Phase 2, open-label study of CUDC-907 with and without rituximab in patients with relapsed/refractory MYC-altered diffuse large B-cell lymphoma

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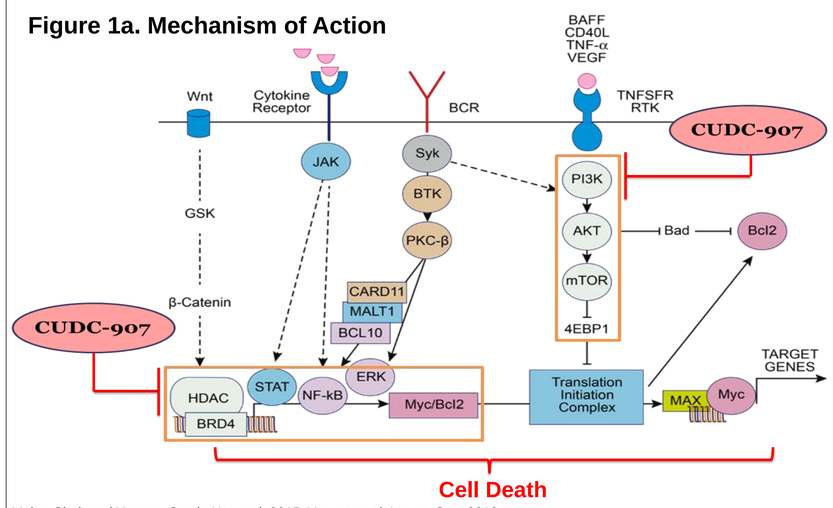
Introduction

- The prognosis for patients with relapsed and/or refractory MYC-altered DLBCL is dismal as they are often ineligible for or progress following autologous stem cell transplantation and respond poorly to subsequent therapies.
- Pharmacologic inhibition of HDAC and PI3K pathway activities has been shown to suppress MYC-driven oncogenic activities and represents a therapeutic option for these patients.

CUDC-907

- CUDC-907 is an orally bioavailable small molecule designed to target class I and II HDAC and class I PI3K enzymes 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.

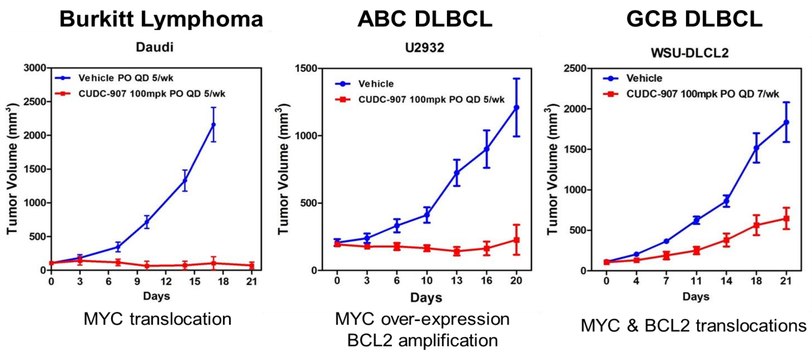
Figure 1a. Mechanism of Action



Mehta-Shah and Younes, Semin Hematol. 2015; Younes et al, Lancet Onc. 2016

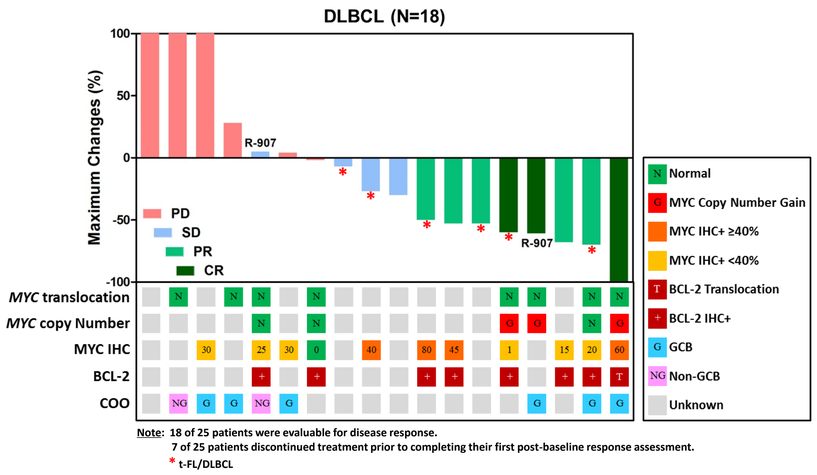
- In MYC-dependent DLBCL cell lines, treatment with CUDC-907, results in a rapid and dramatic decrease in MYC protein levels at single-digit nanomolar concentrations.

