Clinical activity of CC-99282, a novel, oral small molecule cereblon E3 ligase modulator (CELMoD) agent, in patients with relapsed/refractory non-Hodgkin lymphoma (R/R NHL) - results from CC-99282-NHL-001 (NCT03930953) a first-in-human, phase 1, open-label, multicenter study

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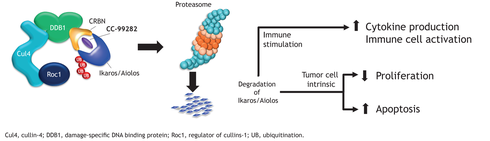
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Introduction

- CC-99282, a novel, small molecule CELMoD agent, co-opts cereblon (CRBN) and induces targeted ubiquitination and proteasome-mediated degradation of Ikaros and Aiolos, transcription factors critical for development of B-cell malignancies (**Figure 2**)
- In preclinical models, compared with IMiD and CELMoD agents, CC-99282 showed similar immunostimulatory effects, stronger antitumor activity, and robust distribution across tissue types[1]
  - CC-99282 exhibited 10- to 100-fold enhanced antiproliferative and apoptotic activity in a range of DLBCL cell lines, independent of subtype or chemotherapy-resistant status[1,2]

Figure 2. CC-99282 mechanism of action



Cul4, cullin-4; DDB1, damage-specific DNA binding protein; Roc1, regulator of cullins-1; UB, ubiquitination.

Objectives

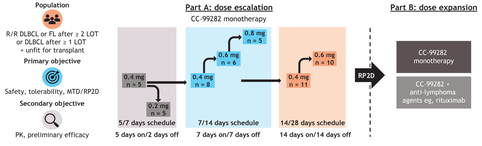
- To report first results from CC-99282-NHL-001 (NCT03930953), a multicenter, phase 1, open-label, dose-finding, first-in-human study evaluating CC-99282 in patients with R/R NHL. The study objectives are:
  - Primary: determine the safety, tolerability, maximum tolerated dose (MTD), and/or the recommended phase 2 dose (RP2D) of CC-99282 monotherapy in R/R NHL
  - Secondary: pharmacokinetics (PK) and preliminary efficacy of CC-99282
  - Exploratory: pharmacodynamics of CC-99282

Methods

Study Design

- This study consists of 2 parts, dose escalation of CC-99282 monotherapy (part A) and expansion with or without anti-lymphoma agents, eg, rituximab (part B) (**Figure 3**)
- Patients are dosed with oral CC-99282 once daily (QD) following 3 different intermittent dosing schedules of 28-day cycles, with ≥ 3 patients in each dosing cohort

Figure 3. CC-99282-NHL-001 study design (NCT03930953)



LOT, line of therapy.

Pharmacokinetic analysis

- The noncompartmental analysis (NCA) was conducted in Phoenix® /WinNonlin (v8, Certara, Sheffield, UK). Additional analyses and PK plots were generated using RStudio® (v1.4, RStudio PBC, Boston, MA, USA)

Pharmacodynamic analysis

- Flow cytometry was used to measure expression of Ikaros in peripheral CD3+ T cells and to assess immune stimulation by CC-99282 by measuring shifts in CD8+ T cell subsets
- Changes in circulating tumor DNA (ctDNA) levels in plasma samples were analyzed using a modified AVENIO workflow (for Research Use Only; not for use in diagnostic procedures) based on cancer personalized profiling by deep sequencing (CAPP-Seq) technology with a panel consisting of 466 genes relevant to NHL

Heatmap analysis

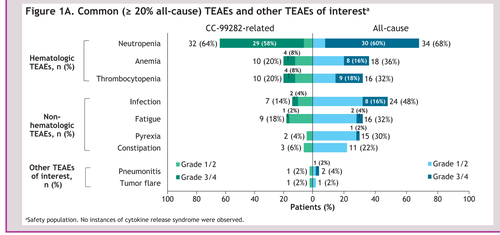
- The regiment count matrix was used to perform complete hierarchical clustering based on its Euclidean distance without considering neutropenia and dose schedule types

CC-99282 monotherapy showed a predictable and manageable safety profile during dose escalation and demonstrated promising efficacy in heavily pretreated patients with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL), with pharmacokinetic/pharmacodynamic data consistent with robust CC-99282-mediated antitumor activity

Safety

- Forty (80%) patients experienced ≥ 1 all-cause grade 3/4 treatment-emergent adverse event (TEAE) (**Figure 1A**)
- TEAEs of grade 3/4 related to CC-99282 were reported in 32 (64%) patients
  - Twenty nine (58%) patients experienced grade 3/4 neutropenia related to CC-99282, a class effect of CELMoD agents
  - Neutropenia was manageable with dose modifications and granulocyte colony-stimulating factor (G-CSF) support (31 [62%] patients)

