Objective Responses Achieved in Patients with MYC-Altered Relapsed/Refractory Diffuse Large B-Cell Lymphoma Treated with the Dual PI3K and HDAC Inhibitor CUDC-907

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Introduction

- The prognosis for patients with relapsed and/or refractory (RR) MYC-altered diffuse large B-cell lymphoma (DLBCL) is dismal as they are often ineligible for or progress following autologous stem cell transplantation and respond poorly to subsequent therapies (*Blood*. 2012 May 17;119(20):4619-24. and *Haematologica*. 2013 Oct;98(10):1554-62; *J Clin Oncol*. 2017 Jan;35(1):24-31; *Cancer*. 2017 Nov 15;123(22):4411-4418).
- CUDC-907, a first-in-class oral dual inhibitor of HDAC (class I and II) and PI3K (class Iα, β, and δ) enzymes, has demonstrated downregulation of MYC mRNA and protein levels in MYC-altered DLBCL cell lines, as well as anti-tumor activity in multiple MYC-driven animal cancer models (*Mol Cancer Ther*. 2017 Feb;16(2):285-299).
- In a Phase 1 study, objective responses were reported in a number of patients with MYC-altered RR DLBCL treated with CUDC-907 (*Haematologica*. 2017 Nov;102(11):1923-1930). This Phase 2 study is designed to further explore the efficacy of CUDC-907 in this population of high unmet need (NCT02674750).

Phase 2 - Patients and Methods

- Up to 200 RR DLBCL patients may be enrolled to enrich for a total of 100 patients with confirmed MYC-altered disease by central immunohistochemistry (IHC) testing. Following central testing, patients are placed into one of the following 3 groups for analysis:
  - MYC-altered by IHC (≥40% MYC expression)
  - Non-MYC-altered by IHC (<40% MYC expression)
  - MYC status unknown/undetermined
- Key eligibility criteria include confirmed diagnosis of DLBCL (including high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements per 2016 WHO classifications), confirmed availability of viable biopsy tissue (fresh or archival) for central testing, ECOG score ≤1, 2-4 prior lines of therapy for DLBCL, and ineligible for/failed prior autologous stem cell transplantation.
- The primary endpoint is to assess the objective response rate (ORR) in MYC-altered patients by IHC. The response-evaluable population in this analysis was defined as any patient who received at least one dose of CUDC-907 and had a post-baseline disease assessment

Parameters	Study Population (n=68)
Male, n (%)	40 (59)
Caucasian, n (%)	59 (87)
Age, median years (range)	64 (33-93)
Histology, n (%)	
Transformed follicular lymphoma	14 (21)
De novo DLBCL	54 (79)
MYC status	
MYC-altered by IHC	46 (68)
Non-MYC-altered by IHC	14 (21)
MYC status unknown	8 (12)
Stage , n (%)	
I-II	10 (21)
III-IV	56 (82)
Unknown	2 (3)
Screening ECOG PS, n (%)	
0	28 (41)
1	34 (50)
2	6 (9)
No. of previous treatments, median (range)	2 (2-4)
Prior stem cell transplant, n (%)	11 (16)
Autologous	10 (15)
Allogenic	2 (3)

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Phase 2 - Safety Results

- A summary of the most frequently reported treatment-emergent AEs (>13%) is provided below.

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)					
Diarrhea	22 (32)	13 (19)	12 (18)	0	0	47 (69)
Nausea	23 (34)	9 (13)	0	0	0	32 (47)
Thrombocytopenia	5 (7)	5 (7)	14 (21)	3 (4)	0	27 (40)
Hypokalemia	8 (12)	4 (6)	8 (12)	0	0	20 (29)
Fatigue	14 (21)	5 (7)	0	0	0	19 (28)
Anorexia	11 (16)	7 (10)	0	0	0	18 (27)
Vomiting	15 (22)	2 (3)	1 (2)	0	0	18 (27)
Hypomagnesemia	12 (18)	2 (3)	1 (2)	0	0	15 (22)
Neutropenia	1 (2)	0	9 (13)	3 (4)	0	13 (19)
Fever	11 (16)	1 (2)	0	0	0	12 (18)
Anemia	2 (3)	3 (4)	6 (9)	0	0	11 (16)
Constipation	7 (10)	4 (6)	0	0	0	11 (16)

