GOLSEEK-1: a Phase 3, double-blind, randomized study of golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, + R-CHOP vs placebo + R-CHOP in patients with previously untreated, high-risk, large B-cell lymphoma

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Background

- Diffuse large B-cell lymphoma (DLBCL) and other large B-cell lymphomas (LBCLs) account for ≈30% of non-Hodgkin lymphoma (NHL) cases[1]
  - Nearly 60% of patients with DLBCL are cured with standard-of-care, first-line chemo-immunotherapy[1]
- Approximately 40% of patients will have either primary refractory disease or experience relapse after an initial response; patients with a high International Prognostic Index (IPI) score have a higher risk of disease progression or death[2]
- The IPI is widely used to predict outcomes; however, it fails to identify patients with inferior prognosis among those with lower scores (IPI 1—2)
- In patients with DLBCL, IPI 1-2, with very high lactate dehydrogenase (> 1.3 × ULN) and/or bulky disease (single lesion of ≥ 7 cm maximum diameter) were identified as a high-risk subset (**Figure 1**)[3]

Figure 1. LEO (lymphoma epidemiology of outcomes) EFS by IPI group[3]

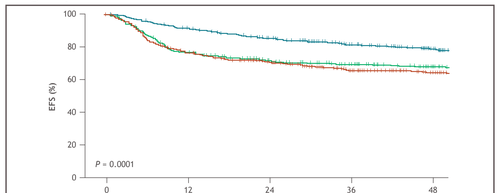
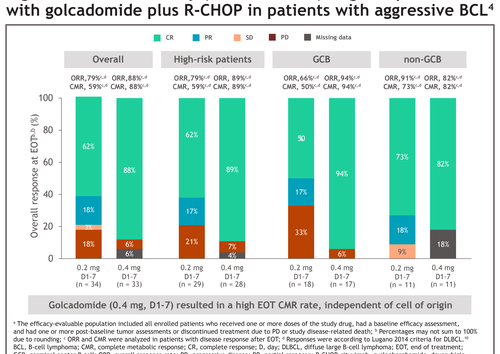


Figure reprinted from reference 3. The presence of bulky disease and/or very high LDH defines a high-risk subset of IPI 1-2 for eligibility in clinical trials of newly diagnosed aggressive BCL.
BCL, B-cell lymphoma; EFS, event-free survival; IPI, International Prognostic Index; LDH, lactate dehydrogenase. © 2023, with permission from Elsevier/American Society of Hematology.

- Golcadomide is a potential, first-in-class, oral CELMoD agent for the treatment of lymphoma that induces rapid, deep, and sustained degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. Relative to other CELMoD agents, golcadomide was purposefully designed for lymphoma, with enhanced lymphoid organ distribution and activity in treatment-resistant cell lines[4-6] (**Key Figure A**)
  - Early-phase studies have demonstrated that golcadomide has promising efficacy and safety in patients with newly diagnosed aggressive B-cell lymphoma (BCL),[4] and relapsed and/or refractory (R/R) DLBCL,[7] as well as follicular lymphoma[7,8]
- In a Phase 1b study investigating patients with aggressive BCL (NCT04884035), first-line treatment with golcadomide at the recommended Phase 2 dose (0.4 mg) plus R-CHOP was well tolerated and effective, including[4]:
  - An end-of-treatment complete metabolic response rate of 88%, which was maintained in patients with high-risk disease and was independent of cell of origin (**Figure 2**)
  - Overall end-of-treatment minimal residual disease negativity rate of 90%
  - A manageable safety profile; the addition of golcadomide to R-CHOP did not compromise the delivery of curative treatment
- Here, we present the study design of GOLSEEK-1 (NCT06356129), a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to compare the efficacy and safety of golcadomide plus R-CHOP vs placebo plus R-CHOP in patients with previously untreated high-risk LBCL

Figure 2. Phase 1b study (NCT04884035): high response rates with golcadomide plus R-CHOP in patients with aggressive BCL[4]