Figure 1A. Common (≥ 20% all-cause) TEAEs and other TEAEs of interest[a]

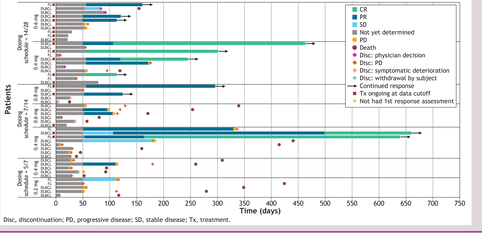


[a]Safety population. No instances of cytokine release syndrome were observed.

Efficacy

- At the tolerated schedules (7/14- and 14/28-days) of dose levels ≥ 0.4 mg, CC-99282 monotherapy demonstrated an overall response rate (ORR) of 42%
  - Among the 36 efficacy-evaluable patients, 15 had objective responses (6 follicular lymphoma [FL] and 9 diffuse large B-cell lymphoma [DLBCL]), including complete responses (CR) in 6 patients and partial responses (PR) in 9 patients (**Figure 1B**)

Figure 1B. Response over time

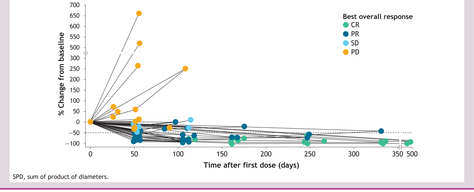


Disc, discontinuation; PD, progressive disease; SD, stable disease; Tx, treatment.

- Median time to response (TTR) was 53 days (range 50-107)[a] (**Figure 1C**)
- Responses were durable
  - 7/14 days dosing schedule: median duration of response[a] (DOR) was 239 (48-587) days with median follow-up time of 247 (21-690) days
  - 14/28 days dosing schedule: median DOR[b] was 112 (63-414) days with median follow-up time of 121 (22-464) days
- Patients showing objective responses included those who had prior treatment with cellular therapy and/or immunomodulatory imide drugs (IMiD®)/CELMoD agents

[a]Based on the time to response observed (not censored) values for responders, patients who did not respond are not included in this calculation.

Figure 1C. Change in SPD of target lesions over time



SPD, sum of product of diameters.

Results

Patients

- 50 eligible patients were treated in part A (38 DLBCL and 12 FL) (**Table 1**)
  - Sixteen (32%) patients had transformed FL and 7 (14%) were double-hit or triple-hit positive
- Enrolled patients in the study were heavily pretreated with a median of 3 prior lines of therapy (range 1-8) (**Table 1**)

Table 1. Patient baseline characteristics and treatment history

Characteristic	All patients (N = 50)
Age, median (range), years	65.5 (35-89)
Sex, male, n (%)	29 (58)
Diagnosis, n (%)	
DLBCL	38 (76)
NOS	22 (44)
Double-hit or triple-hit positive[a]	7 (14)
Transformed	16 (32)
FL (grade I to grade IIIB)	12 (24)
Time from initial diagnosis to first dose, median (range), months	
DLBCL	22.5 (4.5-94.5)
FL	(22.5-135.9)
ECOG performance status score, n (%)	
0	21 (42)
1	25 (50)
2	4 (8)
Stage IV cancer at diagnosis, n (%)	29 (58)
Treatment history	
No. of prior LOT, median (range)	3 (1-8)
Prior stem cell transplant, n (%)	10 (20)
Prior CAR T cell therapy, n (%)	14 (28)
Prior lenalidomide/avadomide treatment, n (%)	11 (22)
Refractory[b] to last regimen, n (%)	25 (50)

[a]Double-hit was defined as positive for MYC + BCL2 or MYC + BCL6 and triple-hit as positive for MYC + BCL2 + BCL6. [b]Refractory was defined as never having achieved an objective response (eg, SD or PD) to prior LOT; patients with short (< 6-month duration) responses to last therapy are not included in this definition. ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PD, progressive disease; SD, stable disease.