Figure 1b. *In vivo* efficacy in MYC+ Xenograft Models



- Safety and efficacy data from the completed dose escalation and ongoing expansion stages of a Phase 1 trial (CUDC-907-101) have demonstrated the therapeutic potential of CUDC-907 administered as monotherapy and in combination with rituximab, as objective responses were observed in patients with relapsed or refractory DLBCL, including a subset of patients with MYC-altered disease.

Figure 1c. Biomarker Analysis in RR DLBCL: CUDC-907 Phase 1 Trial



Note: 18 of 25 patients were evaluable for disease response.
7 of 25 patients discontinued treatment prior to completing their first post-baseline response assessment.
* t-FL/DLBCL

Younes et al, Blood. 2015

Study Rationale

- MYC family genes are among the most frequently deregulated oncogenic drivers in human cancers.
- Although MYC gene translocation, present in 5-17% of DLBCL cases, and protein overexpression, present in ~33% of DLBCL cases, can be mutually exclusive, both aberrations are associated with worse prognosis in patients with DLBCL.
- Patients with MYC-altered DLBCL have much shorter overall survival, usually measured in months. There is no standard of care for these patients and novel therapeutic approaches are needed.

Figure 2a. Overall survival of de novo DLBCL patients with MYC translocation vs. no MYC translocation, following RCHOP

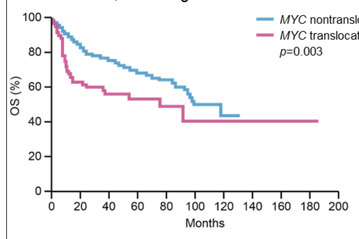
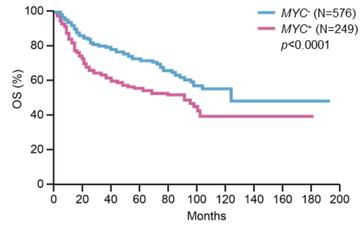


Figure 2b. Overall survival of de novo DLBCL patients with MYC expression vs. no MYC expression, following RCHOP



*MYC protein expression ≥70% by IHC. *Johnson et al, JCO 2012; Thieblemont and Biere, Blood. 2013; Xu-Monette et al., Mod Pathol. 2015; Ye et al, Oncotarget. 2015; Zhou et al, PloS One 2014*

Study Objectives

Primary	➢ To evaluate the efficacy of CUDC-907, as a monotherapy and in combination with rituximab (R-907), as measured by the overall response rate **(ORR)** in subjects with relapsed and/or refractory DLBCL with MYC-altered disease
Secondary	➢ To evaluate progression-free survival **(PFS), median PFS, and PFS at 6 months** ➢ To evaluate overall survival **(OS)** ➢ To evaluate the duration of response **(DOR)** ➢ To evaluate the incidence and severity of adverse events, serious adverse events, and other **safety** parameters in subjects receiving CUDC-907 and R-907 ➢ To characterize the **pharmacokinetics** of CUDC-907 alone and when administered in combination with rituximab
Exploratory	➢ To explore the effects of CUDC-907 and R-907 on disease-associated **biomarkers** ➢ To explore the relationship between disease-associated biomarkers including BCL2 and BCL6 in plasma and tumor tissues ➢ To explore biomarkers of response for patient selection

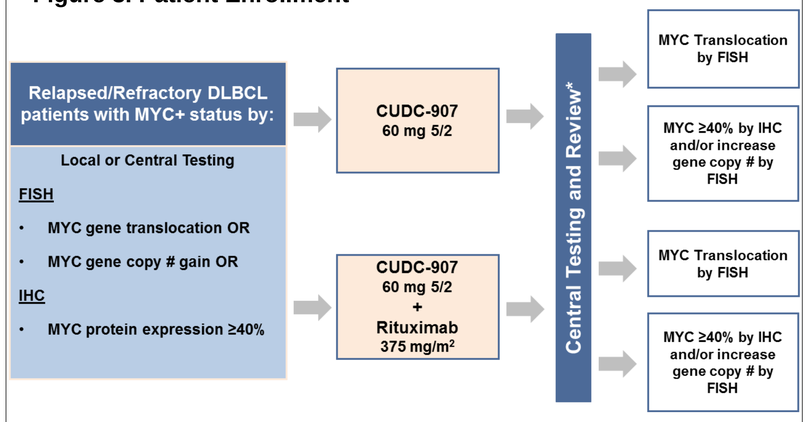
Study Design

Phase 2 open-label study evaluating CUDC-907 as monotherapy and in combination with rituximab in patients with MYC-altered DLBCL

