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CUDC-907 in relapsed/refractory diffuse large B-cell lymphoma, including patients with MYC-alterations: results from an expanded phase I trial

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ABSTRACT

CUDC-907 is a first-in-class, oral small molecule inhibitor of both HDAC (class I and II) and PI3K (class Iα, β, and δ) enzymes, with demonstrated anti-tumor activity in multiple pre-clinical models, including MYC-driven ones. In this report, we present the safety and preliminary activity results of CUDC-907, with and without rituximab, in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), with a particular focus on those with MYC-altered disease. Thirty-seven DLBCL patients were enrolled, 14 with confirmed MYC-altered disease. Twenty-five patients received monotherapy treatment, and 12 received the combination of CUDC-907 with rituximab. CUDC-907 monotherapy and combination demonstrated similar safety profiles consisting primarily of Grade 1/2 hematologic and gastrointestinal events. The most frequently reported Grade ≥3 treatment-related events were thrombocytopenia, neutropenia, diarrhea, fatigue, and anemia. Eleven responses (5 complete responses and 6 partial responses) were reported, for a response rate of 37% (11 out of 30) in evaluable patients [30% (11 out of 37) including all patients]. The objective response rate in evaluable MYC-altered DLBCL patients was 64% (7 out of 11; 4 complete responses and 3 partial responses), while it was 29% (2 out of 7) in MYC unaltered, and 17% (2 out of 12) in those with unknown MYC status. Median duration of response was 11.2 months overall; 13.6 months in MYC-altered patients, 6.0 months in MYC unaltered, and 7.8 months in those with MYC status unknown. The tolerable safety profile and encouraging evidence of durable anti-tumor activity, particularly in MYC-altered patients, support the continued development of CUDC-907 in these populations of high unmet need. (*clinicaltrials.gov identifier: 01742988*).

Introduction

Diffuse large B-cell lymphoma (DLBCL) represents an aggressive and heterogeneous group accounting for approximately 35% of all malignant lymphomas.[1-4] Since the introduction of rituximab in 2004, response rates and survival in DLBCL patients have greatly improved.[5] However, approximately 30-40% of patients still develop relapsed or refractory disease.[1] Treatment options in this setting are limited to salvage therapies with the intent to bridge to hematopoietic stem cell transplantation, or clinical trials.[5,6] Multiple studies of relapsed/refractory DLBCL patients have demonstrated that the progression-free survival (PFS) and overall survival (OS) times are less than one year. Furthermore, over half the patients with

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relapsed/refractory disease are ineligible for stem cell transplantation.[1,6] These patients thus represent a population of urgent unmet clinical need.[7-9]

Given the heterogeneity of DLBCL and the need for new therapeutic options, there is increasing interest in determining treatments based on the genetic/molecular features of the disease.[10] Numerous studies in the past decade have demonstrated that alterations of MYC in DLBCL patients, defined as rearrangements or amplification of the *MYC* gene and/or MYC protein overexpression, confer dismal outcomes and poorer prognoses.[2,11-17] MYC is a transcription factor responsible for many cellular functions including cell proliferation and growth, and the upregulation of MYC is a common driver event in multiple human cancers.[2,3,18,19] Certain rearrangements of *MYC* [determined by fluorescent *in situ* hybridization (FISH)] lead to activation of the gene, increased protein expression [determined by immunohistochemistry (IHC)], uncontrolled cell growth, and increasingly aggressive disease.[2]

MYC gene rearrangements and high MYC protein overexpression (defined as ≥ 40% of lymphoma cells) are estimated to be present in approximately 10% and 30% of all newly diagnosed DLBCL patients, respectively,[2,16,20-22] with similar rates also reported in relapsed patients.[13] The emergence of MYC alterations as defining features of DLBCL is highlighted in the current National Comprehensive Cancer Network (NCCN) guidelines on non-Hodgkin lymphoma and the most recent World Health Organization (WHO) revisions on lymphoma classifications.[5] The 2016 revision of the 2008 WHO classification includes an up-dated subpopulation classified as "high grade B-cell lymphoma (HGBL) with rearrangements in *MYC* and *BCL2* and/or *BCL6*".[23]