Treatment and safety

- The median treatment duration was 8.2 weeks (range 3.7-96.0). As of data cutoff date (Oct 6, 2021),
  - Seventeen (34%) patients were still on treatment
  - Twenty-six (52%) patients had discontinued treatment due to PD
- The most common grade 3/4 TEAEs related to CC-99282 were neutropenia (29 [58%] patients), anemia (4 [8%] patients), and thrombocytopenia (4 [8%] patients) (**Figure 1A**)
  - No patients permanently discontinued treatment with CC-99282 due to neutropenia
- All dose-limiting toxicities (DLT) observed within the DLT window for dose escalation decisions were hematologic (**Table 2**)
- Serious adverse events (SAE) were reported in 33 (66%) patients and included infections (11 [22%] patients; 4 [8%] of whom had pneumonia), febrile neutropenia (5 [10%] patients), and tumor pain (4 [8%] patients)
  - SAEs related to CC-99282 were reported in 8 (16%) patients, including 4 (8%) patients with febrile neutropenia
- Fourteen (28%) patients had ≥ 1 dose reduction of CC-99282
  - The median time to first dose reduction was 13.6 weeks

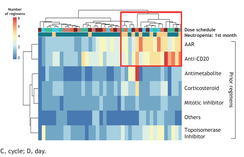
Table 2. DLTs by dose level

Characteristic	Dose	Patients (n)	DLTs
5/7 days	0.2 mg QD	5	-
	0.4 mg QD	5	2 patients: grade 4 neutropenia;[a] grade 3 febrile neutropenia
7/14 days	0.4 mg QD	8	1 patient: grade 4 neutropenia[a]
	0.6 mg QD	6	-
	0.8 mg QD	5	1 patient: grade 4 thrombocytopenia[b]
14/28 days	0.4 mg QD	11	2 patients: grade 4 neutropenia[a]
	0.6 mg QD	10	-

[a]Grade 4 neutropenia lasting > 7 days. [b]Grade 4 thrombocytopenia > 24 hours. [c]As of data cutoff, DLT assessment ongoing for 0.6 mg cohort for 14/28 day dosing schedule.

- Based on the Bayesian logistic regression model and review of the totality of data by the Safety Review Committee, the MTD from part A was 0.6 mg and 0.4 mg on 7/14 and 14/28 days dosing schedules, respectively
- Grade 4 neutropenia appears more associated with number of prior LOT than with dose and schedule of treatment with CC-99282 (**Figure 4**)
  - Specifically, rates are being driven by the number of prior lines of either alkylating agent regimen (AAR) and/or anti-CD20 therapy
  - Occurrence of grade 4 neutropenia in the first month following treatment with CC-99282 appeared to correlate with patients receiving ≥ 4 AAR as prior therapy, including the last AAR received within 3 months prior to the start of CC-99282 treatment

Figure 4. Correlation between grade 4 neutropenia during the first month of treatment and prior treatment regimens



C, cycle; D, day.

Dose schedule
0.4 mg 5d/28 | 0.4 mg 7/14 | 0.6 mg 7/14 | 0.8 mg 7/14 | 0.4 mg 14/28 | 0.6 mg 14/28

Neutropenia 1st month
Grade 4
Non-grade 4

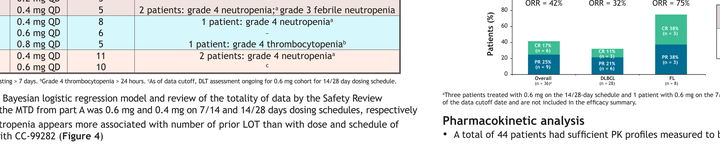
	CC-99282 C1D1 within 3 months of last AAR	CC-99282 C1D1 > 3 months after last AAR
Previously treated with ≥ 4 AAR		
Grade 4	83% (5)	33% (2)
Non-grade 4	17% (1)	67% (4)
Previously treated with < 4 AAR		
	CC-99282 C1D1 within 3 months of last AAR	CC-99282 C1D1 > 3 months after last AAR
Grade 4	0% (0)	19% (4)
Non-grade 4	100% (7)	81% (17)

C, cycle; D, day.

Efficacy

- At the tolerated schedules of dose levels ≥ 0.4 mg, CC-99282 monotherapy demonstrated an ORR of 42%, with 6 (17%) patients achieving CR (**Figure 5A**)
  - Of 28 patients with DLBCL, 9 (32%) patients achieved an objective response
  - Of 8 patients with FL, 6 (75%) achieved an objective response
  - Two patients treated on the 7/14 days dosing schedule achieved CR, while the ORR was 39% (**Figure 5B**)
  - Four patients treated on the 14/28 days dosing schedule achieved CR, while the ORR was 44% (**Figure 5B**)

Figure 5. Best overall response



[a]Three patients treated with 0.6 mg on the 14/28 day schedule and 1 patient with 0.6 mg on the 7/14-day schedule had no post-baseline assessments and were ongoing as of the data cutoff date and are not included in the efficacy summary.

