ABCL-1115

Golcadomide, a CELMoD™ agent, ± rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma: updated Phase 1/2 study results

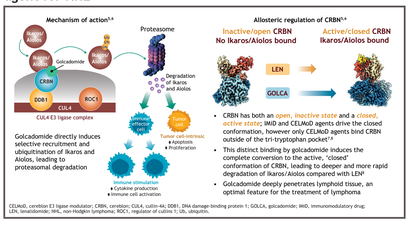
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Introduction

- Approximately 40% of patients with diffuse large B-cell lymphoma (DLBCL) experience relapse after initial treatment with standard-of-care chemo-immunotherapy[1]
- Effective treatment options are limited for patients who experience first-line treatment failure, particularly for those with relapsed or refractory (R/R) disease following CAR T-cell therapy or those not able to receive CAR T-cell therapy
- Golcadomide is a potential, first-in-class, oral CELMoD agent designed for the treatment of lymphoma, with preferential distribution to lymphoid organs and enhanced activity in lymphoma cell lines. Golcadomide drives the closed, active conformation of cereblon to induce rapid and deep degradation of Ikaros and Aiolos, leading to direct cell killing (agnostic of cell of origin) and immunomodulatory activity (**Figure 1**)[1]
- In the first-in-human Phase 1/2 study (NCT03930953), golcadomide was well tolerated and effective in patients with R/R DLBCL, with circulating tumor DNA (ctDNA) level reductions as early as Cycle 1 Day 15 correlating with response[4]
- Here, we report longer follow-up results with golcadomide + rituximab in patients with R/R DLBCL from Part B of the Phase 1/2 CC-99282-NHL-001 trial

Figure 1. Golcadomide is a potential, first-in-class, oral CELMoD agent for NHL

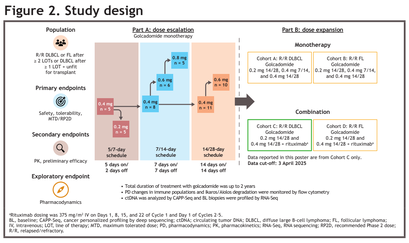


- CRBN has both an *open, inactive state* and a *closed, active state*; IMiD and CELMoD agents drive the closed conformation, however only CELMoD agents bind CRBN outside of the tri-tryptophan pocket[1,4]
- This distinct binding by golcadomide induces the complete conversion to the active, 'closed' conformation of CRBN, leading to deeper and more rapid degradation of Ikaros/Aiolos compared with LEN[4]
- Golcadomide deeply penetrates lymphoid tissue, an optimal feature for the treatment of lymphoma

Methods

- CC-99282-NHL-001 is an ongoing, multicenter, open-label, Phase 1/2 study of golcadomide alone and in combination with rituximab in patients with R/R non-Hodgkin lymphoma (NHL) (**Figure 2**)
  - Patients with R/R DLBCL and disease progression after ≥ 2 lines of therapy or transplant-ineligible patients after ≥ 1 line of therapy were included
  - Following dose escalation in Part A, golcadomide was dosed orally once daily at 0.2 or 0.4 mg (14 days on/14 days off) + rituximab in Part B (dose expansion)
  - The total golcadomide treatment duration was ≤ 2 years or until progressive disease (PD) or unacceptable toxicity
  - Primary objectives included safety and determination of the recommended Phase 2 dose (RP2D)
- The efficacy-evaluable population consisted of patients completing ≥ 1 cycle of golcadomide (taking ≥ 75% of assigned doses) and having a baseline and ≥ 1 postbaseline tumor assessment
- The safety population consisted of patients receiving ≥1 dose of golcadomide or rituximab
- Changes in 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

Figure 2. Study design



*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, biomarker; CAPP-Seq, cancer personalized profiling by deep sequencing; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; LOT, line of therapy; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; RNA-Seq, RNA sequencing; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory.

