Golcadomide, a potential, first-in-class, oral CELMoD ± rituximab in the phase 1/2 CC-99282-NHL-001 study: long-term follow-up results of patients with relapsed/refractory follicular lymphoma

IBCL-141

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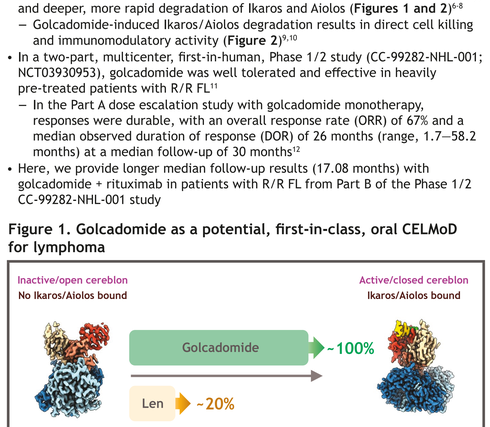
Introduction

- While outcomes in patients with relapsed/refractory (R/R) follicular lymphoma (FL) have improved since the availability of T-cell—redirecting therapies, such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies, there remains an unmet need for safe, efficacious, and easier-to-administer chemotherapy-free treatments[1-5]
- Golcadomide is a potential, first-in-class, oral cereblon (CRBN) E3 ligase modulator (CELMoD) for lymphoma with preferential lymphoid distribution and enhanced activity in lymphoma cell lines[6]
- Both lenalidomide and golcadomide bind CRBN and modulate its activity to induce target protein degradation. Golcadomide's unique structure enables distinct binding outside the tri-tryptophan pocket of CRBN inducing complete conversion to the active, closed conformation vs lenalidomide (~100% vs ~20%), and deeper, more rapid degradation of Ikaros and Aiolos (**Figures 1 and 2**)[6-8]
  - Golcadomide-induced Ikaros/Aiolos degradation results in direct cell killing and immunomodulatory activity (**Figure 2**)[9,10]
- In a two-part, multicenter, first-in-human, Phase 1/2 study (CC-99282-NHL-001; NCT03930953), golcadomide was well tolerated and effective in heavily pre-treated patients with R/R FL[11]
  - In the Part A dose escalation study with golcadomide monotherapy, responses were durable, with an overall response rate (ORR) of 67% and a median observed duration of response (DOR) of 26 months (range, 1.7—58.2 months) at a median follow-up of 30 months[12]
- Here, we provide longer median follow-up results (17.08 months) with golcadomide + rituximab in patients with R/R FL from Part B of the Phase 1/2 CC-99282-NHL-001 study

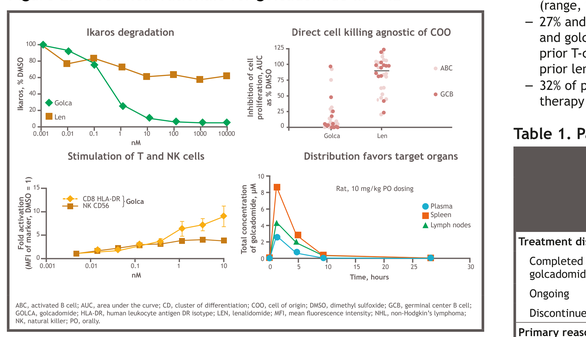
Figure 1. Golcadomide as a potential, first-in-class, oral CELMoD for lymphoma



- Golcadomide's unique structure extends distinct binding to outside the tri-TRP pocket of cereblon, inducing complete conversion to the active, closed conformation vs lenalidomide (~**100%** vs ~**20%**)[6]
- Golcadomide preferentially distributes to lymphoid tissue[6]

Len, lenalidomide; TRP, tryptophan.

Figure 2. Preclinical rationale for golcadomide in NHL

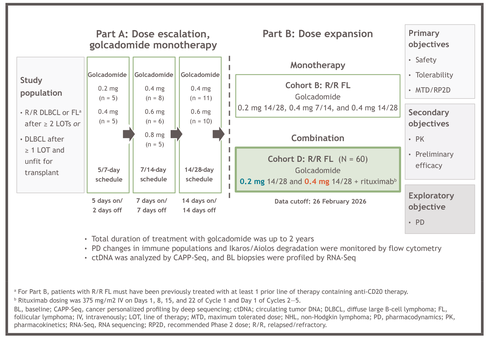


ABC, activated B cell; AUC, area under the curve; CD, cluster of differentiation; COO, cell of origin; DMSO, dimethyl sulfoxide; GCB, germinal center B cell; GOLCA, golcadomide; HLA-DR, human leukocyte antigen DR isotype; LEN, lenalidomide; MFI, mean fluorescence intensity; NHL, non-Hodgkin's lymphoma; NK, natural killer; PO, orally.