- **Study Population**
  - This study will enroll patients with histopathologically confirmed diagnosis of DLBCL that is refractory to or relapsed after 2-4 prior regimens and have MYC positive status
  - MYC status will be determined from local testing, or central testing if local results are unavailable, based on fluorescence *in situ* hybridization (FISH) or immunohistochemistry (IHC)
  - Central testing will be conducted to confirm MYC status and patients will fall into one of two possible groups:
    - MYC gene translocation
    - MYC protein expression ≥40% and/or gene copy number gain
  - Patients who are MYC+ after local testing but who test negative for MYC upon central review will still be allowed to continue on the study
- **Treatment Arms**
  - Patients will be enrolled into one of two possible treatment arms:
    - CUDC-907 monotherapy
    - CUDC-907 in combination with rituximab (R-907)
  - Treatment cycles will consist of 21 days
  - Patients enrolled into either arm will receive oral CUDC-907 60 mg 5 days on/2 days off (5/2) in a continuous manner
  - Patients enrolled into R-907 will also receive intravenous rituximab 375 mg/m^2 on Day 1 of Cycles 1-6
- **Statistical Considerations**
  - A Simon 2-stage design will be used
- **Biomarker Analyses**
  - Changes in biomarkers related to the disease and/or targeted pathway will be analyzed
  - In addition to MYC, BCL2 and BCL6 will also evaluated for protein expression and gene translocation

Study Schematic

Figure 3. Patient Enrollment



*Patients who are MYC+ after local testing but who test negative for MYC upon central review will be allowed to continue on study

Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Known primary mediastinal, ocular, epidural, testicular, breast, or CNS involvement
Received 2-4 prior lines of therapy for DLBCL, including anthracycline, and ineligible for or failed SCT	Recent cytotoxic anticancer therapy or experimental therapy
Histopathologically confirmed diagnosis of RR DLBCL, including transformed follicular lymphoma, and presence of RR disease per Revised Response Criteria for Malignant Lymphoma	Current or planned glucocorticoid therapy, except for ≤ 1 mg/kg/day prednisolone or equivalent
Histopathologically confirmed MYC-altered disease by fresh or archival tumor samples	Graft vs host disease following transplant
Radiological evidence of measurable disease	Uncontrolled diabetes mellitus, serious cardiovascular disease, or serious infection
ECOG performance status ≤ 2	Other invasive malignancy

DLBCL – diffuse large B-cell lymphoma; ECOG – Eastern Cooperative Oncology Group; R/R – relapsed/refractory; SCT – stem cell transplant

Study Status

- This study was initiated in January 2016
- Target enrollment of 120 patients
- The estimated primary completion date is January 2018
- More information is available at www.clinicaltrials.gov (NCT02674750)

References

Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab pluscyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012 Oct 1;30(28):3452–3.

Mehta-Shah N, Younes A. Novel targeted therapies in diffuse large B-cell lymphoma. *Seminars in hematology.* 2015. 52(2):126-137. WB Saunders.

Thieblemont C, Brière J. MYC, BCL2, BCL6 in DLBCL: impact for clinics in the future? *Blood.* 2013;121(12):2165-6.

Xu-Monette ZY, Dabaja BS, Wang X, Tu M, Manyam GC, Tzankov A, et al. Clinical features, tumor biology, and prognosis associated with MYC rearrangement and Myc overexpression in diffuse large B-cell lymphoma patients treated with rituximab-CHOP. *Modern Pathology*. 2015.

Ye Q, Xu-Monette ZY, Tzankov A, Deng L, Wang X, Manyam GC, et al. Prognostic impact of concurrent MYC and BCL6 rearrangements and expression in de novo diffuse large B-cell lymphoma. *Oncotarget*. 2015.

Younes A, Berdeja JG, Patel MR, Kelly KR, Flinn IW, Gerecitano JF, et al. Phase 1 trial testing single agent CUDC-907, a novel, oral dual inhibitor of histone deacetylase (HDAC) and PI3K: initial assessment of patients with relapsed or refractory (RR) diffuse large B-cell lymphoma (DLBCL), including double expressor (DE) lymphoma. *Blood*. 2015;126(23):257.

Younes A, Berdeja JG, Patel MR, Flinn I, Gerecitano JF, Neelapu SS, et al. Safety, tolerability, and preliminary activity of CUDC-907, a first-in-class, oral, dual inhibitor of HDAC and PI3K, in patients with relapsed or refractory lymphoma or multiple myeloma: an open-label, dose-escalation, phase 1 trial. *The Lancet Oncology.* 2016;17(5):622-31.

Zhou K, Xu D, Cao Y, Wang J, Yang Y, Huang M. C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies. *PLoS One*. 2014 Apr 16;9(4):e95020.

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