional sampling occurred on Cycle 1 Day 4 or 5 for patients assigned to the 5/2 schedule & on Cycle 1 Day 17 for those assigned to the BIW or TIW schedule
  - PBMC & plasma biomarker samples were assessed in Cycle 1 on Days 1, 8 & 15 (all schedules); and additionally on Day 5 for patients on the 5/2 schedule
  - Optional tumor sampling within 7 days prior to initiating CUDC-907 dosing & after CUDC-907 dosing



Dose Expansion

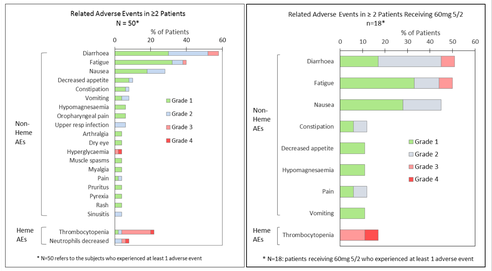
DLBCL, HL & MM
- **60 mg, 5/2**
- **120 mg, TIW**

Patient Characteristics & Disposition

Characteristics & Disposition	Overall N=57
Male, Female	40, 17
Age (median), yrs	61
Disease Type n (%)	
Diffuse large B-cell lymphoma (DLBCL)	9 (16)
t-FL/DLBCL	7 (12)
Hodgkin Lymphoma (HL)	14 (25)
T- Cell Lymphoma	3 (5)
Multiple Myeloma (MM)	9 (16)
Other	15 (26)
Prior Treatment	
No. prior regimens [median (range)]	5 (2-10)
Prior HDACi exposure n (%)	6 (11)
Prior PI3Ki exposure n (%)	5 (9)
No. Discontinued Study Treatment n (%)*	
Progressive Disease	22 (39)
Physician Decision	10 (18)
Adverse Event	6 (10)
Withdrawal of Consent	3 (5)
Other**	2 (4)

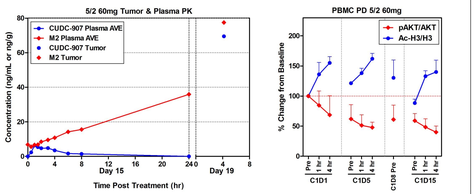
At the time of data cut-off, 14 patients (25%) were on treatment
*Decision to undergo BMT (1), clinical signs of PD (1)

Adverse Events



- AEs have been reversible with standard therapeutic interventions, dose holds and/or dose reductions
- The most common G3/4 related AEs reported in 2 or more patients were:
  - Thrombocytopenia & neutrophils decreased (hematologic)
  - Diarrhoea, hyperglycaemia & fatigue (non-hematologic)
- 4 DLTs consisting of diarrhoea & hyperglycaemia occurred in 3 patients assigned to the highest doses tested on QD & intermittent (BIW or TIW) schedules
  - G3 diarrhoea: 60 mg QD & 150 mg TIW dose groups
  - G4 hyperglycaemia: 60 mg QD & 150 mg BIW dose groups
- 5/2 60 mg & TIW 120 mg dosing was found to be reasonably tolerated while still achieving objective responses. Further assessment in the Expansion Phase is ongoing in patients with DLBCL, HL & MM.

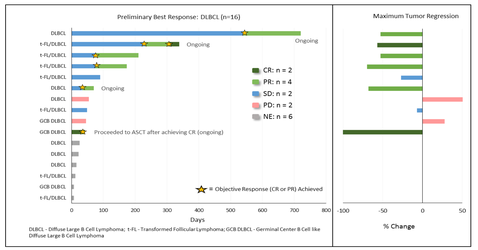
PK - PD



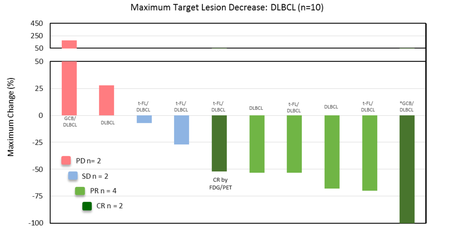
- Plasma PK on day 15 is represented by the average of data from 14 patients (5/2 schedule, 60 mg)
  - M2 is a metabolite of CUDC-907
- Tumor PK represents a single tumor sample obtained from the right axillary lymph node of a patient dosed on the 5/2 schedule (60 mg)
- PBMC PD represents the average of qualified samples from the first 3 patients (5/2 schedule, 60 mg)
  - Analysis of additional PBMC samples from other patients is ongoing