Methods

- CC-99282-NHL-001 is a two-part, multicenter, first-in-human study of dose escalation (Part A) of golcadomide monotherapy and expansion (Part B) with golcadomide ± combination partners (**Figure 3**)
  - Patients with R/R FL and disease progression after ≥ 2 lines of therapy (LOTs), or after ≥1 prior LOT containing anti-CD20 therapy in Part B, were included
  - Following dose escalation in Part A, golcadomide was dosed orally once daily at 0.2 mg or 0.4 mg (14 days on/14 days off) + rituximab in Part B (dose expansion)
  - The total duration of treatment with golcadomide was up to 2 years or until disease progression or unacceptable toxicity occurred
  - Primary objectives included safety and determination of the recommended Phase 2 dose
- 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
- Flow cytometry was used to assess immune modulation by golcadomide by measuring shifts across T-cell populations. Paired tumor biopsies were used for RNA exome sequencing (50 M 50 bp PE). Pathway enrichment analysis was performed using the single-sample gene set variation analysis method

Figure 3. Study design



[a] For Part B, patients with R/R FL must have been previously treated with at least 1 prior line of therapy containing anti-CD20 therapy.
[b] Rituximab dosing was 375 mg/m2 IV on Days 1, 8, 15, and 22 of Cycle 1 and Day 1 of Cycles 2–5.
BL, baseline; CAPP-Seq, cancer personalized profiling by deep sequencing; ctDNA; circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenously; LOT, line of therapy; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RNA-Seq, RNA sequencing; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

Results

Patient disposition and baseline characteristics

- Patient disposition is shown in **Table 1**
- As of 26 February 2026, 60 patients were treated with golcadomide + rituximab in Part B Cohort D
- Patients were similar in terms of age, sex, diagnosis, treatment history, and other features across the study parts (**Table 2**)
  - The median time from diagnosis to treatment was 60 months (range, 15—203) at golcadomide 0.2 mg + rituximab and 59 months (range, 10—420) at golcadomide 0.4 mg + rituximab
  - Patients receiving golcadomide + rituximab had received a median of 3 (range, 1—12) prior lines of therapy (LOT) at both doses
  - 27% and 29% of patients at the golcadomide 0.2 mg + rituximab and golcadomide 0.4 mg + rituximab doses, respectively, had received prior T-cell—redirecting therapy, and 32% at both doses had received prior lenalidomide
  - 32% of patients at both doses had disease that was refractory to their last therapy regimen

Table 1. Patient disposition

	Part B Cohort D		
	Golcadomide 0.2 mg + RTX (n = 22)	Golcadomide 0.4 mg + RTX (n = 38)	Overall (N = 60)
Treatment disposition, n (%)			
Completed 2 years of golcadomide tx	2 (9)	2 (5)	4 (7)
Ongoing	3 (14)	12 (32)	15 (25)
Discontinued	17 (77)	24 (63)	41 (68)
Primary reason for tx discontinuation, n (%)			
Progressive disease	11 (50)	5 (13)	16 (27)
Physician decision	1 (5)	7 (18)	8 (13)
Symptomatic deterioration	0	0	0
Adverse event	2 (9)	7 (18)	9 (15)
Death[a]	3 (14)	2 (5)	5 (8)
Withdrawal by patient	0	2 (5)	2 (3)
Loss to follow-up	0	1 (3)	1 (2)
Lack of efficacy	0	0	0
Disease relapse	0	0	0
Pregnancy	0	0	0

[a] Sudden death (n = 1), meningitis listeria (n = 1), pneumonia (n = 1), respiratory failure (n = 1), not coded (n = 1). RTX, rituximab, tx, treatment.