The histone deactylase (HDAC) and phosphatidylinositol 3-kinase (PI3K) enzymes and their associated signaling pathways are established therapeutic targets in multiple hematologic cancers. Responses have been reported from the use of HDAC inhibitors in a limited number of relapsed/refractory DLBCL patients.[8,24,25] Individually, HDAC inhibitors have been reported to reduce the expression of MYC and associated tumorigeneic oncogenes such as *BCL2*, while PI3K inhibitors have been reported to decrease MYC family protein stability by disrupting their regulation at the post-transcriptional level.[26-34] When combined, reports from multiple DLBCL cell lines and mouse xenograft models have demonstrated that dual HDAC and PI3K inhibition results in synergistic anti-cancer effects, including suppression of MYC-induced oncogenic transcriptional programs.[8,29,35-40]

CUDC-907 is a rationally designed, first-in-class, oral small molecule that dually inhibits HDAC (class I and II) and PI3K (class Iα, β, and δ) enzymes.[8,19,35] Pre-clinical data in multiple solid and hematologic cell lines and animal models have shown that the pro-apoptotic and tumor growth inhibition activities of CUDC-907 are more potent than single-targeting HDAC or PI3K inhibitors. In addition, CUDC-907 treatment has demonstrated decreased MYC gene and protein expression and anti-tumor activity in multiple MYC-driven tumor models, including DLBCL.[19]

Despite increased awareness, the optimal treatment strategies for relapsed/refractory DLBCL and MYC-altered DLBCL patients remain poorly defined, highlighting the need for development of novel therapies targeting MYC.[3,13,41] The mechanistic rationale and pre-clinical observations support the investigation of CUDC-907 in DLBCL and MYC-altered DLBCL patients. Preliminary safety and activity results from the dose escalation of CUDC-907 across multiple lymphoma types and multiple myeloma have been presented previously.[8] Here, we present results from the dose escalation and expansion of CUDC-907 in relapsed/refractory DLBCL, with a particular focus on those with MYC-altered disease. The trial is registered at *clinicaltrials.gov identifier: 01742988.*

Table 1. Screening characteristics of diffuse large B-cell lymphoma (DLBCL) patients.

Male, n (%)	27 (73)
Age, median years (range)	60.6 (20-85)
Ethnicity, n (%)	
White	30 (81)
Other	7 (19)
Histology, n (%)	
MYC-altered	14 (38)
t-FL/DLBCL	13 (16)
Both	5 (14)
Non-MYC-altered	8 (22)
MYC status unknown	15 (40)
Cell of origin, n (%)	
GCB	6 (16)
Non-GCB	3 (8)
ABC	1 (3)
Unknown/unclassifiable	27 (76)
Years since diagnosis, median (range)	2.4 (0.6-20.9)
MYC-altered patients	2.5 (0.6-15.1)
t-FL/DLBCL patients	3.6 (0.6-11.4)
ECOG performance status, n (%)	
0	13 (35)
1	22 (60)
2	2 (5)
Number of previous treatments, median (range)	4 (2-10)
MYC-altered patients	3 (2-10)
t-FL/DLBCL patients	4 (2-10)
Previous treatments, n (%)	
Prior HDAC or PI3K inhibitor	2 (5)
Stem cell transplants	12 (32)
Autologous	11 (30)
Allogeneic	1 (3)

n: number; ECOG: Eastern Co-operative Oncology Group; t-FL/DLBCL: transformed follicular lymphoma to DLBCL; ABC: activated B-cell like, GCB: germinal B-center

Methods

Results presented here are from dose escalation and expansion of CUDC-907 in relapsed/refractory DLBCL patients. In dose expansion, the CUDC-907 recommended phase II dose (RP2D) of 60 mg for 5 days on/2 days off (5/2) was further explored as a monotherapy and in combination with rituximab at 375 mg/m^2 on day (d)1 of every cycle for 6 cycles (R-907).

In total, 37 adult patients with relapsed/refractory DLBCL were enrolled across 6 US cancer centers. Major inclusion criteria included confirmed relapsed/refractory disease, at least 2 prior anti-can-

cer regimens, measurable or evaluable disease, adequate hematologic, renal, and hepatic functions, and the ability to provide written informed consent and follow protocol requirements. Patients with DLBCL that had transformed from follicular lymphoma (t-FL/DLBCL) were eligible to enroll. Major exclusion criteria included active central nervous system (CNS) involvement of disease, gastrointestinal disorders interfering with study drug absorption, uncontrolled or severe cardiovascular disease, HIV infection, and hepatitis B or C infection. The trial was approved by the institutional review boards of all participating centers, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice.