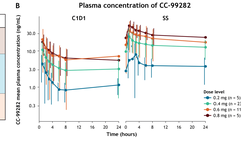
Pharmacokinetic analysis

- A total of 44 patients had sufficient PK profiles measured to be included in the PK analysis (**Figure 6**)
- The NCA of CC-99282 plasma concentrations showed that CC-99282 was rapidly absorbed (T_{max} = ~1 h) with a prolonged terminal half-life (median of ~50 h at doses ≥ 0.4 mg)
  - The data show dose-dependent exposure with overall dose-exposure proportionality
- CC-99282 plasma PK profiles and preliminary analyses revealed considerable distribution of CC-99282 to the peripheral compartment

Figure 6. Pharmacokinetic dose-level correlation

A Patients included in PK analysis per dose and schedule

Dose schedule	Dose	Patients (n)
5/7 days	0.2 mg QD	5
	0.4 mg QD	5
7/14 days	0.4 mg QD	8
	0.6 mg QD	5
	0.8 mg QD	5
14/28 days	0.4 mg QD	10
	0.6 mg QD	6

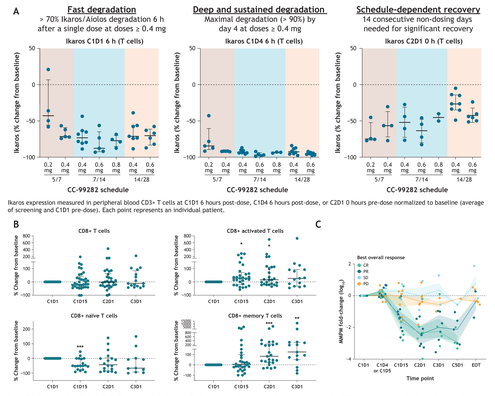


Data source: Unaudited PK data with cutoff date of September 17, 2021.
SS, steady state including nominal day 4/5, day 7, and day 14.

Pharmacodynamic analysis

- Increases in plasma CC-99282 and degradation of Ikaros/Aiolos in peripheral T cells occurred in a dose-dependent manner, and maximum degradation (> 90%) occurred by day 4 of treatment at doses ≥ 0.4 mg (**Figure 7A**)
- Within 2 weeks of initiating CC-99282, peripheral T cell subsets showed a significant shift toward a more activated phenotype, with an increase in activated and memory T cells and a decrease in naive T cells (**Figure 7B**)
- Analysis of single nucleotide variants in ctDNA showed a reduction in mutant ctDNA levels as early as C1D15 that correlated with response to CC-99282 treatment (**Figure 7C**)
  - Fast decrease in ctDNA suggests strong tumor cell-intrinsic activity in the clinic, however increase of activated CD8+ T cells may also be a significant contributor

Figure 7. Pharmacodynamics and circulating tumor DNA analyses following treatment with CC-99282



Ikaros expression measured in peripheral blood CD3+ T cells at C1D1 6 hours post-dose, C1D4 6 hours post-dose, or C2D1 0 hours pre-dose normalized to baseline (average of screening and C1D1 pre-dose). Each point represents an individual patient.

Figure 7B: Total peripheral blood CD8+ T cells and shifts in CD8+ T cell subsets (naive, activated, memory) analyzed at different time points. Absolute values for different subsets of CD8+ T cells were normalized as percentage of baseline (C1D1). Each point represents an individual patient. *P < 0.05; **P < 0.01; ***P < 0.001.

Figure 7C: Changes in ctDNA level in plasma samples are represented as $\log_{10}$ of MAPM normalized to pre-treatment samples (C1D1). Lines represent mean values. EOT, end of treatment; MAPM, mutant molecules per milliliter.

Conclusions

- CC-99282 as a single oral agent showed a manageable and predictable safety profile, dominated by the class effect of neutropenia, and promising efficacy (ORR 42%) in heavily pretreated patients with R/R NHL
- Pharmacodynamic data were consistent with promising CC-99282 antitumor activity and early responses correlated with a reduction in single nucleotide variants of tumor DNA
- Doses of 0.2 mg (14/28 days dosing schedule) and 0.4 mg (7/14 and 14/28 days dosing schedules) are continuing to be evaluated in the expansion phase
- This study is ongoing with patients actively being enrolled in the monotherapy expansion cohort and additional cohorts, including combination with rituximab and tafasitamab, coming next in part B

References

1. Lopez-Girona A, et al. *Hematol Oncol* 2021;39(suppl S2). Abstract 232.
2. Carrancio S, et al. Poster presentation at the American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021; Atlanta, GA, USA. Abstract 1200.

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