Table 2. Baseline characteristics

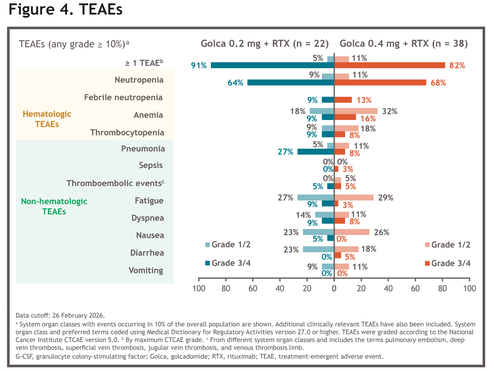
Characteristic	Part B Cohort D	
	Golcadomide 0.2 mg + RTX (n = 22)	Golcadomide 0.4 mg + RTX (n = 38)
Age, median (range), years	55 (33—83)	63.5 (38—82)
Sex, male, n (%)	10 (46)	20 (53)
Diagnosis, n (%)		
FL Stage III—IV	18 (82)	33 (87)
Time from initial diagnosis to first dose, median (range), months	60 (15—203)	59 (10—420)
ECOG PS, n (%)		
0	10 (46)	18 (47)
1	11 (50)	20 (53)
2	1 (5)	0
Treatment history		
Number of median prior LOTs (range)	3 (1—9)	3 (1—12)
Prior T-cell-redirecting therapy (CAR T and/or bispecific antibodies), n (%)	6 (27)	11 (29)
Prior lenalidomide treatment, n (%)	7 (32)	12 (32)
Best response to last regimen, n (%)		
Refractory	7 (32)	12 (32)
CR or PR	12 (55)	19 (50)
Unknown	3 (14)	7 (18)

CAR, chimeric antigen receptor; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LOT, line of therapy; PR, partial response; R/R, relapsed/refractory; RTX, rituximab.

Safety

- In the safety population, neutropenia was the most frequent Grade 3/4 treatment-emergent adverse event (TEAE), occurring in 64% of patients at the golcadomide 0.2 mg + rituximab dose and 68% at the golcadomide 0.4 mg + rituximab dose (**Figure 5**)
  - Neutropenia is an expected, on-target effect due to Ikaros degradation in neutrophil precursors
  - Neutropenia was transient and manageable with Granulocyte Colony-Stimulating Factor (G-CSF) support; 59% and 68% of patients at the golcadomide 0.2 mg + rituximab dose and golcadomide 0.4 mg + rituximab dose, respectively, received G-CSF treatment
  - The median time to neutrophil recovery was 8 days at both doses
  - Rates of febrile neutropenia and pneumonia/sepsis remained low
- Golcadomide dose reductions were mostly due to neutropenia (17%) and febrile neutropenia (5%)
- Golcadomide dose interruptions were mostly due to infections (48%) and neutropenia (32%)
- There were no Grade 5 AEs related to golcadomide

Figure 4. TEAEs

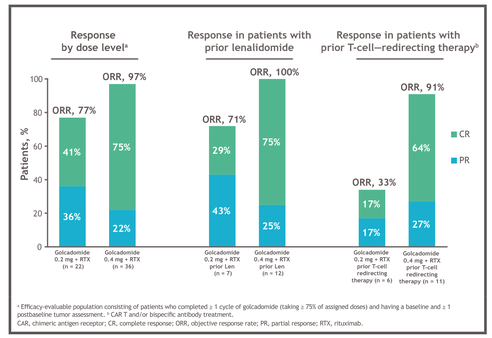


Data cutoff: 26 February 2026.
[a] System organ classes with events occurring in 10% of the overall population are shown. Additional clinically relevant TEAEs have also been included. System organ class and preferred terms coded using Medical Dictionary for Regulatory Activities version 27.0 or higher. TEAEs were graded according to the National Cancer Institute CTCAE version 5.0. [b] By maximum CTCAE grade. [c] From different system organ classes and includes the terms pulmonary embolism, deep vein thrombosis, superficial vein thrombosis, jugular vein thrombosis, and venous thrombosis limb.
G-CSF, granulocyte colony-stimulating factor; Golca, golcadomide; RTX, rituximab; TEAE, treatment-emergent adverse event.

Efficacy

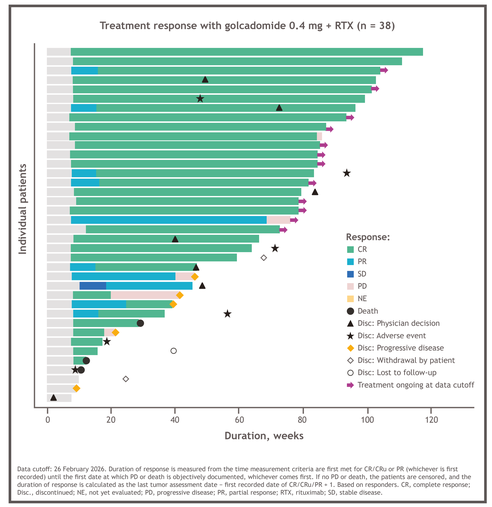
- In efficacy-evaluable patients the ORR was 97% (complete response rate [CRR], 75%) in the 0.4 mg golcadomide + rituximab group (n = 36) (**Figure 5**)
  - The ORR and CRR in high-risk subsets, including patients with prior treatment with lenalidomide and/or T-cell-redirecting therapy, were consistent with the results in the overall 0.4 mg golcadomide + rituximab treatment group
  - At a median follow-up of 18.0 months (range, 2.8—28.3) in responders, the median time to response was 1.9 months (range, 1.6—4.2) and the median DOR was 14.16 months (range, 0.0—24.7) (**Figure 6**)
  - 23/27 patients who achieved a CR remained in CR at the time of data cutoff
  - 29 patients had responses lasting > 12 months (**Figure 6**)

