Golcadomide, a Potential, First-In-Class, Oral CELMoD™ Agent, ± Rituximab in Patients With Relapsed/Refractory Follicular Lymphoma: Phase 1/2 Study Extended Follow-Up Results

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Introduction

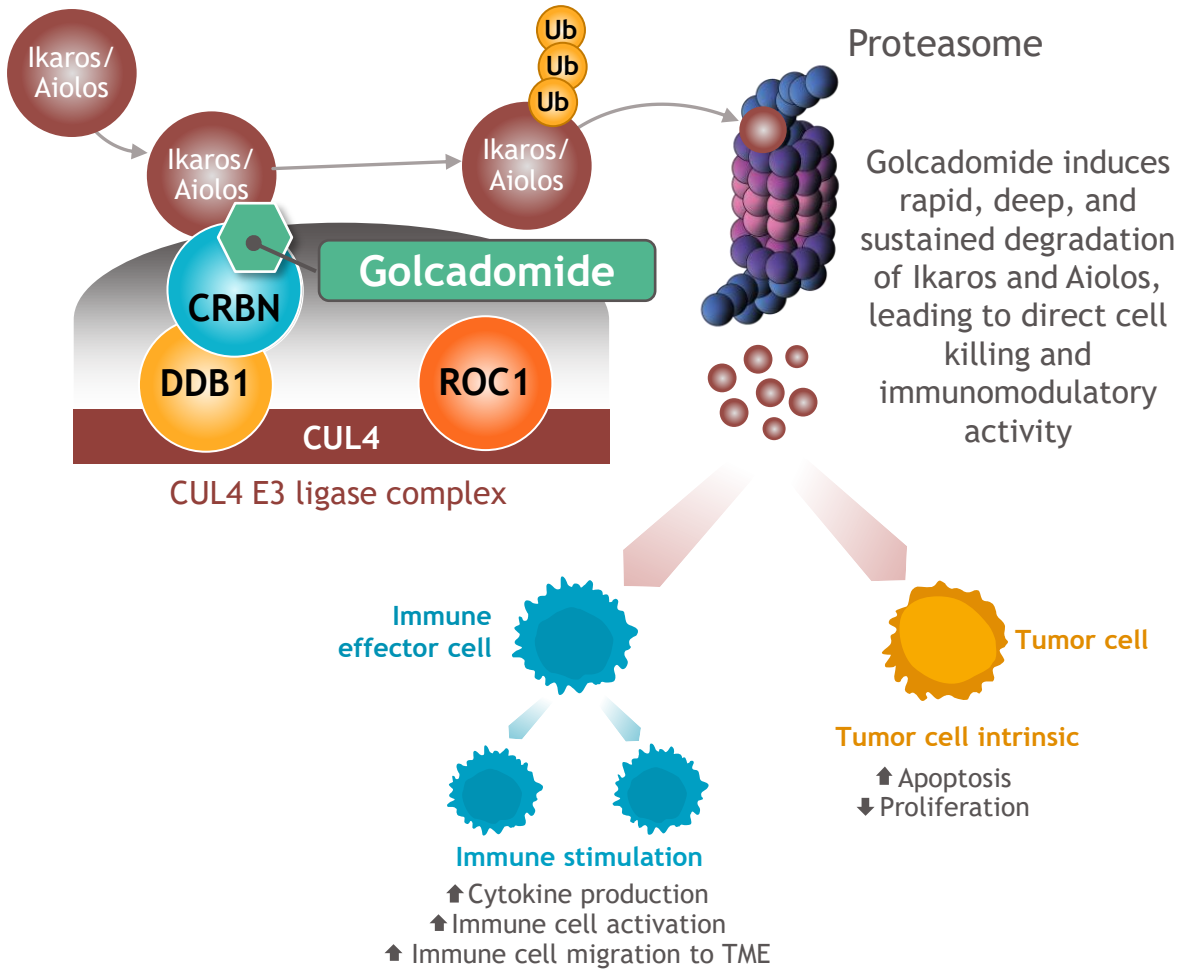
- While outcomes in patients with R/R FL have improved since the availability of T-cell—redirecting therapies, such as CAR T cell therapy and bispecific antibodies, there remains an unmet need for safe, efficacious, and easier-to-administer treatments[1–5]
- Golcadomide is a potential, first-in-class, oral CELMoD agent designed for the treatment of lymphoma. It drives the closed, active conformation of CRBN to induce rapid, deep, and sustained degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity[6]
- 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[7]
  - In the Part A dose escalation study with golcadomide monotherapy, responses were durable, with an ORR of 67% and a median observed DOR of 26 months (range, 1.7—58.2 months) at a median follow-up of 30 months[8]
- Here, we provide longer follow-up results with golcadomide ± rituximab in patients with R/R FL from Part B of the Phase 1/2 CC-99282-NHL-001 study