Patients received CUDC-907 capsules (Pharmatek Laboratories Inc., San Diego, CA, USA) orally, within 30 minutes of a meal, in 21-day cycles until disease progression or other criteria for treatment discontinuation were met. Dose delays and modifications were permitted to ameliorate toxicities. Safety was assessed at screening, throughout the trial, and at follow up 30 days after the last dose of CUDC-907. The incidence and severity of adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v.4.03).

Standard, single 12-lead electrocardiograms (ECGs) were performed and monitored locally during screening, and before and after dosing on d1, d2, d8 and d15 of the first cycle of treatment, and at the end of treatment visit. Parameters measured included heart rate, PR, QRS, QT, and QTc (Bazett's formula) intervals.

The safety population includes all DLBCL patients of the trial who received at least one dose of CUDC-907. The response-evaluable population includes all DLBCL patients who received at least one dose of study drug and completed at least one post-baseline disease assessment. DLBCL patients were re-staged according to the Revised Response Criteria for Malignant Lymphoma, during the last week of cycles 2, 4, and 6, then every 4 cycles thereafter, and at the end of treatment.[42]

MYC-altered disease was defined per central testing of patient tumor tissue as MYC gene translocation or amplification (≥3 copies in >20% of cells) as determined by FISH, or MYC protein expression in ≥40% of lymphoma cells as determined by IHC. Where central testing could not be conducted, local results from pathology reports were used when available. Patients without abnormality by FISH and without protein overexpression were designated as MYC negative. Patients without tumor tissue available for testing, or without prior testing results of their MYC status were designated as MYC unknown. Cell-of-origin (COO), and translocation and expression status of BCL2 and BCL6 were also assessed or collected where available.

Results

Patients' characteristics

In total, 37 relapsed/refractory DLBCL patients were enrolled between 23 January 2013 and 12 May 2016. Twenty-five patients received CUDC-907 monotherapy and 12 received R-907.

Demographic and study disposition information are summarized in Tables 1 and 2, respectively. As of the 7th July 2017, 3 DLBCL patients (all MYC-altered) remained on active treatment; one patient was receiving the RP2D, and 2 patients were receiving R-907. Median duration of treatment for all patients was 1.3 (range: 0.1-35.4) months, 1.4 (range: 0.2-35.4) months for monotherapy patients, and 1.2 (range: 0.5-21.9+) for R-907 patients. Fifteen (41%) patients stayed on treatment beyond cycle 2 (42 days).

Table 2. Disposition of diffuse large B-cell lymphoma (DLBCL) patients.

Discontinued study treatment	34 (92)
Progressive disease	20 (54)
Physician's decision	5 (14)
Withdrawal of consent	4 (11)
Toxicity	3 (8)
Lost to follow up	1 (3)
Other*	1 (3)
Duration on treatment, median months (range)	1.3 (0.1-35.4)
Responders	15.5 (1.0-20.8+)
MYC-altered patients	2.8 (0.2-25.4)
Monotherapy	1.4 (0.2-35.5)
MYC-altered patients	2.8 (0.2-25.4)
R-907	1.2 (0.5-21.9+)
MYC-altered patients	1.3 (0.7-21.9+)

*Patient discontinued study treatment to proceed to autologous stem cell transplantation after achieving a complete response at cycle 2 of study treatment. R-907: CUDC-907 on 60 mg 5/2 schedule with rituximab at 375 mg/m^2 on day 1 of every cycle for 6 cycles.

Among responding patients, the median duration of treatment was 15.5 (range: 1.0-20.8+) months (Table 3).

Through central testing of available tissue and/or information from pathology reports, 14 (38%) patients were determined to have MYC-altered disease, 8 (22%) had non-MYC altered disease, and 15 (40%) had disease of unknown MYC status. Among 13 t-FL/DLBCL patients, 5 (38%) were determined to have MYC-altered disease, 4 (31%) were non-MYC-altered, and 4 (31%) had disease of unknown MYC status.

BCL2 and BCL6 protein expression and/or gene alteration (translocation and/or amplification) status was available for 11 (30%) patients. Two patients had confirmed MYC and BCL2 protein overexpression (double-expressors) while no patients had both *MYC* and *BCL2* translocations present (double-hit). Three (8%) patients had some form of MYC, BCL2, and BCL6 protein expression and/or gene alteration status available. There were no reported double-hit, triple-hit, or triple-expressor lymphoma patients on the study.