Results

Baseline characteristics and patient disposition

- As of 3 April 2025, 77 patients (golcadomide 0.2 mg + rituximab, n = 39; golcadomide 0.4 mg + rituximab, n = 38) with R/R DLBCL were included in the safety population (**Table 1**)
  - The median age was 66 years (range, 20-86 years)
  - The median number of prior lines was 4 (range, 1-11)
  - 55% of patients had prior CAR T-cell therapy, and 38% had prior bispecific antibody therapy; ≥ 44% were refractory to their last line of therapy
- At the time of the data cut-off, treatment was ongoing in 10 patients (13%), and 4 patients had completed 2 years of treatment
  - Sixty-three patients (82%) had discontinued treatment, mostly due to progressive disease (n = 43; 56%) (**Table 2**)

Table 1. Demographic and baseline characteristics

Characteristic	Part B Cohort C: Golcadomide 0.4 mg + RTX (n = 38)	Part B Cohort C: Overall (golcadomide 0.2 mg + RTX and golcadomide 0.4 mg + RTX) (N = 77)
Age, median (range), years	68.5 (21-78)	66.0 (20-86)
Sex, male, n (%)	24 (63)	48 (62)
Diagnosis, n (%)		
DLBCL	37 (97)	76 (99)
Double-hit[a]/triple-hit[b] positive	13 (34)	19 (25)
FL Grade 3b	1 (3)	1 (1)
Stage III-IV	31 (82)	61 (79)
Cell of origin, n (%)		
GCB	7 (18)	18 (23)
ABC/non-GCB	3 (8)	7 (9)
Unknown	28 (74)	52 (68)
ECOG PS, n (%)		
0	16 (42)	28 (36)
1	17 (45)	41 (53)
2	5 (13)	8 (10)
Treatment history		
No. of prior LOTs (range), median	4.5 (1-11)	4 (1-11)
Prior stem cell transplant, n (%)	7 (18)	11 (14)
Prior CAR T-cell therapy, n (%)	21 (55)	42 (55)
Prior bispecific antibody, n (%)	15 (40)	29 (38)
Prior lenalidomide treatment, n (%)	10 (26)	20 (26)
Best response to last regimen		
CR or PR	15 (39)	28 (36)
Never achieved objective response	13 (34)	32 (42)
Unknown	10 (26)	17 (22)

Data cut-off: 3 April 2025. Data are from the safety population of n = 77.
[a]Double hit is defined as a positive case of MYC + BCL2 or MYC + BCL6 determined by FISH. [b]Triple hit is defined as a positive case of MYC + BCL2 + BCL6 determined by FISH.
ABC, activated B-cell-like; BCL, B-cell lymphoma; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; FL, follicular lymphoma; GCB, germinal center B cell; LOT, line of therapy; PR, partial response; RTX, rituximab.

Table 2. Patient disposition

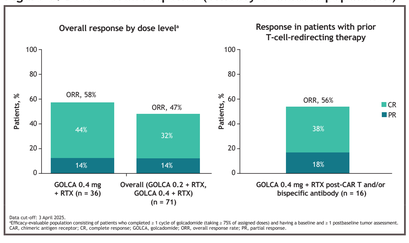
	Part B Cohort C: Golcadomide 0.4 mg + RTX (n = 38)	Part B Cohort C: Overall (golcadomide 0.2 mg + RTX and golcadomide 0.4 mg + RTX) (N = 77)
Treatment disposition, n (%)		
Completed	2 (5)	4 (5)
Ongoing	8 (21)	10 (13)
Discontinued	28 (74)	63 (82)
Primary reason for treatment discontinuation, n (%)		
Progressive disease	18 (47)	43 (56)
Adverse event	1 (3)	5 (7)
Withdrawal by patient	2 (5)	4 (5)
Symptomatic deterioration	3 (8)	3 (4)
Physician decision	1 (2)	2 (3)
Death	2 (5)	3 (4)
Lack of efficacy	0	1 (1)
Disease relapse	0	1 (1)
Loss to follow-up	1 (3)	1 (1)
Pregnancy	0	0

Data cut-off: 3 April 2025.
RTX, rituximab.