CAR, chimeric antigen receptor; CRBN, cereblon; DOR, duration of response; FL, follicular lymphoma; ORR, overall response rate; R/R, relapsed or refractory.

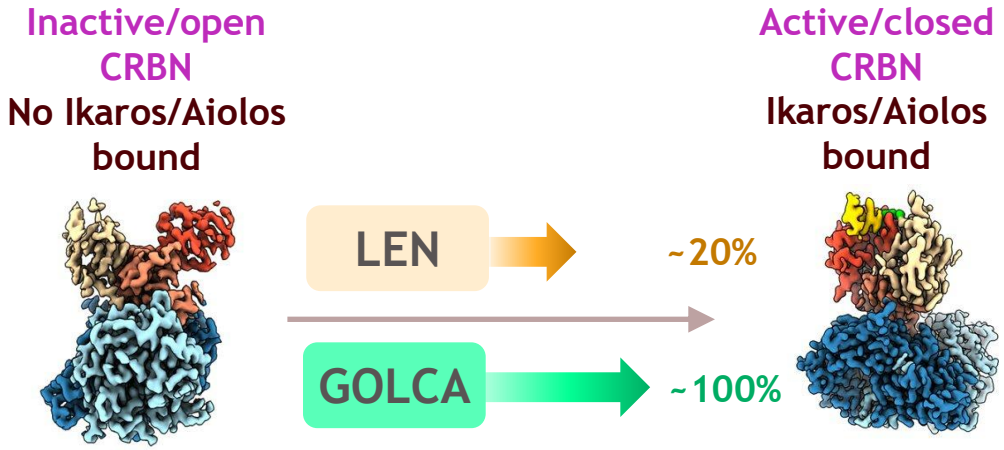
1. Bartlett NL, et al. Blood 2022;140(supp. 1):1467–1470; 2. Jacobson CA, et al. Lancet Oncol 2022;23:91–103; 3. Fowler NH, et al. Nat Med 2022;29:325–332; 4. Dreyling M, et al. Ann Oncol 2021;32:298–308; 5. Caridà G, et al. Eur J Haematol 2025;114(5):775–784; 6. Mo Z, et al. Blood Cancer Discov 2025; doi:10.1158/2643-3230.BCD-25-0059. Online ahead of print; 7. Cordoba R, et al. ICML 2025. Poster presentation 441; 8. Cordoba R, et al. SOHO 2025. Poster presentation 1109.

Golcadomide is a potential, first-in-class, oral CELMoD agent for the treatment of lymphoma[1,2]

Mechanism of action[1,3,4]



Allosteric regulation of CRBN[1]



- 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

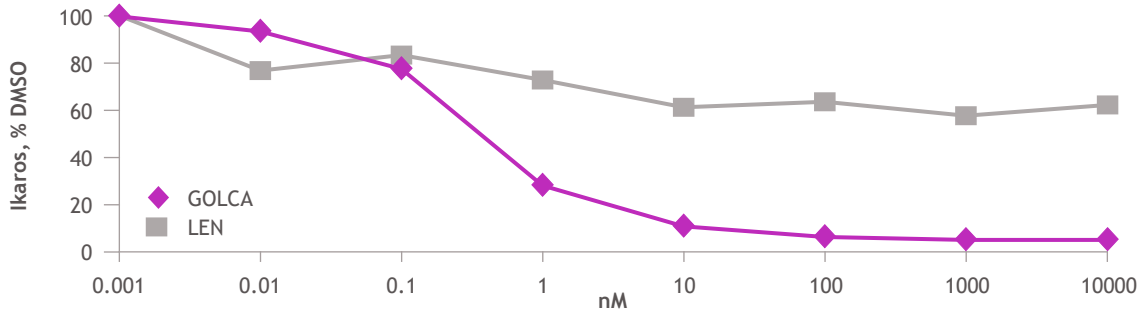
CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; GOLCA, golcadomide; LEN, lenalidomide; ROC, regulator of cullins; TME; tumor microenvironment; TRP, tryptophan; Ub, ubiquitin.

