Efficacy and safety of golcadomide, a novel cereblon E3 ligase modulator (CELMoD) agent, combined with rituximab in a phase 1/2 open-label study of patients with relapsed/refractory non-Hodgkin lymphoma

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Introduction

- Golcadomide is a novel, oral, small-molecule CELMoD® agent that co-opts cereblon to induce targeted degradation of the transcription factors Ikaros/Aiolos, which are crucial to B-cell malignancy development[1] (**Figure 1**)
- Compared with existing agents targeting Ikaros/Aiolos, such as lenalidomide, avadomide, and iberdomide, golcadomide had 10- to 100-fold enhanced antiproliferative and apoptotic activity in preclinical models of diffuse large B-cell lymphoma (DLBCL), while maintaining immunostimulatory effects[2,3]
- We previously reported a predictable and manageable safety profile and promising efficacy of golcadomide in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL)[4]
- Here, we report efficacy and safety results from the CC-99282-NHL-001 trial for golcadomide + rituximab in patients with DLBCL treated in Part B expansion on a 14 days on/14 days off schedule (cohort C)

Methods

- CC-99282-NHL-001 (NCT03930953) is a 2-part, multicenter, first-in-human study with dose escalation (Part A) of golcadomide monotherapy and expansion (Part B) with golcadomide ± combination partners (**Figure 2**)
  - Patients with R/R DLBCL or R/R follicular lymphoma and disease progression after ≥ 2 lines of therapy or transplant-ineligible patients with R/R DLBCL after ≥ 1 line of therapy were included
  - Following dose exploration in Part A, golcadomide was administered at 0.2 or 0.4 mg alone or with rituximab on 2 intermittent schedules in Part B
  - Total duration of treatment is up to 2 years
- The efficacy-evaluable population consisted of patients completing ≥ 1 cycle of golcadomide (taking ≥ 75% of assigned doses) and having baseline and ≥ 1 post-baseline tumor assessment
- The safety population consisted of patients receiving ≥ 1 dose of golcadomide or rituximab
- 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 technology (CAPP-Seq) with a panel consisting of 466 genes relevant to NHL

Results

Baseline characteristics and patient disposition

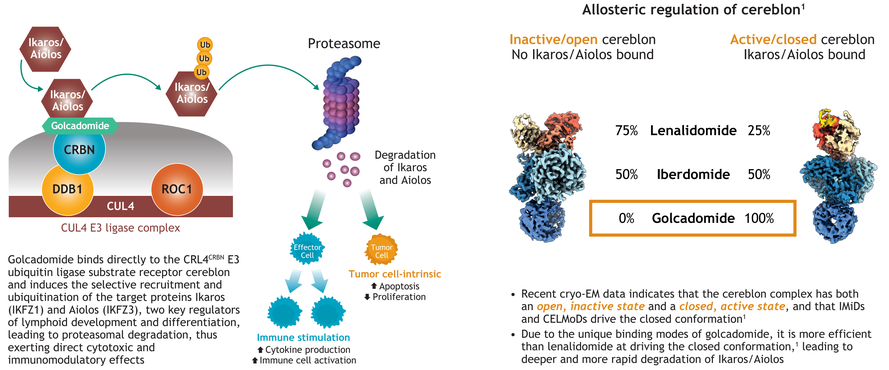
- Patient characteristics are shown in **Table 1**
- As of September 7, 2023, 46 patients with DLBCL were enrolled in cohort C, 44 of whom received ≥ 1 dose of golcadomide or rituximab (safety population)
  - The median age was 64 years (range, 20-86)
  - The median number of prior lines of systemic anti-cancer therapies was 4 (range, 1-11)
  - 61% (n/N = 27/44) of patients had received prior chimeric antigen receptor (CAR) T-cell therapy
  - 26% (n/N = 12/46) achieved an objective response to their last regimen

Table 1. Demographics and baseline characteristics

Characteristic	Part B cohort C Golcadomide + RTX (N = 46)
Age, years, median (range)	64 (20-86)
Sex, male, n (%)	30 (65)
Diagnosis, n (%)[a]	
DLBCL	43 (93)
Double-hit positive[b]	3 (7)
Triple-hit positive[c]	3 (7)
Cell of origin, n (%)	
GCB	11 (24)
ABC	7 (15)
Unknown[d]	28 (61)
Time from initial diagnosis to first dose, months, median (range)	23 (1-219)
ECOG PS score, n (%)	
0	15 (33)
1	24 (52)
2	5 (11)
Treatment history	
No. of prior lines of systemic anti-cancer therapy, median (range)	4 (1-11)
Prior stem cell transplant, n/N (%)[e]	5/44 (11)
Prior CAR T cell therapy, n/N (%)[e]	27/44 (61)
Best response to last regimen, n (%)[a]	
CR or PR	12 (26)
Never achieved objective response	24 (52)
Missing/unknown	7 (15)