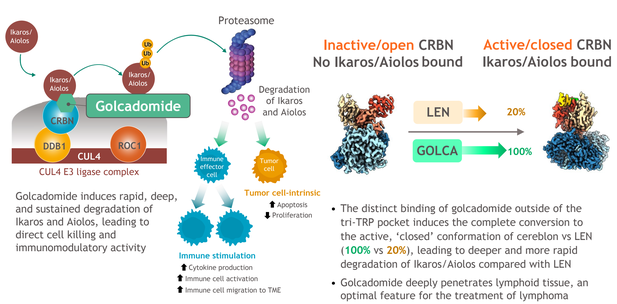


Golcadomide (0.4 mg, D1-7) resulted in a high EOT CMR rate, independent of cell of origin

[a] The efficacy-evaluable population included all enrolled patients who received one or more doses of the study drug, had a baseline efficacy assessment, and had one or more post-baseline tumor assessments or discontinued treatment due to PD or study disease-related death; [b] Percentages may not sum to 100% due to rounding; [c] ORR and CMR were analyzed in patients with disease response after EOT; [d] Responses were according to Lugano 2014 criteria for DLBCL.[9]
BCL, B-cell lymphoma; CMR, complete metabolic response; CR, complete response; D, day; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; GCB, germinal center B cell; ORR, overall response rate; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease. Figure from reference 4: Nowakowski G, et al. ASH 2025. Oral presentation (abstract 476).

Golcadomide, a potential, first-in-class, oral CELMoD™ agent for high-risk LBCL – design of the Phase 3, global, double-blind, placebo-controlled GOLSEEK-1 study

Key Figure A. Golcadomide is a potential, first-in-class, oral Ikaros/Aiolos degrading CELMoD™ agent for lymphoma[4,6]

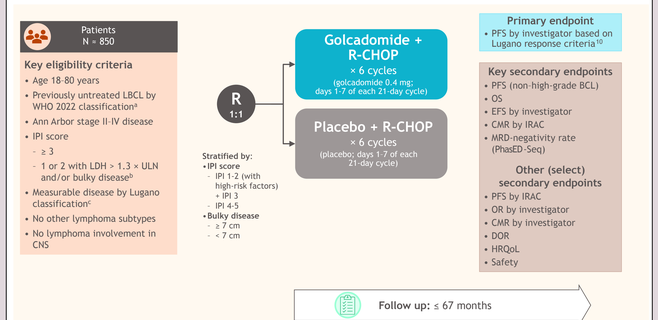


Golcadomide induces rapid, deep, and sustained degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity

- The distinct binding of golcadomide outside of the tri-TRP pocket induces the complete conversion to the active, 'closed' conformation of cereblon vs LEN (**100%** vs **20%**), leading to deeper and more rapid degradation of Ikaros/Aiolos compared with LEN
- Golcadomide deeply penetrates lymphoid tissue, an optimal feature for the treatment of lymphoma

CRBN, cereblon; CUL4, cullin-4A; DDB1, DNA damage-binding protein 1; GOLCA, golcadomide; LEN, lenalidomide; ROC1, regulator of cullins 1; TME, tumor microenvironment; TRP, tryptophan; Ub, ubiquitin.

Key Figure B. Overview of the global double-blind Phase 3 GOLSEEK-1 study (NCT06356129; CA073-1020)



[a] Includes DLBCL (including GCB and ABC types, or not specified); high-grade BCL (including *MYC* and *BCL2* rearrangements, or not specified); T-cell/histiocyte-rich LBCL; Epstein-Barr virus-positive DLBCL; [b] Single lesion of ≥ 7 cm; [c] One or more FDG-avid lesion for FDG-avid subtype and one bi-dimensionally measurable (> 1.5 cm in longest diameter) disease, by CT or MRI.[10] ABC, activated B cell; BCL, B-cell lymphoma. CMR, complete metabolic rate; CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; FDG, fluorodeoxyglucose; GCB, germinal center B cell; HRQoL, health-related quality of life; IPI, International Prognostic Index; IRAC, Independent Radiology Adjudication Committee; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; MRD, minimal residual disease; MRI, magnetic resonance imaging; OR, overall response; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper limit of normal; WHO, World Health Organization.

