Phase 1 Trial of Oral CUDC-907, a Dual Inhibitor of HDAC and PI3K, in Patients with Refractory/Relapsed Lymphoma or Multiple Myeloma

J. G. Berdeja[1], Y. Oki[2], M. R. Patel[3], Amy Copeland[4], I. Flinn[1], S. S. Neelapu[2], J. Viner[5], J. Wang[5], J. F. Gerecitano[4], A. Younes[4]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Florida Cancer Specialists, Sarasota, FL; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]Curis, Lexington, MA

#8537 ASCO 2015

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

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

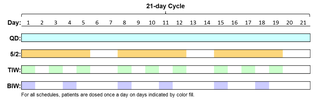
Study Design

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



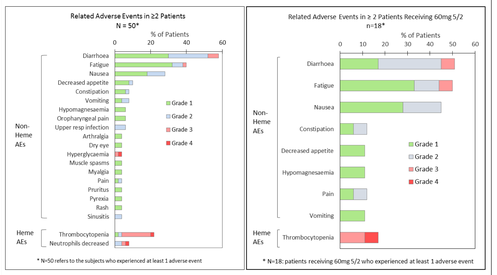
DISCLOSURES: JB: none; YA: none; MRP: none; AC: none; IF: none; SSN: none; JV, JW: employment (Curis); JFG: none; AY: research funding (Curis)

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

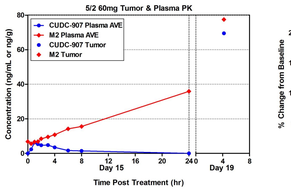


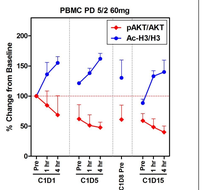
* N=50 refers to the subjects who experienced at least 1 adverse event

* N=18: patients receiving 60mg 5/2 who experienced at least 1 adverse event

- 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

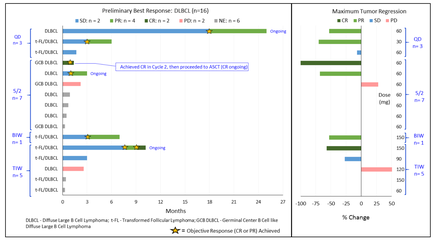




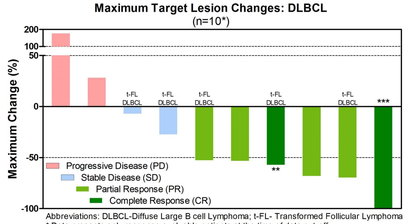
- Plasma PK on day 15 is represented by the average of data from 14 patients (5/2 schedule, 60 mg)
  - M2 is a metabolite of CUDC-907
- Tumor PK represents a single tumor sample obtained from the right axillary lymph node of a patient dosed on the 5/2 schedule (60 mg)
- PBMC PD represents the average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



10 of 16 patients with DLBCL were evaluable for disease response; 6 patients were NE due to withdrawal from study before completing Cycle 1 and/or before being assessed for response due to AE (2, hypercalcaemia [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).



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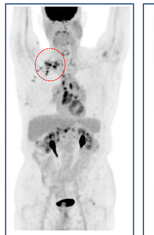
RR t-FL/DLBCL: Case Report

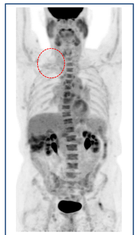
Subject ID:	03-2404
Tumor Type:	t-FL/DLBCL
Age/Gender	71 yo Male
Assigned Dose/Schedule:	150 mg TIW*
Best Response to CUDC - 907:	PR (C10) CR (C12)
Duration on CUDC-907:	287 Days **
Treatment Status:	Ongoing