Activity in RR DLBCL

RR DLBCL - Duration on Treatment



DLBCL - Diffuse Large B Cell Lymphoma; t-FL - Transformed Follicular Lymphoma; GCB DLBCL - Germinal Center B Cell like Diffuse Large B Cell Lymphoma



DLBCL - Diffuse Large B Cell Lymphoma; t-FL - Transformed Follicular Lymphoma; GCB DLBCL - Germinal Center B Cell like Diffuse Large B Cell Lymphoma
* Achieved CR Cycle 2, proceeded to ASCT (CR ongoing)

10 of 16 patients with DLBCL were evaluable for disease response; 6 patients were NE due to withdrawal from study treatment before completing Cycle 1 and/or before being assessed for response due to AE (2, hypercalcemia [rel day 8, unrelated] & sepsis [rel day 5, unrelated]); early clinical progression (2, rel days 16 & 17); withdrawal of consent (1, rel day 5); or restaging pending (1).

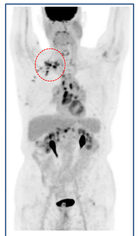
RR t-FL/DLBCL: Case Report

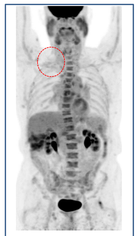
Subject ID:	03-2404
Tumor Type:	t-FL/DLBCL
Age/Gender	71 yo Male
Assigned Dose/Schedule:	150 mg TIW*
Best Response to CUDC - 907:	PR (C10) CR (C12)
Duration on CUDC-907:	287 Days **
Treatment Status:	Ongoing

*Dose reduction C3 (120 mg) & C15 (90 mg) for cytopenias
**As of 27-April-2015

Prior Treatment		Best Response
1. R-CHOP	2011	CR
2. R-ICE	2012	PR
3. ASCT	2012	CR

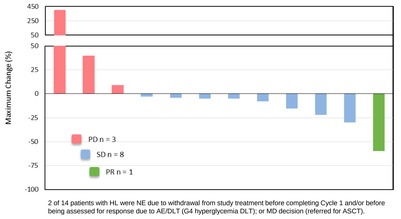
Abbreviations: R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; ASCT=autologous stem cell transplant (rituximab, carmustine, etoposide, cytarabine, melphelan)


Baseline PET/CT


Cycle 10 PET/CT (-52%)

Activity in RR HL

RR HL – Duration on Treatment



2 of 14 patients with HL were NE due to withdrawal from study treatment before completing Cycle 1 and/or before being assessed for response due to AE/DLT (G4 hyperglycemia DLT), or MD decision (referred for ASCT).

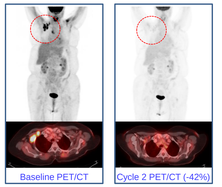
RR HL: Case Report

Subject ID (Initials):	02-S103
Tumor Type:	R/R Hodgkin Lymphoma
Age/Gender	64 yo Female
Assigned Dose/Schedule:	60 mg 5/2*
Best Response to CUDC - 907:	PR (C6)
Duration of Response:	211 Days**
Treatment Status:	Ongoing

*Dose reduction C6 (30 mg) for diarrhoea
**As of 27-April-2015

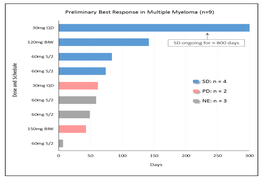
Prior Treatment	Response
1. ABVD 2006	CR
2. ICE 2006	CR
3. EVAC 2009	CR
4. BV 2012	CR