- The most frequently reported Grade ≥3 treatment-related AEs were thrombocytopenia (23.5%), diarrhea (14.7%), neutropenia (13.2%), and hypokalemia (6.3%). In total, 31 (46%) patients reported serious adverse events (SAEs), of which 5 were considered treatment-related: diarrhea (3), hypomagnesemia, and CMV viremia.
- Four patients (6%) discontinued treatment due to AEs; (Grade 5 worsening of lymphoma [2], Grade 5 Guillain-Barre Syndrome, and Grade 2 vomiting [related]).

Phase 2 - Efficacy Results

- The objective response rates (ORR) in each Group and overall are summarized below by the Evaluable and Intent-to-Treat (ITT) population definitions. The median duration of response (DOR) and progression-free survival (PFS) times (months) are also provided.

Group	Total Responses	ORR		Median DOR (95% CI)	Median PFS (95% CI)
		Evaluable Population	ITT population		
MYC-altered by IHC	7 (4 CR, 3 PR)	19% (7/37)	15% (7/46)	NC (0.8, NC)	1.4 (1.1, 2.7)
Non-MYC-altered by IHC	1 (1PR)	10% (1/10)	7% (1/14)	NC (NC, NC)	1.4 (1.1, 1.6)
MYC status unknown	0	0% (0/5)	0% (0/8)	N/A	1.35 (0.6, 4.7)
All	8 (4 CR, 4 PR)	15% (8/52)	12% (8/68)	NC (0.8, NC)	1.4 (1.3, 1.4)

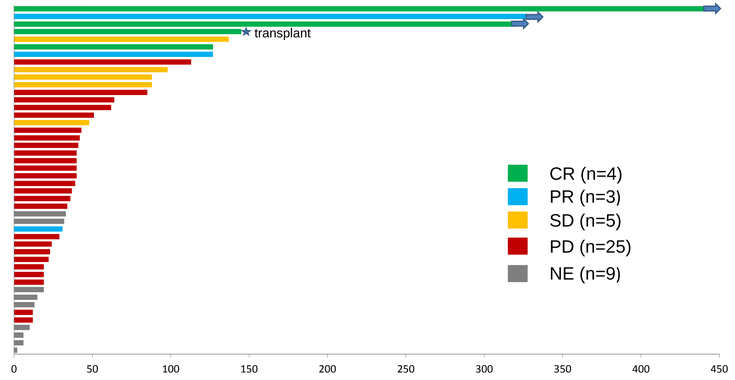
CI: confidence interval; NC: not calculable/reached

- Among the 7 Group 1 responders, all were triple-expressors (overexpression of MYC, BCL2, and BCL6), including both ongoing CRs. Further, 2 of the CRs (including 1 ongoing) were also double-hit patients (MYC and BCL2 rearrangements). The table below summarizes the prior therapies and MYC, BCL2, and BCL6 status by both FISH (translocation [TL] and copy number gain [CN]) and IHC for all responders.

