GOLSEEK-4: A multicenter Phase 3 randomized open-label study comparing efficacy and safety of golcadomide + rituximab vs investigator's choice in patients with relapsed/refractory follicular lymphoma who have received ≥1 line of systemic therapy

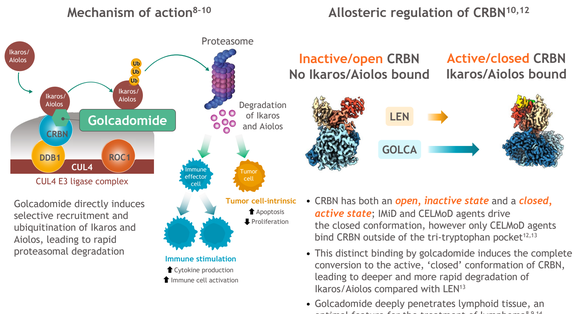
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Golcadomide, a potential first-in-class, oral CELMoD™ agent for follicular lymphoma – design of the Phase 3, global, randomized, open-label GOLSEEK-4 study

Key Figure A. Golcadomide is a potential first-in-class, oral CELMoD agent for lymphoma

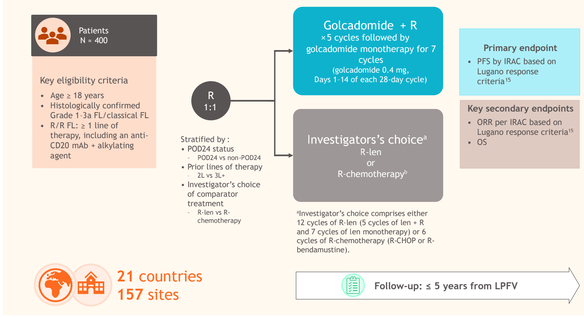


Golcadomide directly induces selective recruitment and ubiquitination of Ikaros and Aiolos, leading to rapid proteasomal degradation

- 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[12,13]
- 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[13]
- Golcadomide deeply penetrates lymphoid tissue, an optimal feature for the treatment of lymphoma[8,9,14]

CRBN, cereblon; CUL4, cullin-4A; DDB1, DNA damage-binding protein 1; Golca, golcadomide; IMiD, immunomodulatory drug; LEN, lenalidomide; NHL, Non-Hodgkin lymphoma; ROC1, regulator of cullins 1; ub, ubiquitin.

Key Figure B. Overview of the multicenter, open-label, Phase 3 GOLSEEK-4 study (NCT06911502)



[a]Investigator's choice comprises either 12 cycles of R-len (5 cycles of len + R and 7 cycles of len monotherapy) or 6 cycles of R-chemotherapy (R-CHOP or R-bendamustine).

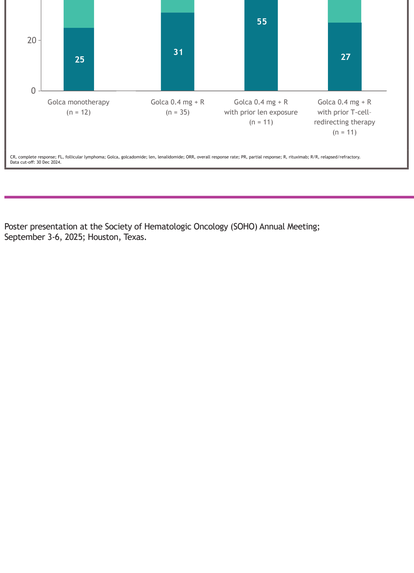
[b]For patients receiving R-chemotherapy, maintenance therapy with an anti-CD20 antibody is not allowed.

2L, second line; 3L+, third line and beyond; CD, cluster of differentiation; FL, follicular lymphoma; IRAC, Independent Radiology Adjudication Committee; LEN, lenalidomide; LPFV, last patient first visit; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PODZ4, progression of disease within 24 months; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