Data cutoff: September 7, 2023.
[a]Diagnosis and prior therapies missing for 3 patients. [b]Double hit is defined as positive case of MYC + BLC2 or MYC + BCL6. [c]Triple hit is defined as positive case of MYC + BCL2 + BCL6. [d]Includes unclassified, not done, unknown, and missing. [e]Data are from the safety population of n = 44.
ABC, activated B-cell-like; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; PR, partial response; RTX, rituximab.

Figure 1. Golcadomide is a potent first-in-class lymphoma CELMoD with pleotropic MoA

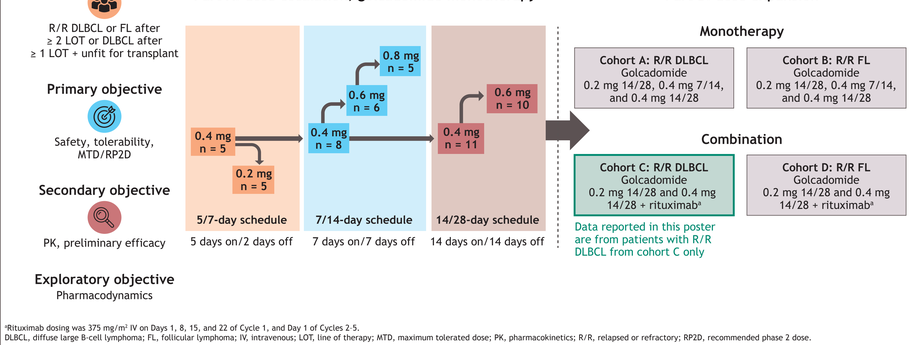


Golcadomide binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor cereblon and induces the selective recruitment and ubiquitination of the target proteins Ikaros (IKFZ1) and Aiolos (IKFZ3), two key regulators of lymphoid development and differentiation, leading to proteasomal degradation, thus exerting direct cytotoxic and immunomodulatory effects

- Recent cryo-EM data indicates that the cereblon complex has both an *open, inactive state* and a *closed, active state*, and that IMiDs and CELMoDs drive the closed conformation[1]
- Due to the unique binding modes of golcadomide, it is more efficient than lenalidomide at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; cryo-EM, cryogenic electron microscopy; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IMiD, immunomodulatory drug; MoA, mechanism of action; ROC1, regulator of cullins 1; Ub, ubiquitin.

Figure 2. CC-99282-NHL-001 study design



[a]Rituximab dosing was 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-5.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; LOT, line of therapy; MTD, maximum tolerated dose; PK, pharmacokinetics; R/R, relapsed or refractory; RP2D, recommended phase 2 dose.

- Fourteen (30%) patients were ongoing and 30 (65%) had discontinued treatment, mostly due to progressive disease (PD; n = 21, 46%, **Table 2**)
  - Four patients (9%) died (all due to grade 5 treatment-emergent adverse events [TEAEs])
  - One patient (2%) discontinued treatment due to non-fatal TEAE (grade 4 thrombocytopenia)

Table 2. Patient disposition

Treatment disposition, n (%)	Part B cohort C Golcadomide + RTX (N = 46[a])
Ongoing	14 (30)
Discontinued	30 (65)
Primary reason for discontinuation	
Progressive disease	21 (46)
Death	4 (9)[b]
Lack of efficacy	2 (4)
Withdrawal by patient	1 (2)
Lost to follow-up	1 (2)
Adverse event	1 (2)[c]

[a]Two patients were enrolled but not treated. [b]Four patients died, all due to grade 5 TEAEs. [c]One patient discontinued treatment due to non-fatal TEAE (grade 4 thrombocytopenia).
RTX, rituximab; TEAE, treatment-emergent adverse event.