Efficacy

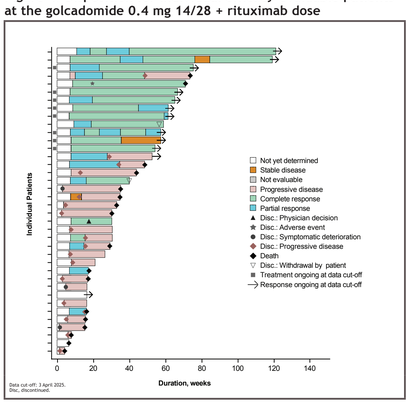
- Overall, objective response rate (ORR) was 47% (complete response rate [CRR], 32%) in efficacy-evaluable patients (n = 71) (**Figure 3**)
  - The ORR was 58% (CRR, 44%) in the golcadomide 0.4 mg Cohort (n = 36)
  - In those with prior T-cell-redirecting treatment (CAR T-cell therapy and/or bispecific antibody, n = 16 at the 0.4-mg dose), the ORR was 56% (CRR, 38%)
  - At a median follow-up of 15.7 months (range, 3.1-35.1 months), the median observed duration of response was 14.7 months (range, 1.5-33.4 months), including durable responses > 12 months in 21 patients (n = 14 at the 0.4-mg dose) (**Figure 4**; **Table 3**)
  - The median time to response was 1.8 months in efficacy-evaluable patients

Figure 3. Best overall response (efficacy-evaluable population)



Data cut-off: 3 April 2025.
[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.
CAR, chimeric antigen receptor; CR, complete response; GOLCA, golcadomide; ORR, overall response rate; PR, partial response.

Figure 4. Disposition for individual efficacy-evaluable patients at the golcadomide 0.4 mg 14/28 + rituximab dose



Data cut-off: 3 April 2025.
Disc., discontinued.

Table 3. Median follow-up, observed duration of response, and median time to response in the efficacy-evaluable population

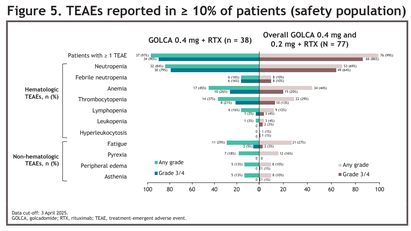
	Golcadomide 0.4 mg + RTX (n = 36)	Overall (golcadomide 0.2 mg + RTX and golcadomide 0.4 mg + RTX) (N = 71)
Median follow-up in all patients (range), months	7.8 (1.0-31.4)	6.7 (1.0-35.1)
Median follow-up in responders only (range), months	16.2 (3.8-31.4)	15.7 (3.1-35.1)
Median observed duration of response (range), months	14.5 (1.9-29.7)	14.7 (1.5-33.4)
Patients with response > 12 months, n (%)	14 (39)	21 (30)
Patients with response > 24 months, n (%)	2 (6)	5 (7)
Median time to response (range), months	1.8 (1.6-2.6)	1.8 (1.6-2.6)

Data cut-off: 3 April 2025.
RTX, rituximab.
Note: Observed duration of response is measured from the time at which measurement criteria are first met for complete response (CR) or partial response (PR) (whichever is first recorded) until the first date at which progressive disease (PD) or death is objectively documented, whichever comes first. If no PD or death, then patients are censored and calculated as cut-off date - first recorded date of CR/PR + 1. Based on responders only.