Study design

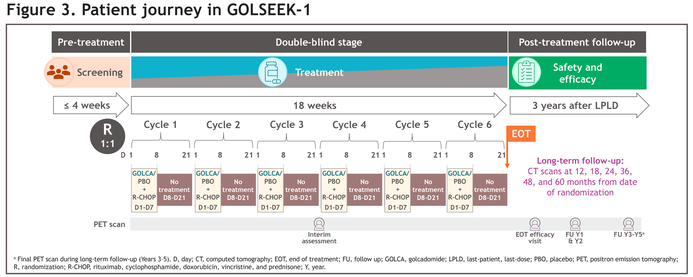
- See Key **Figure B** and **Figure 3** for summaries of the study design
- Eligible patients are aged 18-80 years with a histologically confirmed diagnosis of LBCL per the World Health Organization (WHO) 2022 classification
- See **Table 1** for key eligibility criteria
- Following screening, approximately 850 patients will be randomized 1:1 to golcadomide plus R-CHOP or placebo plus R-CHOP (**Key Figure B** and **Figure 3**)
  - Screening is limited to a maximum of 4 weeks
  - Randomization is stratified by IPI score (IPI 1-2 with high-risk factors and IPI 3 vs IPI 4-5) and bulky disease (≥ 7 cm vs < 7 cm)
  - Golcadomide (0.4 mg) or placebo are administered once daily on days 1-7 of a 21-day cycle in combination with R-CHOP, for a total of 6 treatment cycles
- The primary objective is to evaluate the efficacy of golcadomide plus R-CHOP vs placebo plus R-CHOP in patients with previously untreated high-risk LBCL
- **Table 2** lists primary, key secondary, and other secondary endpoints

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Men and women aged 18-80 years • Histologically confirmed (per local evaluation) diagnosis of previously untreated LBCL according to 2022 WHO classification including: — DLBCL, not otherwise specified (including GCB and ABC types) — High-grade BCL with *MYC* and *BCL2* rearrangements — High-grade BCL not otherwise specified — T-cell/histiocyte-rich LBCL — Epstein-Barr virus-positive DLBCL • IPI — IPI score 1 or 2 with LDH > 1.3 × ULN and/or bulky disease defined as a single lesion of ≥ 7 cm — IPI score ≥ 3 • Ann Arbor Stage II—IV disease • Measurable disease defined by at least one FDG-avid lesion (for FDG-avid subtype), and one bi-dimensionally measurable (> 1.5 cm in longest diameter) disease by CT or MRI, as defined by the Lugano classification	• Any significant medical condition, active infection, laboratory abnormality, or psychiatric illness that would prevent the participant from participating in the study • Any other subtype of lymphoma, including: — Primary mediastinal (thymic) LBCL — Primary cutaneous DLBCL-leg type — Grade 3b follicular lymphoma — Indolent lymphoma transformed to LBCL — ALK-positive LBCL — Primary effusion lymphoma — Burkitt lymphoma • Documented or suspected CNS involvement by lymphoma • Chronic systemic immunosuppressive therapy or corticosteroids

ABC, activated B cell; ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FDG, fluorodeoxyglucose; GCB, germinal center B cell; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; ULN, upper limit of normal; WHO, World Health Organization.

Figure 3. Patient journey in GOLSEEK-1



[a] Final PET scan during long-term follow-up (Years 3-5). D, day; CT, computed tomography; EOT, end of treatment; FU, follow up; GOLCA, golcadomide; LPLD, last-patient, last-dose; PBO, placebo; PET, positron emission tomography; R, randomization; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; Y, year.

Table 2. Endpoints

Primary

- PFS per investigator by Lugano response criteria[10]

Key secondary

- PFS per investigator by Lugano response criteria[10] in patients with non-high-grade BCL
- EFS by investigator
- OS
- CMR by IRAC
- End-of-treatment MRD-negativity rate (PhasED-Seq)