Efficacy

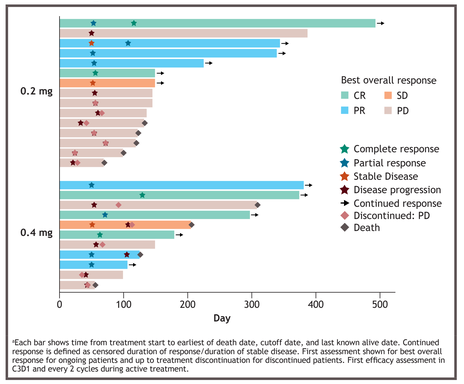
- Median duration of golcadomide treatment was 8 weeks (range, 2.4-68), and median follow-up was 5.9 weeks (range, 0.3-16.2)
- In the efficacy-evaluable population (n = 26), overall response rate (complete response [CR] + partial response [PR]) was 42% (n = 11), with CR occurring in 19% (n = 5) of patients (**Table 3**)
- Median duration of response was 7.5 months (range, 1.8-14.5), including a durable response > 14 months in 1 patient (**Figure 3**)
- Median time to response in efficacy evaluable patients with response (n = 11) was 1.81 months (range, 1.7-4.3)

Table 3. Best overall response in the efficacy evaluble population at the 0.2-mg and 0.4-mg doses

Response, n (%)	Efficacy-evaluable population		
	0.2 mg (n = 15)	0.4 mg (n = 11)	Overall (n = 26)
Overall response rate	5 (33)	6 (55)	11 (42)
Complete response 95% CI	2 (13) 1.7-40.5	3 (27) 6.0-61.0	5 (19) 6.6-39.4
Partial response 95% CI	3 (20) 4.3-48.1	3 (27) 6.0-61.0	6 (23) 9.0-43.6
Stable disease 95% CI	1 (7) 0.2-31.9	1 (9) 0.2-41.3	2 (8) 0.9-25.1
Progressive disease 95% CI	9 (60) 16.3-67.7	4 (36) 30.8-89.1	13 (50) 29.9-70.1

CI, confidence interval.

Figure 3. Disposition for individual efficacy evaluable patients at 0.2 and 0.4mg doses[a]

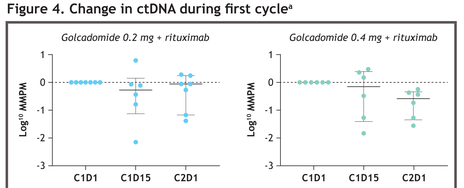


[a]Each bar shows time from treatment start to earliest of death date, cutoff date, and last known alive date. Continued response is defined as censored duration of response/duration of stable disease. First assessment shown for best overall response for ongoing patients and up to treatment discontinuation for discontinued patients. First efficacy assessment in C3D1 and every 2 cycles during active treatment.

ctDNA

- Longitudinal plasma samples were analyzed using AVENIO ctDNA NHL Analysis Workflow. As previously reported, reduction in the single nucleotide variants correlated with response to golcadomide[5]
- In patients with ctDNA data available (n = 13), reduction in mutant molecules per ml (MMPM) from baseline at the end of cycle 1 (Cycle 2 Day1) was more pronounced in patients treated with rituximab plus golcadomide at 0.4 mg than at 0.2 mg (**Figure 4**)

Figure 4. Change in ctDNA during first cycle[a]



[a]Data shown are for patients treated with 0.2 mg golcadomide + rituximab (Cohort C1; n = 7) and patients treated with 0.4 mg golcadomide + rituximab (Cohort C2; n=6).
MMPM, mutant molecules per ml.

Safety

- In the safety population (n = 44), neutropenia was the most common any-grade TEAE, occurring in 22 (50%) patients, all of which were grade 3/4 (**Table 4**)
  - All neutropenia was considered related to golcadomide, comprising 10/24 (42%) patients treated at the 0.2-mg and 12/20 (60%) patients treated at the 0.4-mg dose level (**Table 5**)
  - Febrile neutropenia occurred in 2 (5%) patients, 1 patient at each dose level
  - Granulocyte colony-stimulating factors were used in 22 (50%) patients
- Six patients had serious adverse events (SAEs) related to golcadomide; the only SAEs occurring in > 1 patient were pneumonia and pyrexia (both n = 2)
- Four grade 5 TEAEs occurred (infection, n = 3; tubulo-interstitial nephritis, n = 1); only 1 (pneumonia) was considered related to study treatment
- TEAEs led to golcadomide discontinuation in 5 (11%) patients (0.2 mg, n = 3; 0.4 mg, n = 2) and rituximab discontinuation in 5 (11%) patients

Table 4. TEAEs reported in ≥ 4 patients (safety population)