1. Mo Z, et al. Blood Cancer Discov 2025; doi:10.1158/2643-3230.BCD-25-0059. Online ahead of print; 2. Amzallag A, et al. ASH 2024. Oral presentation 579; 3. Carrancio S, et al. ASH 2024. Poster presentation 3104; 4. Nakayama Y et al. ASH 2024. Poster presentation 1617.

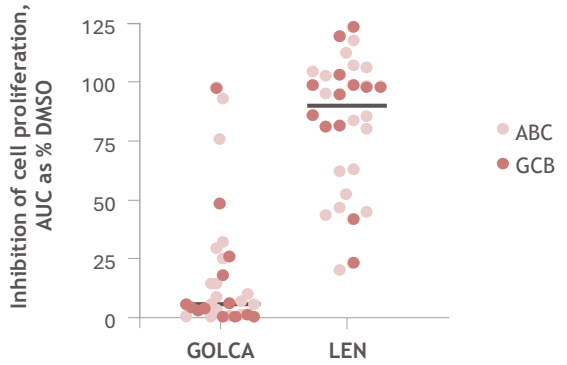
Chavez J, et al. ASH 2025. Abstract 1006.

Golcadomide has potent tumoricidal and immune stimulatory effects in lymphoma with preferential tissue distribution

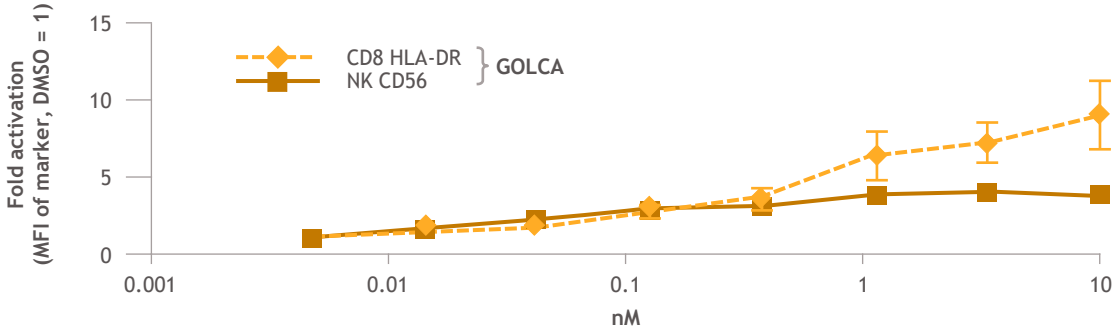
Potent Ikaros degradation[1,2]



Inhibits proliferation agnostic of COO[1]

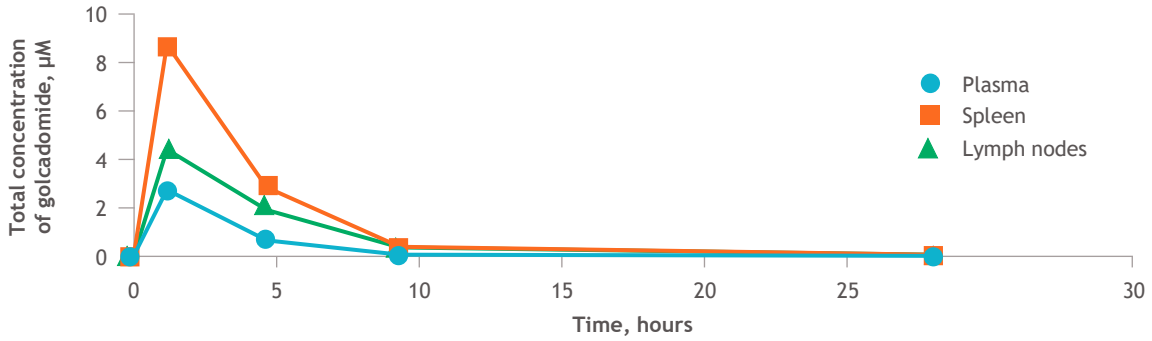


Stimulation of T and NK cells[1]