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; ICE = ifosfamide, carboplatin, etoposide; EVAC = etoposide, vincristine, adriamycin, cytoxan; BV = Brentuximab vedotin


Baseline PET/CT

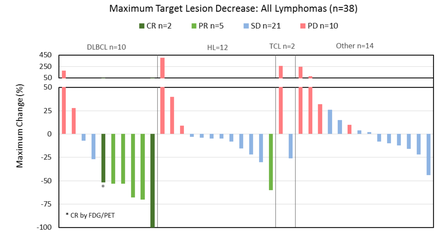
Cycle 2 PET/CT (-42%)

Activity in Multiple Myeloma



3 of 9 patients with MM were NE due to withdrawal from study treatment before completing Cycle 1 and/or before being assessed for response. AE/DLT (n=2): pelvic fracture (unrelated), hyperglycaemia DLT (related), Investigator decision (n=1, rising M spike & serum kappa).

Activity in All Lymphomas



Other Lymphomas: Burkitts Lymphoma; Follicular Lymphoma, Gray Zone Lymphoma; Lymphoplasmacytic Lymphoma; Mantle Cell Lymphoma; Marginal Zone Lymphoma; Small Lymphocytic Lymphoma;

Summary: Best Response Assessment

Indication	N	Best Response, N (%)					Median Treatment Duration, days (range)
		CR	PR	SD	PD	NE**	
All DLBCL*	16	2 (13)	4 (25)	2 (13)	2 (13)	6 (38)	50 (5-727+)
➢ t-FL/DLBCL	7	1 (14)	2 (29)	2 (29)	-	2 (29)	96 (5-287+)
HL	14	-	1 (7)	8 (57)	3 (21)	2 (14)	106 (7-271+)
MM	9	-	-	4 (44)	2 (22)	3 (33)	71 (43-825+)
Other lymphoma	18	-	-	11 (61)	5 (28)	2 (11)	60 (17-468+)
Total	57	2 (4)	5 (9)	25 (44)	12 (21)	13 (23)	71 (5-825+)

* Includes t-FL/DLBCL and DLBCL
**44 patients were evaluable for disease response as of the April 27, 2015 data cut-off. NE includes patients who received less than 1 cycle of study treatment (N=12) and one patient who had yet to be re-staged. Withdrawal from treatment during Cycle 1 was due to toxicity / AE (N=5), physician decision (N=3), PD (N=3) or withdrawal of consent (N=1).

Conclusions

- The dose escalation phase of this Phase 1 study has been completed. The ongoing expansion phase is evaluating the safety and tolerability of CUDC-907 at RP2D's of 60 mg 5/2 and 120 mg TIW in patients with RR DLBCL, HL & MM. ClinicalTrials.gov Identifier: NCT01742988
- CUDC-907 has been shown to be reasonably tolerated with self-limiting AEs that most commonly consist of G1-2 diarrhoea, fatigue, nausea and thrombocytopenia.
- Objective responses have occurred on all dosing schedules and across all investigational sites. Among the response-evaluable patients:
  - RR DLBCL: 6 objective responses (2 CRs, 4 PRs) were observed. Median treatment duration in these patients is 3 months (range: 1.6 - 24.2+ months, ongoing). Long-term responders have included patients with t-FL/DLBCL , one with a triple hit status involving MYC, BCL-2 and BCL-6.
  - RR HL: 1 objective response (1 PR) was observed. Median treatment duration in these patients is 5.4 months (range: 1.1 – 9+ months, ongoing).
  - Median treatment duration in these patients is 3 months (range: 1.5 – 27.5+ months, ongoing).
- The trial is currently enrolling patients with DLBCL to treatment with CUDC-907 monotherapy and in combination with standard dose rituximab.
- Registration-directed Phase 2 trial testing CUDC-907 in combination with rituximab in patients with RR DLBCL projected with earliest start date in Q4 2015.
- A Phase 1 trial evaluating CUDC-907 in patients with advanced/relapsed solid tumors (60 mg 5/2 and 120 mg TIW doses and schedules) is ongoing. ClinicalTrials.gov Identifier: NCT02307240

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