Other secondary

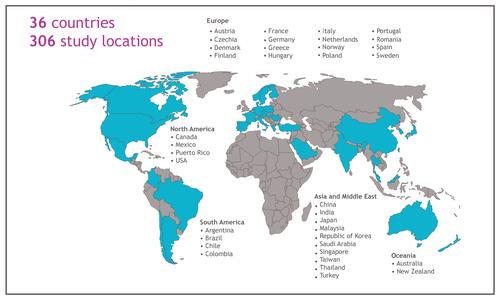
- PFS by IRAC
- OR by investigator
- CMR by investigator
- PFS24 by investigator
- DOR
- PFS2 by investigator
- Relative dose intensity
- HRQoL
  - EORTC QLQ-C30: time from randomization to meaningful improvement; mean change from baseline
  - FACT-LymS: time from randomization to meaningful improvement; mean change from baseline
- Safety
  - TEAEs
  - Laboratory abnormalities
  - Vital sign abnormalities

BCL, B-cell lymphoma; CMR, complete metabolic response; DOR, duration of response; EFS, event-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-LymS, Functional Assessment of Cancer Treatment-Lymphoma; HRQoL, health-related quality of life; IRAC, Independent Response Adjudication Committee; MRD, minimal residual disease; OR, objective response; OS, overall survival; PFS, progression-free survival; PFS2, time to a second progression event; PFS24, progression-free survival 24 months after randomization; TEAE, treatment-emergent adverse event.

Global enrollment

- The study is planned to be conducted at 306 sites in 36 countries worldwide (**Figure 4**)
- The study start date was June 19, 2024, and enrollment is ongoing
- Estimated primary analysis completion date: August 14, 2028
- Estimated study completion date: November 20, 2029

Figure 4. Participating countries



References

1. Shen LH, Salles G. N Engl J Med 2021;384:842—858.
2. Ruppert AS, et al. Blood 2020;135:2041—2048.
3. Maurer M, et al. Blood 2023;142(suppl 1):4512.
4. Nowakowski G, et al. ASH 2025. Oral presentation (abstract 476).
5. Lopez-Girona A, et al. Hematol Oncol 2021;39(suppl 1):315—316.
6. Mo Z, et al. Blood Cancer Discov 2025; doi: 10.1158/2643-3230.BCD-25-0059. Online ahead of print.
7. Michot JM, et al. ASH 2024. Oral presentation (abstract 869).
8. Chavez JC, et al. ASH 2024. Poster presentation 3018.
9. Hartley-Brown MA, et al. Cancers (Basel) 2024;16:1166.
10. Cheson BD, et al. J Clin Oncol 2014;32:3059—3068.
11. Carrancio S, et al. ASH 2024. Poster 3104.
12. Nakayama Y, et al. ASH 2024. Poster 1617.

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Thank you for your attention today, and please note the related presentations that may be of interest

Oral Presentation: 476
Nowakowski et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, plus R-CHOP in patients (Pts) with previously untreated aggressive B-cell lymphoma (a-BCL): 24-month efficacy results
Sunday, December 7th, 2025. Presentation time: 9:45 AM - 10:00 AM
Room: OCCC - Tangerine Ballroom F3-4

Oral Presentation: 479
Hoffmann et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, ± rituximab (R) in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Phase 1/2 study extended follow-up results
Sunday, December 7th, 2025. Presentation time: 10:30 AM - 10:45 AM
Room: OCCC - Tangerine Ballroom F3-4

Oral Presentation: 1006
Chavez et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, ± rituximab (R) in patients with relapsed/refractory follicular lymphoma (R/R FL): Phase 1/2 study extended follow-up results
Monday, December 8th, 2025. Presentation Time: 5:15 PM - 5:30 PM
Room: OCCC - Tangerine Ballroom F2

Oral Presentation: 66
Andreadis et al.
Mosunetuzumab (Mosun) or glofitamab (Glofit) in combination with golcadomide (Golca) demonstrates a manageable safety profile and encouraging efficacy in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL)
Saturday, December 6, 2025. Presentation time: 10:45 AM - 11:00 AM
Room: OCCC - Tangerine Ballroom F2

Poster Presentation: 3615
Hawkes et al.
GOLSEEK-4: A Phase 3, randomized study of golcadomide, a potential, first-in-class, oral CELMoD™ agent, plus rituximab versus investigator's choice in patients with relapsed/refractory follicular lymphoma who have received ≥1 line of systemic therapy
Sunday, December 7th, 2025. Session time: 6:00 PM - 8:00 PM
Room: OCCC - West Halls B3-B4

Poster presentation at the American Society of Hematology (ASH) Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida.

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