Distribution favors target organs[3]

Rat, 10 mg/kg PO dosing



ABC, activated B cell; AUC, area under the curve; 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 fluorescent intensity; NK, natural killer; PO, orally.

1. Thiebelmont C, et al. ASH 2022. Oral presentation 233; 2. Mo Z, et al. Blood Cancer Discov 2025; doi:10.1158/2643-3230.BCD-25-0059. Online ahead of print; 3. Bristol Myers Squibb. Data on file. BMS-REF-HEMA-0004.

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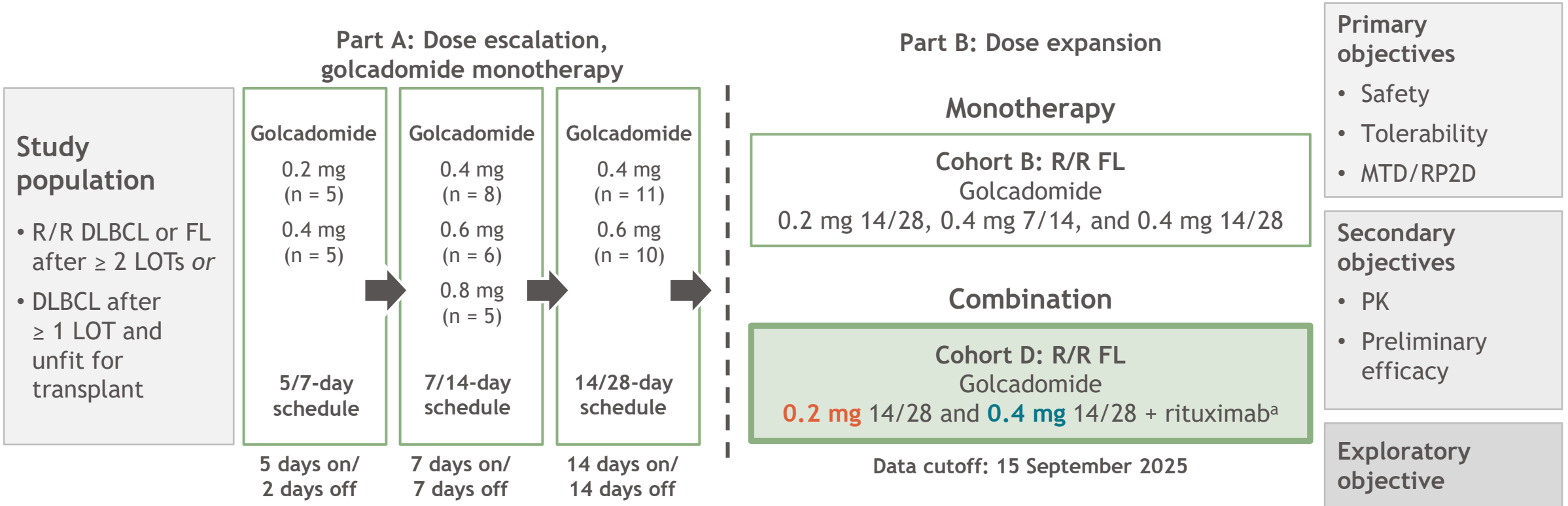
CC-99282-NHL-001: A two-part, multicenter, Phase 1/2 study of golcadomide as monotherapy and in combination with rituximab in patients with R/R NHL



- Total duration of treatment with golcadomide was up to 2 years
- PD changes in immune populations and Ikaros/Aiolos degradation were monitored by flow cytometry
- ctDNA was analyzed by CAPP-Seq, and BL biopsies were profiled by RNA-Seq

[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.
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.