TEAE, n (%)	Golcadomide + RTX (n = 44)	
	Any grade	Grade 3/4
Patients with at least one TEAE	38 (86)	32 (73)
Neutropenia	22 (50)	22 (50)
Infections[a]	20 (46)	8 (18)
Constipation	10 (23)	0
Anemia	10 (23)	5 (11)
Thrombocytopenia	8 (18)	5 (11)
Dyspnea	8 (18)	0
Pyrexia	6 (14)	1 (2)
Fatigue	5 (11)	1 (2)
Diarrhea	5 (11)	0
Asthenia	4 (9)	1 (2)
Lymphopenia	4 (9)	1 (2)

[a]Infections are reported from entire system organ class. Infections occurring in ≥ 4 patients included COVID-19 (n = 6, 14%), pneumonia (n = 4, 9%), and bronchitis (n = 4, 9%).
COVID-19, coronavirus disease 2019; RTX, rituximab; TEAE, treatment-emergent adverse event.

Table 5. TEAEs related to golcadomide reported in ≥ 2 patients at the 0.2-mg and 0.4-mg doses

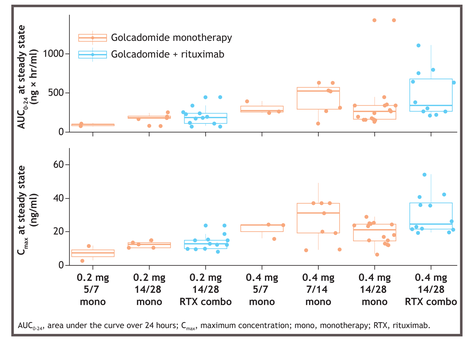
TEAE, n (%)	Golcadomide 0.2 mg + RTX (n = 24)		Golcadomide 0.4 mg + RTX (n = 20)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with at least one TRAE	16 (67)	11 (46)	14 (70)	12 (60)
Neutropenia	10 (42)	10 (42)	12 (60)	12 (60)
Diarrhea	4 (17)	0	0	0
Constipation	2 (8)	0	2 (10)	0
Anemia	1 (4)	0	3 (15)	3 (15)
Asthenia	2 (8)	1 (4)	1 (5)	0
Fatigue	1 (4)	0	2 (10)	1 (5)
Pyrexia	1 (4)	0	2 (10)	1 (5)
Lymphopenia	0	0	3 (15)	0
Thrombocytopenia	0	0	3 (15)	3 (15)

RTX, rituximab; TRAE, treatment-related adverse event.

Pharmacokinetics (PK)

- Similar PK exposures of golcadomide were observed when golcadomide was dosed alone and in combination with rituximab, indicating no apparent impact of rituximab on golcadomide PK (**Figure 5**)

Figure 5: Comparable exposures of golcadomide when administered as monotherapy vs combined with rituximab



AUC$_{ss}$, area under the curve over 24 hours; C$_{max}$, maximum concentration; mono, monotherapy; RTX, rituximab.

Conclusions

- Golcadomide oral therapy combined with rituximab showed promising efficacy in heavily pretreated patients with R/R DLBCL, including those resistant to chemotherapy and CAR T cell therapy, with an overall response rate of 42% and a CR rate of 19% in the efficacy evaluable population
- Golcadomide can be safely combined with rituximab, and the combination showed a safety profile similar to that previously reported for golcadomide monotherapy
  - When combined with rituximab, similar safety profiles were observed for both the 0.2-mg and 0.4-mg dose levels of golcadomide
  - Neutropenia was the most common TRAE
- ctDNA was identified as a potential biomarker for response in patients treated with golcadomide + rituximab
  - ctDNA levels decreased from baseline in responding patients and may serve as a biomarker for monitoring MRD
- This study is ongoing, with patient enrolment continuing in the monotherapy and golcadomide + rituximab combination expansion cohorts in R/R DLBCL and R/R follicular lymphoma

References

1. Watson ER, et al. *Science* 2022;378:549-553.
2. Lopez-Girona A, et al. *Hematol Oncol* 2021;39(suppl S2). Abstract 232.
3. Carrancio S, et al. Poster presentation at the American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021; Atlanta, GA, USA. Abstract 1200.
4. Michot JM, et al. Oral presentation at the International Conference on Malignant Lymphoma (ICML) Annual Meeting; June 13-17, 2023; Lugano, Italy. Abstract 90.
5. Michot JM, et al. *Blood* 2021;138(suppl 1). Abstract 3574.

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