Cell-of-origin subtypes were determined for 11 (32%) patients, of which 7 were germinal center B-cell (GCB), 3 were non-GCB, and one was activated B-cell (ABC).

Safety

Adverse events were generally mild to moderate in severity (Grade 1/2) in both monotherapy and R-907, and reversible with standard medications, or with dose holds or reductions (Table 3). The most frequently reported adverse events reported were diarrhea [21 (57%)], thrombocytopenia [20 (54%)], fatigue [15 (41%)], nausea [14 (38%)], constipation [9 (24%)], vomiting [9 (24%)], and neutropenia [8 (22%)]. Grade ≥3 adverse events were reported in 16 (43%) patients, and Grade ≥3 treatment-related adverse events were reported in 15 (40%). The most frequently reported Grade ≥3 treatment-related events were thrombocytopenia [12 (32%)], neutropenia [6 (16%)], anemia [2 (5%)], diarrhea [2 (5%)], and fatigue [2 (5%)] (Table 4).

Serious adverse events were reported in 4 (28%) patients, none of which were considered treatment-related. They consisted of Grade 2 atrial fibrillation, Grade 3

abdominal pain, Grade 5 worsening of lymphoma, and Grade 3 pleural effusion that eventually progressed to Grade 5 respiratory failure. In this case, the patient entered the study with an Eastern Co-operative Oncology Group (ECOG) performance status of 2 and extra-nodal lung involvement of the disease. Symptoms of pleural effusion were reported within 11 days of starting R-907; treatment was then discontinued and the patient was reported deceased due to respiratory failure 13 days later. Two other adverse events resulted in treatment discontinuations: Grade 4 hypercalcemia and Grade 5 sepsis, neither of which were considered treatment-related.

Adverse events resulting in dose holds were reported in 16 (43%) patients, consisting primarily of treatment-related Grade 1-4 diarrhea, thrombocytopenia, and neutropenia. Adverse events leading to dose reductions were reported on 10 occasions in a total of 5 (13.5%) patients. The events were all considered treatment-related and consisted of Grade 2-4 thrombocytopenia and Grade 3 neutropenia, fatigue, and diarrhea.

The onset of diarrhea varied across the study and was generally well controlled by the use of anti-diarrheal medication and/or dose modifications. Patients were recommended to continue prophylactic use of anti-diarrheals from the first onset throughout study treatment. The majority of diarrhea events were Grade 1/2, though 2 patients reported Grade 3 diarrhea (both related to study treatment); both events were resolved within one week of onset. The onset in these 2 cases varied from during the first week of treatment to after one year of treatment. There were no events of colitis or use of colonoscopies noted.

Grade ≥3 hematologic toxicities such as thrombocytopenia, neutropenia, and anemia were reported from within the first few days of treatment to more than one year after starting treatment. The majority of these events resolved within one week through dose holds and/or reductions, though 2 events persisted for over a month and did not result in any dose modifications.

There were no reports of any major pulmonary toxicities such as pneumonitis, though 2 patients reported unrelated Grade 1-2 pneumonia events. One patient also reported Grade 1 metapneumovirus infection that was considered unrelated to study treatment and resolved within two weeks without any dose modification. The study protocol did not mandate the use of prophylactic measures for potential pulmonary toxicities or infections.

One event of atrial fibrillation and tachycardia each were reported (both unrelated to study treatment) and no events of QTc prolongation were noted. Minimal evidence of hepatotoxicity was reported, with 2 patients reporting unrelated Grade 1/2 events of alanine transaminase increase and no reports of aspartate transaminase increase.

Efficacy

Of the 37 patients enrolled, 30 were evaluable for response. Seven patients discontinued treatment prior to a post-baseline disease assessment. Two monotherapy patients discontinued due to adverse events (Grade 4 unrelated hypercalcemia and Grade 5 unrelated sepsis), and 4 patients withdrew consent. The single non-evaluable R-907 patient was lost to follow up during the second week of treatment.

Eleven DLBCL patients achieved objective responses; 9 receiving monotherapy and 2 receiving R-907, for an overall response rate of 37% among evaluable patients (30% for all 37 enrolled patients). Objective responses were reported in 9 of 19 (47%) with monotherapy and 2 of 11 (18%) with combination therapy. Three responses with monotherapy and both responses in R-907 were complete responses (CR).