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Cohort D consisted of a heavily pretreated R/R FL patient population

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	22 (100)	37 (97)
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		
Median prior LOTs (range), No.	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)

Data cutoff: 15 September 2025.

CAR, chimeric antigen receptor; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LOT, line of therapy; No, number; PR, partial response; R/R, relapsed/refractory; RTX, rituximab.

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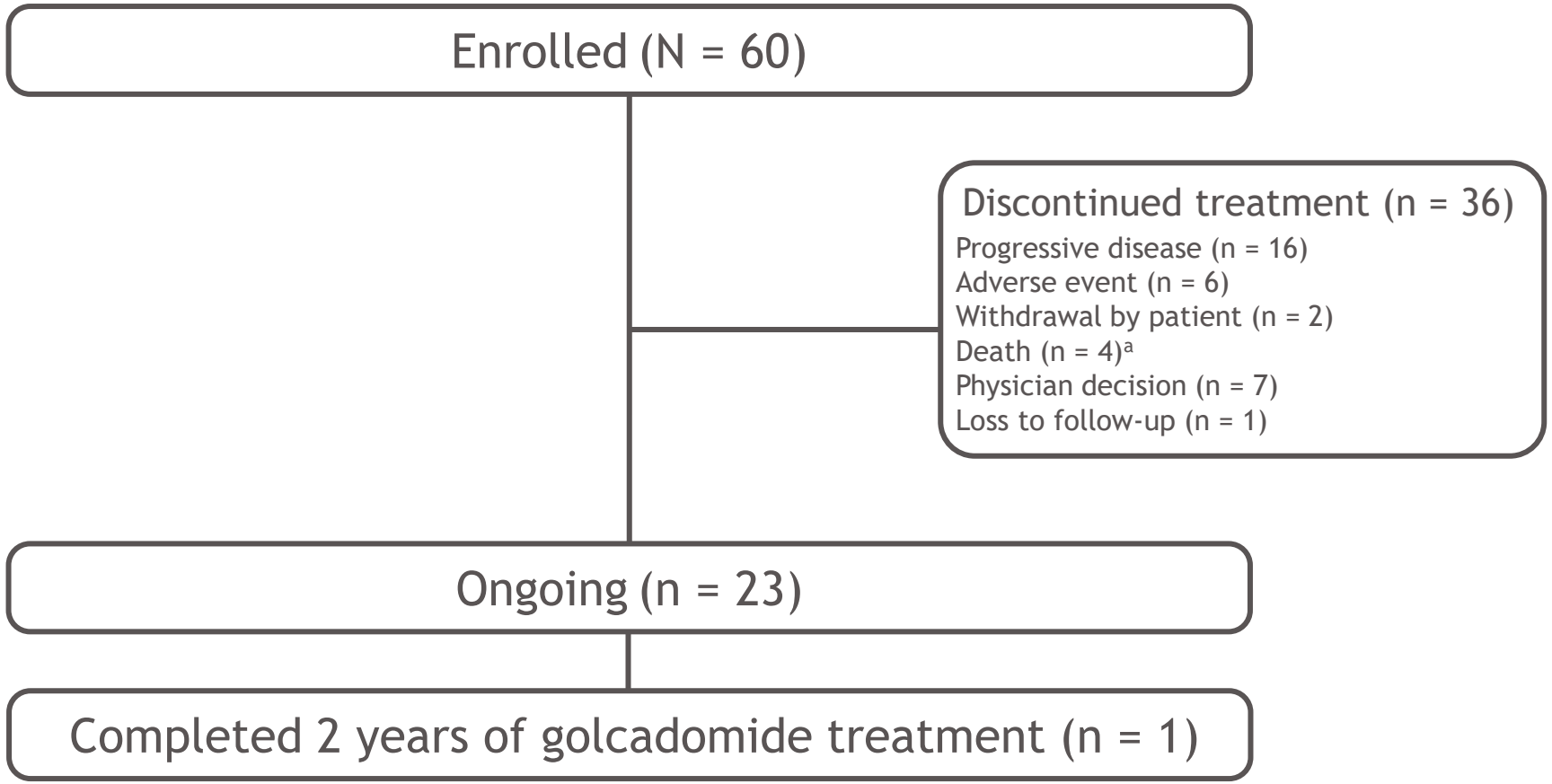
Patient disposition in Cohort D



Median follow-up was 13.4 (range, 0.4—33.1) months (ITT population)

Data cutoff: 15 September 2025.
[a] Sudden death (n = 1), meningitis listeria (n = 1), and respiratory failure (n = 2).
ITT, intention to treat.