Safety

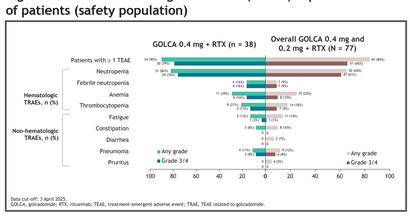
- In the safety population, the most common any-grade treatment-emergent adverse events (TEAEs) were neutropenia, an on-target effect resulting from golcadomide-mediated Ikaros degradation leading to reversible neutrophil maturation arrest, and anemia (in 69% and 44%, respectively) (**Figure 5**)
  - Grade 3/4 neutropenia and febrile neutropenia occurred in 64% and 10% of patients, respectively
  - Granulocyte colony-stimulating factor was used in 45 of 53 patients with neutropenia and 7 of 8 patients with febrile neutropenia
  - Median time to resolution of any-grade febrile neutropenia was 8.5 days (7 days in the golcadomide 0.4 mg Cohort)
- Overall, 51% of patients had dose interruptions (mainly due to infections/neutropenia); 7% of patients discontinued treatment due to adverse events (AEs)
- The most common any-grade TEAEs related to golcadomide were neutropenia (65%) and anemia (25%) (**Figure 6**)
  - Non-hematologic AEs such as fatigue and diarrhea were all low grade, with none at Grade ≥ 3
  - One Grade 5 TEAE (pneumonia) was considered related to study treatment

Figure 5. TEAEs reported in ≥ 10% of patients (safety population)



Data cut-off: 3 April 2025.
GOLCA, golcadomide; RTX, rituximab; TEAE, treatment-emergent adverse event.

Figure 6. TEAEs related to golcadomide (TRAEs) reported in ≥ 10% of patients (safety population)

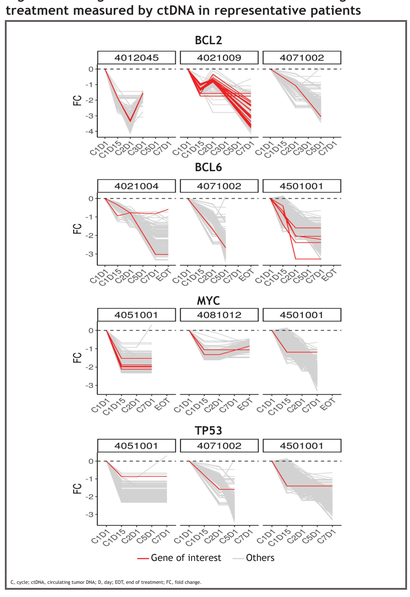


Data cut-off: 3 April 2025.
GOLCA, golcadomide; RTX, rituximab; TRAE, treatment-emergent adverse event; TRAE, TEAE related to golcadomide.

ctDNA

- In the patients who responded to golcadomide, ctDNA reduction from baseline was observed across mutant variants, including those in driver genes or associated with high-risk disease (eg *TP53*, *BCL2*) (**Figure 7**)

Figure 7. Changes in individual mutant variants during treatment measured by ctDNA in representative patients



C, cycle; ctDNA, circulating tumor DNA; D, day; EOT, end of treatment; FC, fold change.

Conclusions

- With additional follow-up, golcadomide oral therapy combined with rituximab continued to show promising efficacy in heavily pretreated patients with R/R DLBCL, including those with a prior history of T-cell-redirecting therapy
  - Durable responses were shown in heavily pretreated patients with R/R DLBCL (ORR of 58% and CR rate of 44% with golcadomide 0.4 mg + rituximab)
  - Responses were also observed in patients with a prior history of T-cell-redirecting therapy (ORR of 56% and CR rate of 38% in the 0.4-mg dose group)
- The safety profile of golcadomide + rituximab was manageable and predictable, and no new safety signals were observed with longer follow-up
  - On-target neutropenia was manageable with the use of granulocyte colony-stimulating factors and/or dose interruption
  - Incidence of febrile neutropenia in patients receiving golcadomide + rituximab was 10.4%
  - Non-hematologic AEs were primarily low grade and manageable with supportive care, with low incidence of dose interruption or dose reduction
- In responders, golcadomide + rituximab induced a decrease in ctDNA, including mutant variants associated with high risk
- This study is ongoing, with additional follow-up to confirm the promising efficacy of the 0.4-mg dose and the manageable safety profile; these data support the ongoing development of golcadomide + rituximab for patients with R/R NHL

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Disclosures

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