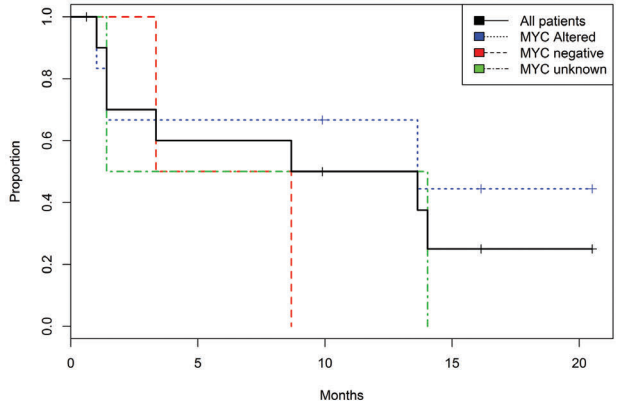

Figure 1. Extended progression-free survival (PFS) in MYC-altered patients. Kaplan-Meier PFS curve for all patients (n=37) on the trial (solid black line) along with subsets based on MYC status. MYC-altered patients (n=14, blue dotted line), MYC negative patients (n=8, red dashed line) and MYC unknown (n=15, green dash-dotted line). Median PFS was 2.9 months for all diffuse large B-cell lymphoma (DLBCL) patients and 21.8 months for the MYC-altered patients, respectively. x-axis in months; y-axis is the proportion of patients.

Median duration of response for all 11 responding patients was 11.1 (range: 1.0-20.8+) months; 6.0 (range: 1.0-16.4) months for monotherapy-treated patients. Both R-907 complete responses were ongoing at durations of 10.2 and 20.8 months, respectively (Table 5 and Figure 2). Median time to response was 2.4 (range: 1.2-15.3) months. Eight of 11 responses were reported within the first 2-3 disease assessments (by end of cycle 6), while 3 were reported at cycle 10 or beyond (cycles 10, 17 and 22). Of the 3 monotherapy patients achieving CR, one was reported at the first disease assessment (and the subject ultimately discontinued treatment to pursue a stem cell transplant), one PR at cycle 10 converted to CR at cycle 14, and one PR at cycle 2 converted to a CR at cycle 10.

Median PFS for all DLBCL patients on the study was 2.9 (range: 0.2-35.5) months. Among patients receiving monotherapy, the median PFS was 5.7 (range: 0.5-35.5) months and for patients treated with R-907 1.3 (range: 0.5-21.9+) months (Table 5 and Figure 1).

Efficacy in MYC-altered and other subgroups

Of the 19 evaluable monotherapy patients, 7 were MYC-altered, and, of the 11 evaluable R-907 patients, 4 were MYC-altered. Objective responses in evaluable MYC-altered patients were reported in 5 of 7 (71%) monotherapy patients, and 2 of 4 (50%) patients receiving R-907, for an overall response rate of 64% (7 of 11) in this group. Two CRs in the monotherapy group and both CRs in the R-907 group occurred in MYC-altered patients. In MYC non-altered patients, the evaluable response rate was 29% (2 of 7) and 17% (2 of 12) in those with unknown MYC status.

Median duration of response was 13.6 (range: 1.0-20.8+) months for MYC-altered patients. Among monotherapy

Table 3. Treatment emergent adverse events (>10% of patients).