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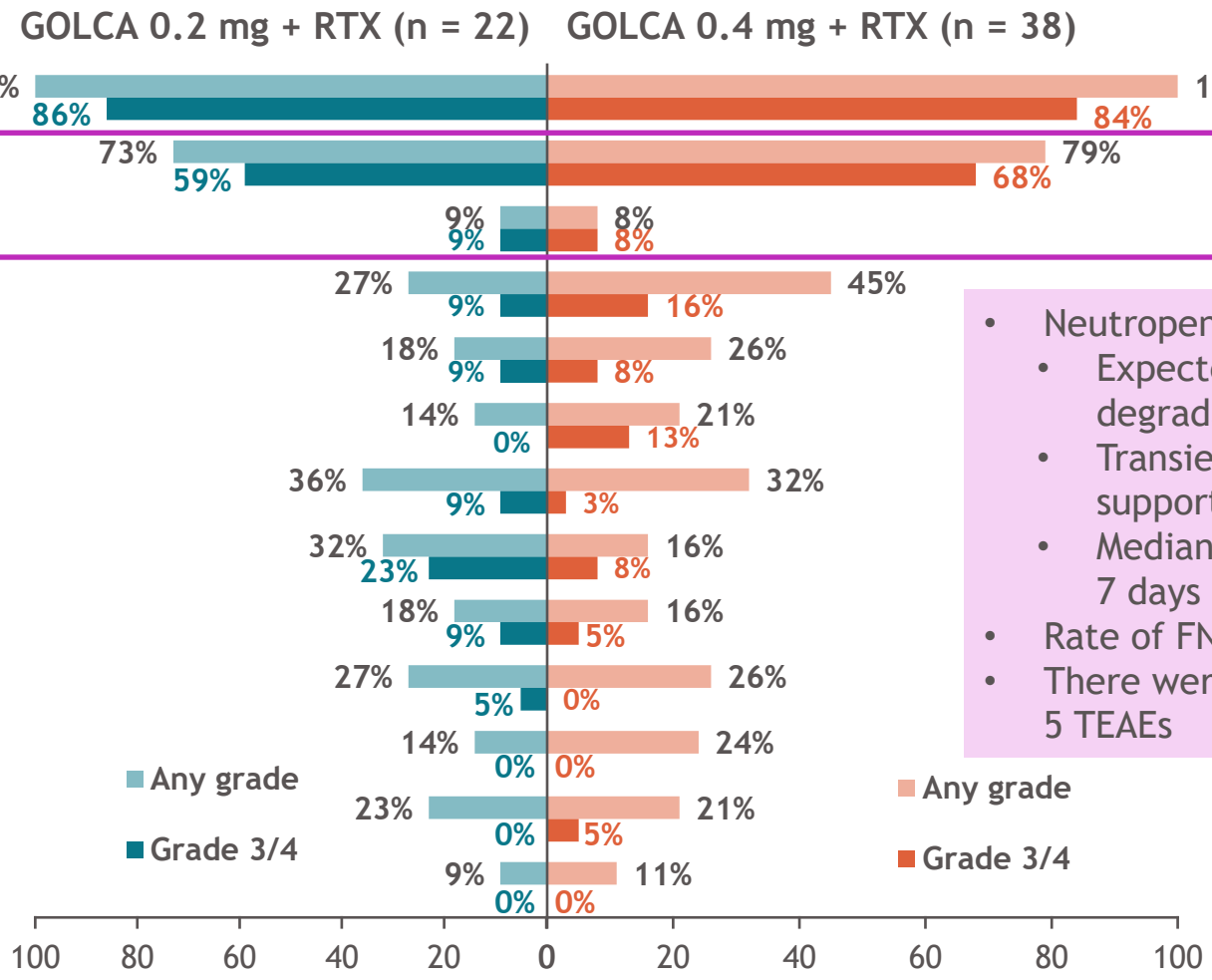
TEAEs were mainly hematologic, and non-hematologic TEAEs were infrequent and mostly low grade

TEAEs (any grade ≥ 10%)[a]



- Neutropenia:
  - Expected, on target effect due to Ikaros degradation in neutrophils precursors
  - Transient and manageable with G-CSF support
  - Median time to neutrophil recovery: 7 days
- Rate of FN and infections remained low
- There were no golcadomide related grade 5 TEAEs

Data cutoff: 15 September 2025.