Background

- Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL), accounting for ~20% of all NHL cases[1]
- While a long remission with frontline treatment can be expected in many patients with FL, the disease remains incurable, and subsequent relapses are associated with significantly shorter remissions[2]
- Commonly used treatment regimens for relapsed/refractory (R/R) FL include rituximab (R), lenalidomide (len), or non-cross-resistant chemoimmunotherapy such as R + cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or R-bendamustine[3]
- More recently, T-cell-directed therapies such as chimeric antigen receptor T cells and bispecific antibodies in the third line or later have improved outcomes; however, they are associated with tolerability concerns and logistical challenges[4-7]
- An unmet need remains for highly efficacious, well tolerated, and more convenient chemotherapy-free regimens that improve outcomes in patients with R/R FL who have received 1 or more prior lines of systemic 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[8-10] (**Key Figure A**)
- In the Phase 1/2 study CC-99282-NHL-001 (NCT03930953), the median number of prior treatments was 3 (range, 1-12); approximately one-third of the treated patients were exposed to prior T-cell-redirecting therapy, approximately one-third had prior lenalidomide (len) exposure, and approximately one-third were refractory to the last regimen received. Golcadomide alone or in combination with R showed promising efficacy and a tolerable safety profile in patients with heavily pretreated R/R FL (**Figure 1**)[11]
  - In efficacy-evaluable patients receiving golcadomide monotherapy (n = 12), the overall response rate (ORR) was 67% (complete response rate [CRR], 42%) (**Figure 1**)
  - In efficacy-evaluable patients receiving golcadomide 0.4 mg + R (n = 35), the ORR was 94% (CRR, 63%) (**Figure 1**)
  - Notably, the ORR and CRR in high-risk subsets, including patients with prior treatment with len and/or T-cell-redirecting therapy, were consistent with the results in the overall golcadomide 0.4 mg + R treatment group
  - The safety profile of golcadomide + R was manageable and predictable, and the most common treatment-emergent adverse event (TEAE) was neutropenia, an on-target effect resulting from golcadomide-mediated Ikaros degradation leading to reversible neutrophil maturation arrest
- Here, we present the study design of GOLSEEK-4 (NCT06911502), a multicenter, randomized, open-label, Phase 3 study comparing efficacy and safety of golcadomide + R vs investigator's choice (IC) in patients with R/R FL who have received ≥1 line of systemic therapy

Figure 1. Phase 1/2 study (CC-99282-NHL-001): High response rates were observed with golcadomide 0.4 mg + R in heavily pre-treated R/R FL[11]



CR, complete response; FL, follicular lymphoma; Golca, golcadomide; len, lenalidomide; ORR, overall response rate; PR, partial response; R, rituximab; R/R, relapsed/refractory.
Data cut-off: 30 Dec 2024.

Study design

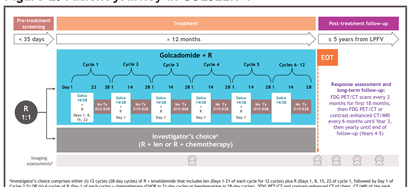
- A summary of the GOLSEEK-4 study design is presented in **Key Figure B**, and the patient journey and treatment schedule is summarized in **Figure 2**
- See **Table 1** for key eligibility criteria
- The primary objective is to assess the efficacy of golcadomide + R vs investigator's choice of R-len or R-chemotherapy in patients with R/R FL
- **Table 2** lists primary, key secondary, and other secondary endpoints, including exploratory objectives

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Participant must be ≥ 18 years of age • Participant has histologically confirmed FL (Grade 1, 2, or 3a) • Participant must have PET-positive disease with ≥ 1 PET-positive lesion and measurable disease by CT as defined by Lugano classification[15] • Participants must require anti-lymphoma treatment per investigator assessment based on modified GELF criteria • Participant has received ≥ 1 line(s) of systemic therapy with 1 line consisting of a combination, including an anti-CD20 monoclonal antibody (e.g. rituximab, obinutuzumab) and alkylating agent (e.g. cyclophosphamide, bendamustine)	• Evidence or history of composite DLBCL and FL, transformed NHL, or any other indolent lymphoma • Follicular large-cell disease as per 5th WHO sub-classification (or Grade 3b FL per 4th WHO classification) or duodenal-type FL • Presence or history of CNS involvement by lymphoma • Participants who are refractory to both chemotherapies as well as lenalidomide, defined as: – SD/PD as best response to CHOP and bendamustine-based immunochemotherapy or a response to CHOP and bendamustine-based immunochemotherapy that lasted less than 6 months AND – SD/PD as best response to lenalidomide-based regimen or a response to lenalidomide-based regimen that lasted less than 6 months Note: Participants previously refractory to lenalidomide and/or exposed to lenalidomide are eligible but will not be randomized in the R-lenalidomide arm; participants who are refractory to R-chemotherapy (both CHOP and bendamustine) are eligible but will not be randomized to R-chemotherapy arm

CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; NHL, non-Hodgkin lymphoma; PD, progressive disease; PET, positive emission tomography; SD, stable disease; WHO, World Health Organization.