Figure 5. Overall response



[a] Efficacy-evaluable population consisting of patients who completed ≥ 1 cycle of golcadomide (taking ≥ 75% of assigned doses) and having a baseline and ≥ 1 postbaseline tumor assessment. [b] CAR T and/or bispecific antibody treatment.
CAR, chimeric antigen receptor; CR, complete response; ORR, objective response rate; PR, partial response; RTX, rituximab.

Figure 6. Treatment response

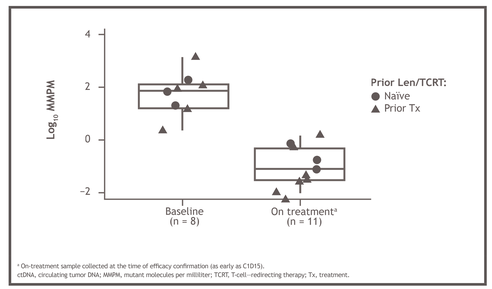


Data cutoff: 26 February 2026. Duration of response is measured from the time measurement criteria are first met for CR/CRu or PR (whichever is first recorded) until the first date at which PD or death is objectively documented, whichever comes first. If no PD or death, the patients are censored, and the duration of response is calculated as the last tumor assessment date – first recorded date of CR/CRu/PR + 1. Based on responders. CR, complete response; Disc., discontinued; NE, not yet evaluated; PD, progressive disease; PR, partial response; RTX, rituximab; SD, stable disease.

ctDNA analysis

- Golcadomide 0.4 mg + rituximab drives ctDNA reductions in heavily pre-treated patients, including those with prior Len or T-cell—redirecting therapy exposure (**Figure 7**)

Figure 7. ctDNA reduction with golcadomide 0.4 mg

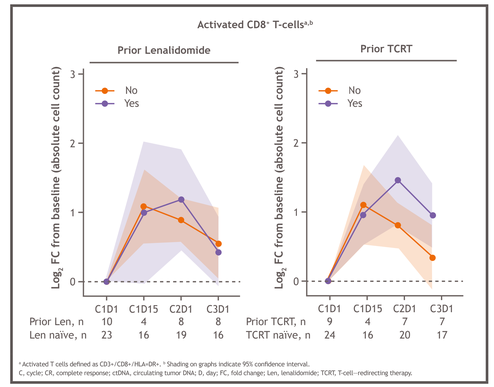


[a] On-treatment sample collected at the time of efficacy confirmation (as early as C1D15).
ctDNA, circulating tumor DNA; MMPM, mutant molecules per milliliter; TCRT, T-cell—redirecting therapy; Tx, treatment.

Immune modulation

- Golcadomide 0.4 mg + rituximab induces immune activation, independent of prior lenalidomide or T-cell—redirecting therapy exposure, as shown by the increase of activated CD8+ T-cells (**Figure 8**)

Figure 8. Immune modulation with golcadomide 0.4 mg



[a] Activated T cells defined as CD3+/CD8+/HLA-DR+. [b] Shading on graphs indicate 95% confidence interval.
C, cycle; CR, complete response; ctDNA, circulating tumor DNA; D, day; FC, fold change; Len, lenalidomide; TCRT, T-cell—redirecting therapy.

Conclusions

- Golcadomide + rituximab continued to demonstrate a predictable and manageable safety profile, similar to that reported previously; no new safety signals were observed with longer follow-up
  - TEAEs were mainly hematologic, with low rates of non-hematologic toxicity
- Golcadomide 0.4 mg + rituximab showed promising efficacy, with 97% ORR and 75% CRR in heavily pre-treated patients with R/R FL
  - Durable responses were observed, including in those with prior Len and/or T-cell—redirecting therapy
- Golcadomide 0.4 mg + rituximab resulted in strong ctDNA reductions and T-cell activation independent of prior Len or T-cell—redirecting therapy
- These data continue to support the ongoing Phase 3 GOLSEEK-4 study evaluating golcadomide 0.4 mg + rituximab as a fixed-duration, chemotherapy-free, outpatient option for patients with 2L + FL (NCT06911502)[13]

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