[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 Common Terminology Criteria for Adverse Events version 5.0. GOLCA, golcadomide; RTX, rituximab; TEAE, treatment-emergent adverse event.

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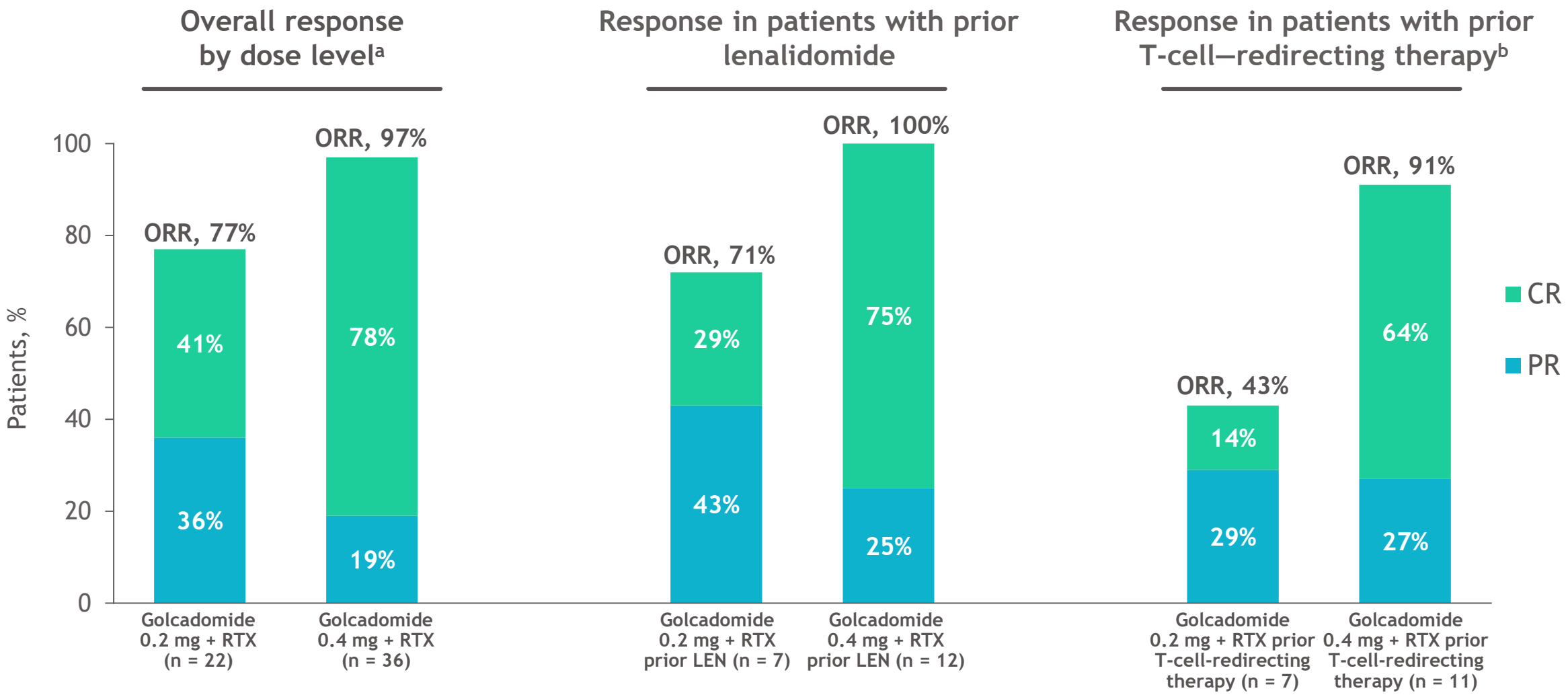
Golcadomide + RTX achieved a high ORR and CRR in a heavily pretreated patient population, including patients with prior LEN and/or T-cell–redirecting therapy



Data cutoff: 15 September 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.; [b] **CAR T and/or bispecific antibody treatment.**

CAR, chimeric antigen receptor; CR., complete response; CRR, complete response rate; LEN, lenalidomide; ORR, overall response rate; PR, partial response; RTX, rituximab.