Figure 2. Patient journey in GOLSEEK-4



[a]Investigator's choice comprises either (i) 12 cycles (28-day cycles) of R + lenalidomide that includes len (Days 1-21 of each cycle for 12 cycles) plus R (Days 1, 8, 15, 22 of cycle 1, followed by Day 1 of cycles 2-12) or (ii) 6 cycles (28-day cycles) of R-chemotherapy (R-CHOP or R-bendamustine). [b]Tumor assessments (CT scans of the chest, abdomen, pelvis and all other known and/or suspected sites of disease required every 3 months for the first 18 months. For subsequent imaging assessment, contrast-enhanced CT/MRI would be acceptable and performed every 6 months until Year 3 and then yearly thereafter until disease progression, withdrawal of consent, or initiation of new anti-lymphoma therapy, whichever occurs earlier. CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CT, computed tomography; EOT, end of treatment; FDG, fluorodeoxyglucose; golca + R, golcadomide plus rituximab; len, lenalidomide; LPFV, last patient first visit; MRI, magnetic resonance imaging; PET, positron emission tomography; R, rituximab; Tx, treatment.

Table 2. Primary, Secondary, and Exploratory Endpoints

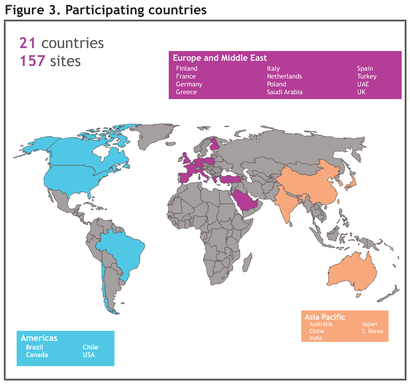
Primary	
• PFS by IRAC by Lugano response criteria[15]	
Key secondary	
• ORR per IRAC by Lugano response criteria[15] • OS	
Other secondary	
• PFS by investigator • ORR by investigator • CMRR by investigator • DOR • EFS • MRD by ctDNA	• PFS2 • TTNT • HRQoL – Change from baseline in domains of the EORTC QLQ-C30 and the EORTC QLQ-NHL-LG20
Exploratory endpoints	
• Safety • PK	• Biomarkers • Healthcare resource utilization

CMRR, complete metabolic response rate; ctDNA, circulating tumor DNA; DOR, duration of response; EFS, event-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; EORTC QLQ-NHL-LG20, European Organisation for Research and Treatment of Cancer Non-Hodgkin Lymphoma Low Grade 20 Items; HRQoL, health-related quality of life; IRAC, Independent Response Adjudication Committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to a second progression event; PK, pharmacokinetics; TTNT, time to next anti-lymphoma treatment.

Global enrollment

- The study is being conducted at 157 sites in 21 countries worldwide (**Figure 3**)
- The first patient's first visit was 28 July 2025, and enrollment is ongoing
- Estimated primary analysis completion date: 24 April 2028
- Estimated study completion date: 31 July 2030

Figure 3. Participating countries



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Bachy et al.
Golcadomide, a CELMoD™ Agent, With or Without Rituximab in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL): Updated Phase 1/2 Results
Wednesday, September 3, 2025. **Session time:** 6:25 PM-7:55 PM. **Room:** George R. Brown Convention Center, Hall B3, on Level 3

Poster presentation: IBCL-1109
Cordoba et al.
Golcadomide, a CELMoD™ Agent, With or Without Rituximab in Patients With Relapsed/Refractory Follicular Lymphoma (R/R FL): Updated Phase 1/2 Results
Wednesday, September 3, 2025. **Session time:** 6:25 PM-7:55 PM. **Room:** George R. Brown Convention Center, Hall B3, on Level 3

Poster presentation: ABCL-1176
Munoz et al.
GOLSEEK-1: A Phase 3, Double-Blind, Randomized Study of Golcadomide+R-CHOP vs Placebo+R-CHOP in Patients With Previously Untreated, High-Risk, Large B-Cell Lymphoma
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Poster presentation at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 3-6, 2025; Houston, Texas.

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