Event	Monotherapy (n = 25)				R-907 (n = 12)				Overall (n = 37)			
	Grades 1-2	Grade 3	Grade 4	Total	Grades 1-2	Grade 3	Grade 4	Total	Grades 1-2	Grade 3	Grade 4	Total
Diarrhea	12 (48)	2 (8)	0	14 (56)	7 (28)	0	0	7 (28)	19 (51)	2 (5)	0	21 (57)
Thrombocytopenia	4 (16)	8 (32)	1 (4)	13 (52)	4 (16)	2 (8)	1 (4)	7 (28)	8 (22)	10 (27)	2 (5)	20 (54)
Fatigue	10 (40)	1 (4)	0	11 (44)	3 (12)	1 (4)	0	4 (16)	13 (35)	2 (5)	0	15 (41)
Nausea	7 (28)	0	0	7 (28)	7 (28)	0	0	7 (28)	14 (38)	0	0	14 (38)
Neutropenia	3 (12)	3 (12)	1 (4)	7 (20)	1 (4)	2 (8)	0	3 (12)	4 (11)	5 (14)	1 (3)	10 (22)
Constipation	5 (20)	0	0	5 (20)	4 (16)	0	0	4 (16)	9 (24)	0	0	9 (24)
Vomiting	2 (8)	0	0	2 (8)	6 (24)	1 (4)	0	7 (28)	8 (22)	1 (3)	0	9 (24)
Fever	2 (8)	0	0	2 (8)	4 (16)	1 (4)	0	5 (20)	6 (16)	1 (3)	0	7 (19)
Anemia	1 (4)	0	0	1 (4)	3 (12)	2 (8)	0	5 (20)	4 (11)	2 (5)	0	6 (16)
Cough	3 (12)	0	0	3 (12)	3 (12)	0	0	3 (12)	6 (16)	0	0	6 (16)
Hypokalemia	2 (8)	0	0	2 (8)	3 (12)	1 (4)	0	4 (16)	5 (14)	1 (3)	0	6 (16)
Abdominal pain	2 (8)	0	0	2 (8)	2 (8)	1 (4)	0	3 (12)	4 (11)	1 (3)	0	5 (14)
Edema	3 (12)	0	0	3 (12)	1 (4)	0	0	1 (4)	4 (11)	0	0	4 (11)
Hyperglycemia	0	1 (4)	0	1 (4)	3 (12)	0	0	3 (12)	3 (8)	1 (3)	0	4 (11)
Hypomagnesemia	0	0	0	0	4 (16)	0	0	4 (16)	4 (11)	0	0	4 (11)

Number (n) of diffuse large B-cell lymphoma patients (%) experiencing treatment-emergent adverse events. Only events reported in >10% of patients are presented. Six Grade 5 events were reported, none of which were treatment related; sepsis (n = 2) and worsening of lymphoma/progression of disease (n = 4). Note: subjects with multiple intensities under the same preferred term were counted only once in the highest severity.

MYC-altered responses, median duration was 7.5 (range: 1.0-16.4) months. Both R-907 CRs in MYC-altered patients were ongoing with durations of 10.2 and 20.8 months each, and the median duration of response was not reached. Median duration of response in MYC negative and MYC status unknown patients was 6.0 (range: 3.4-8.7) months and 7.7 (range: 1.4-14 months) months, respectively, none of which were ongoing (Table 5 and Figure 2).

Median PFS was 21.8 months (range: 1.0+ - 25.4+ months) for MYC-altered patients, with a median PFS of 21.8 (range: 1.0-16.4) months for patients treated with monotherapy, and not reached for patients treated with R-907. Median PFS in MYC negative and MYC status unknown patients was 1.3 (range: 0.4-15.5) months and 1.3 (range: 0.2 -35.3) months, respectively (Table 5 and Figure 1).

Other subgroups included patients with t-FL/DLBCL and those tested for COO, BCL2, and BCL6 status. Among the 10 evaluable t-FL/DLBCL patients, 6 responses were noted (4 PR, 2 CR), 4 of which occurred in MYC-altered patients. When considering COO, 3 of 7 GCB patients reported responses while none of the 3 non-GCB patients did. Of the 2 double-expressor patients, one discontinued after eight days of treatment due to unrelated Grade 4 hypercalcemia, while the other achieved a CR at cycle 2 before discontinuing to pursue a stem cell transplant.

Patients who did not report objective responses almost all discontinued treatment within the first 4 cycles. One exception was an MYC-altered patient who maintained stable disease for over two years before leaving the study due to physician's decision.