*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

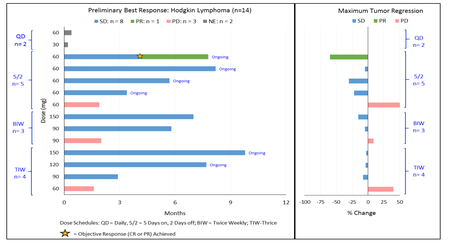
Abbreviations: R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; ASCT-autologous stem cell transplant [rituximab, carmustine, etoposide, cytarabine, melphelan]

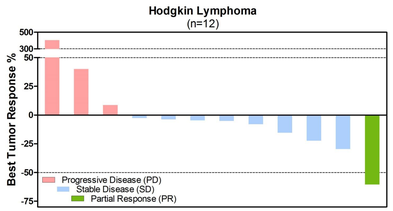




Activity in RR HL

RR HL – Duration on Treatment





2 of 14 patients with HL were NE due to withdrawal from treatment before completing Cycle 1 and/or before being assessed for response due to AE/DLT (G4 hyperglycaemia DLT); or MD decision (referred for BMT rel day 7).

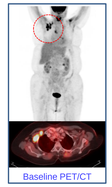
RR HL: Case Report

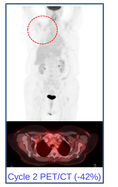
Subject ID (initials):	02-5103
Tumor Type:	R/R Hodgkin Lymphoma
Age/Gender	64 yo Female
Assigned Dose/Schedule:	60 mg 5/2*
Best Response to CUDC - 907:	PR (C6)
Duration of Response:	211 Days**
Treatment Status:	Ongoing

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

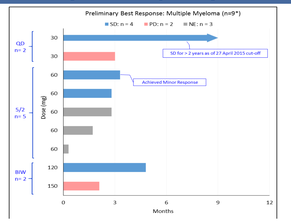
Prior Treatment	Response
1. ABVD 2006	CR
2. ICE 2006	CR
3. EVAC 2009	CR
4. BV 2012	CR

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



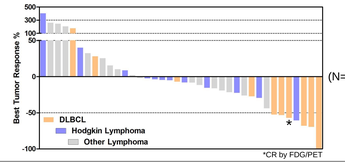


Activity in Multiple Myeloma



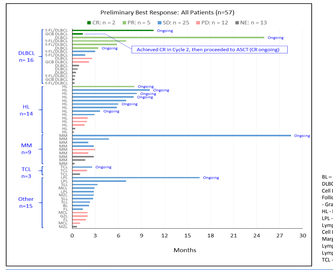
3 of 9 patients with MM were NE due to withdrawal from treatment before completing Cycle 1 and/or before being assessed for response due to AE/DLT (2, hyperglycaemia DLT & pelvic fracture [rel day 2, unrelated]); or MD decision (1, rising M spike & serum kappa).

Activity in All Lymphoma



(N=38)

Summary: Best Response Assessment



BL – Burkitt's Lymphoma; DLBCL - Diffuse Large B Cell Lymphoma; FL - Follicular Lymphoma, GZL - Gray Zone Lymphoma; HL - Hodgkin Lymphoma, LPL - Lymphoplasmacytic Lymphoma; MCL - Mantle Cell Lymphoma; MZL - Marginal Zone Lymphoma; SLL - Small Lymphocytic Lymphoma; TCL - T Cell Lymphoma

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 treatment (N=12) and one patient who has 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 this Phase 1 study has been completed. The ongoing expansion phase of 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).
  - MM: Minor response was observed 1 patient. Median treatment duration in these patients is 3 months (range: 1.5 – 27.5+ months, ongoing).
- An expansion arm of the trial is currently enrolling patients with DLBCL to treatment with CUDC-907 in combination with standard dose rituximab.
- A Phase 2 trial of CUDC-907 in combination with rituximab in patients with RR DLBCL who are not eligible for high dose chemotherapy is expected to be initiated in 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

Poster presented at ASCO 2015 in Chicago, IL May 29 – June 2, 2015; Poster # 8537

We express deepest gratitude to all the patients and clinical sites participating on this trial.
This trial is sponsored by Curis, Inc. with financial support from the Leukemia & Lymphoma Society.