Response	Prior therapies (Best response)	Prior SCT?	MYC status	BCL2 status	BCL6 status	DOR (months)
CR	1. R-CHOP (CR), 2. R-ICE (SD), 3.R-lenalidomide (PR)	No	TL-, CN- IHC+ (40%)	IHC+ (100%)	IHC+ (50%)	11.8+
CR	1. R-EPOCH (PD) 2. R + dexamethasone + cytarabine + cisplatin (PD)	No	TL+, CN- IHC+ (90%)	TL+, CN- IHC+ (100%)	TL-, CN- IHC+ (100%)	7.7+
CR	1. R-CHOP (CR), 2.R-DICE + HDT + ASCT (CR)	Yes	TL-, CN- IHC+ (65%)	TL-^ IHC+^(100%)	TL-^ IHC+^(100%)	3.7*
CR	1. R-CHOP + MTX + cytarabine (CR) 2. R-ICE (PD)	No	TL+, CN+ IHC+ (95%)	TL+^, CN-^ IHC+ (100%)^	TL-^, CN-^ IHC+ (75%)	2.8
PR	1. R-CHOP + MTX + etoposide (PD) 2. R + methylprednisolone + etoposide + cytarabine + cisplatin (PD)	No	TL+^ IHC+ (70%)	TL+^ IHC+^	TL-^ IHC+^	8.0+
PR	1. R-CHOP (CR), 2. R-ICE (SD), 3. R-lenalidomide (SD), 4. GemOx (NE)	No	TL-, CN- IHC+ (95%)	TL-, CN+ IHC+ (70%)	TL+, CN- IHC+ (80%)	2.1
PR	1. R-EPOCH (CR), 2.GemOx + obinotuzumab (PD)	No	IHC+ (80%)	TL-, CN- IHC+ (70%)	TL-, CN- IHC+ (30%)	0.8
PR	1. R-CHOP (CR), 2. R-ICE + HDT + ASCT (CR)	Yes	TL-, CN- IHC- (12%)	TL+^ IHC+ (90%)	TL-^ IHC- (5%)	1.1+

*patient discontinued treatment after 7 cycles to pursue SCT; + indicates ongoing; ^denotes per local testing when central results not available; HDT: high dose therapy; ASCT: autologous stem-cell transplant

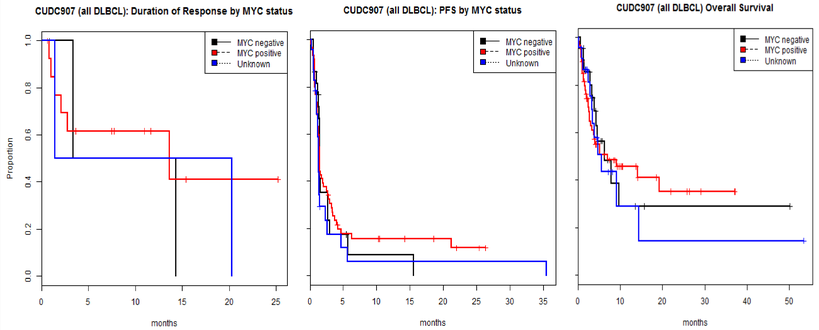
- Swimmer plot of MYC-altered by IHC patients best response and duration on treatment (days) is provided below.



Combined Phase 1 and 2 Analysis

- When including the 37 DLBCL (14 MYC-altered) patients from the Phase 1 study (*Haematologica*. 2017 Nov;102(11):1923-1930) in a combined analysis of MYC status per study definition, the following table, DOR, PFS, and overall survival (OS) plots (all times in months) are provided below.

Group	Total Responses	ORR		Median DOR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)
		Evaluable Population	ITT Population			
MYC-altered	14 (8 CR, 6 PR)	29% (14/48)	23% (14/60)	13.6 (2.1, NC)	1.4 (1.2, 2.1)	7 (3.0, NC)
Non-MYC-altered	3 (1 CR, 2PR)	18% (3/17)	14% (3/22)	8.8 (3.3, 14.3)	1.4 (1.3, 2.7)	6.3 (3.3, NC)
MYC unknown	2 (2 PR)	13% (2/16)	9% (2/23)	10.8 (1.4, 20.2)	1.3 (1.0, 2.3)	5.7 (3.4, 14.4)
All	19 (9 CR, 10 PR)	24% (19/81)	18% (19/105)	13.6 (1.4, 20.2)	1.4 (1.3, 1.5)	6.3 (3.9, 14.2)



Conclusions

- The Phase 2 results further support the hypothesis from the Phase 1 study that CUDC-907 treatment particularly benefits patients with MYC-altered disease.
- CUDC-907 treatment has demonstrated durable clinical activity in primarily MYC-altered patients, including double-hit and double-expressors.
- The biological rationale, tolerable safety profile, and evidence of lasting anti-tumor activity support the continued development of CUDC-907 in this population of high unmet need.