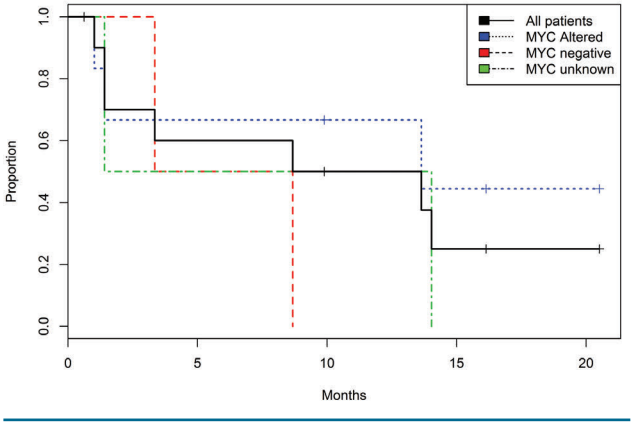

Figure 2. Extended duration of response in MYC-altered patients. Kaplan-Meier duration of response curve for all responding patients (n=11) on the trial (solid black line) along with subsets based on MYC status. MYC-altered patients (n=7, blue dotted line), MYC negative patients (n=2, red dashed line) and MYC unknown (n= 2, green dash-dotted line). x-axis in months; y-axis is the proportion of patients.

Pharmacokinetics and pharmacodynamics

Plasma pharmacokinetics (PK) of CUDC-907 and major metabolites M1 and M2 were determined for each dose level and schedule on the basis of samples obtained on d1 and d15 of cycle 1. *In vitro* studies have demonstrated that M1 and M2 both have reduced PI3K inhibitory activity (31% and 76%, respectively) and no HDAC inhibitory activity.

CUDC-907 demonstrated rapid absorption with maximum plasma concentrations occurring approximately two hours post administration (T_{max}) at the RP2D schedule. The metabolites reached their highest concentrations at later times; the T_{max} of M1 was approximately 16-20 hours (h), and the T_{max} of M2 was approximately 20-24 h. There was no accumulation of CUDC-907 in plasma on d15 after two weeks of dosing at the RP2D with an area

Table 4. Grade ≥3 treatment-related adverse events.

Event	Monotherapy (n = 25)			R-907 (n = 12)			Overall (n = 37)		
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Thrombocytopenia	8 (32)	1 4	9 (36)	2 (17)	1 (8)	3 (25)	10 (27)	2 (5)	12 (32)
Neutropenia	3 (12)	1 4	4 (16)	2 (17)	0	2 (17)	5 (14)	1 (3)	6 (16)
Anemia	0	0	0	2 (17)	0	2 (17)	2 (5)	0	2 (5)
Diarrhea	2 (8)	0	2 (8)	0	0	0	2 (5)	0	2 (5)
Fatigue	1 (4)	0	1 (4)	1 (8)	0	1 (8)	2 (5)	0	2 (5)
Hyperglycemia	1 (4)	0	1 (4)	0	0	0	1 (3)	0	1 (3)
Hypokalemia	0	0	0	1 (8)	0	1 (8)	1 (3)	0	1 (3)
Vomiting	0	0	0	1 (8)	0	1 (8)	1 (3)	0	1 (3)

Number (n) of diffuse large B-cell lymphoma patients (%) reporting Grade ≥3 treatment-related events. No related Grade 5 events were reported. Note: subjects with multiple intensities under the same preferred term were counted only once in the highest severity

Table 5. Summary of disease assessments in diffuse large B-cell lymphoma (DLBCL) patients.

	N	Evaluable, n	CR, n	PR, n	Evaluable ORR, %	DoR, median months (range)	SD, n	PD, n	PFS, median months (range)
Monotherapy	25	19	3	6	47	6.0 (1.0-16.4)	4	6	5.7 (0.5-35.5)
MYC+	10	7	2	3	71	7.5 (1.0-16.4)	1	1	21.8 (0.8-25.4)
R-907	12	11	2	0	18	NR (10.2-20.8+)	1	8	1.3 (0.5-21.9+)
MYC+	4	4	2	0	50	NR (10.2-20.8+)	0	2	NR (0.7-21.9+)
Total	37	30	5	6	37	11.1 (1.0-20.8+)	5	14	2.9 (0.5-35.5)
MYC+	14	11	4	3	64	13.6 (1.0-20.8+)	1	3	21.8 (0.7-25.4)

n: number; MYC+: MYC translocation or amplification by FISH, or MYC protein expression in ≥40% lymphoma cells per IHC; CR: complete response; PR: partial response; ORR: objective response rate; SD: stable disease; PD: progressive disease; DoR: duration of response; PFS: progression-free survival; NR: not reached; + : ongoing as of 7th July 2017 data cut-off date.

under the concentration-time curve from time 0 to 24 h ($AUC_{0\text{-}24h}$) of 37.8 ng·h/mL on d1 and 24.5 ng·h/mL on d15 (*Online Supplementary Table S1 and Online Supplementary Figure S1*).

As reported previously, peripheral blood mononuclear cell western blot analysis from patients in the RP2D dose schedule demonstrated post-treatment accumulation of acetylated histone H3 and decreased AKT phosphorylation.[8] These pharmacodynamic effects further support the mechanism of action of CUDC-907 and the use of 60 mg 5/2 as the RP2D.

Discussion

CUDC-907 monotherapy and R-907 demonstrated similar and tolerable safety profiles at doses able to achieve responses in heavily pre-treated relapsed/refractory DLBCL patients. Adverse events were generally mild to moderate in severity, reversible, and manageable with standard medications or by dose modifications. Diarrhea, fatigue, nausea, thrombocytopenia, and neutropenia were the most frequently associated adverse events of CUDC-907. These events are all also associated class toxicities of HDAC inhibitors.[43,44]

As described above, diarrhea events were largely Grade 1/2 and managed with over-the-counter medications (i.e. loperamide) and/or dose modifications, and there were no cases of colitis reported. Grade ≥3 cytopenias were generally considered treatment related, varied in their time of onset, and were most often resolved within one week through dose holds or reductions. Minimal adverse events reported were attributed solely to rituximab. Overall, the safety profile of CUDC-907 shares characteristics with currently FDA approved HDAC and PI3K inhibitors, consisting primarily of gastrointestinal and hematologic events, while not associated with other serious associated risks such as colitis, pneumonitis, hepatotoxicity, and cardiac toxicities.[8,43,45-47]

CUDC-907 demonstrated an encouraging ORR with durable responses in relapsed/refractory DLBCL, particularly in patients with MYC-altered disease. The monotherapy response rate was greater than that of R-907, but the small sample size of R-907 (11 evaluable patients) limits comparisons. A similar finding regarding response rates with and without rituximab was reported in a phase II study of the HDAC inhibitor panobinostat in relapsed/refractory DLBCL patients. Interestingly, the same study also reported no responses and an inferior PFS in patients with MYC-altered disease.[48]

Median duration of treatment among responders and the median duration of response times suggest durable anti-tumor activity for all responders. The durability of responses may be due to the novel dual inhibitory mechanism of CUDC-907, mitigating the development of resistance through simultaneous inhibition of multiple signaling pathways, as supported by pharmacodynamic data. MYC-altered patients demonstrated a notable median PFS time of 21.8 months, with all 3 active patients remaining being MYC-altered, further supporting the durable benefits of CUDC-907 treatment in this population.

MYC protein overexpression alone and with BCL2 have been reported to be among the worst prognostic factors in DLBCL, independent of *MYC* gene alterations or other prognostic parameters.[17] Five of the 7 MYC-altered responders were positive by IHC and one CR was reported in a double-expressor. This patient left the study early to pursue a stem cell transplant, and although this resulted in censored duration of response and PFS times, CUDC-907 has demonstrated activity in these particularly poor prognosis populations. CUDC-907 also demonstrated promising activity in t-FL/DLBCL, with 6 responses occurring in this therapeutically challenging patient population.[9]

Patients with relapsed/refractory DLBCL and MYC-altered DLBCL represent populations of unmet medical needs requiring the incorporation of novel agents into their treatment paradigms.[8,32,41,48] In this phase I study, CUDC-907 demonstrated a moderate safety profile and durable anti-tumor activity in these populations, particularly in those with MYC-altered disease. However, the relatively small sample sizes and incomplete capture of MYC information and other disease characteristics (BCL2, BCL6, and COO status) highlight the need for additional investigations.

A phase II study is currently ongoing to further explore the activity of CUDC-907 at the RP2D in relapsed/refractory DLBCL patients, with a primary analysis population consisting of patients with centrally confirmed MYC-altered disease by IHC analysis (*clinicaltrials.gov identifier: 02674750*). In addition, the study aims to better understand the potential relationship of other disease characteristics with CUDC-907 activity by implementing central testing of MYC, BCL2, and BCL6 protein expression and gene status, as well as collecting the COO status for all patients. CUDC-907 has also demonstrated synergistic anti-tumor activity when combined with the BCL2 inhibitor venetoclax in multiple DLBCL cell lines.[49] Although only preliminary results are available, this may highlight a promising potential for CUDC-907 combinations with other therapies targeting MYC-related pathways or signals in DLBCL.

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