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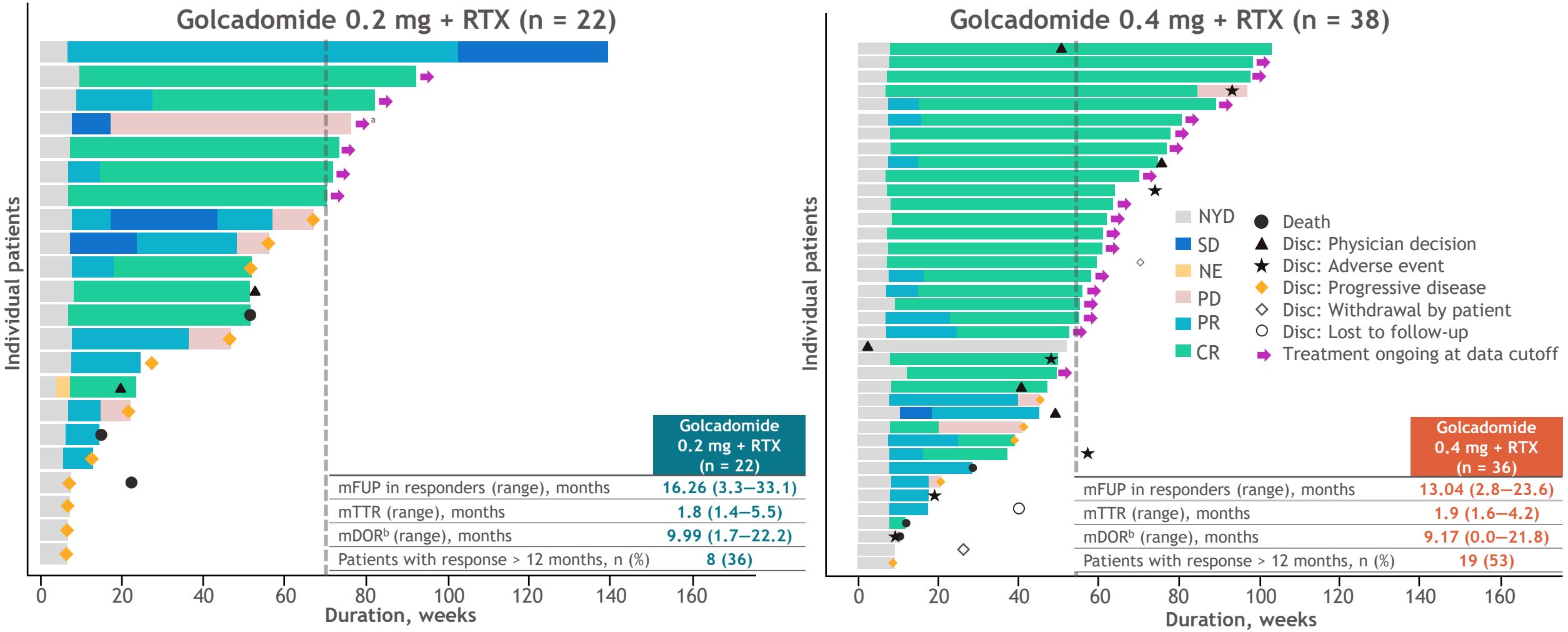
Golcadomide 0.4 mg + RTX in Part B Cohort D demonstrated durable responses



With Golcadomide 0.4 mg + RTX, 91% of patients (25/28) who achieved a CR remained in CR at the time of data cutoff

Data cutoff: 15 September 2025. [a] Patient remains on treatment in accordance with physician decision. [b] 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.

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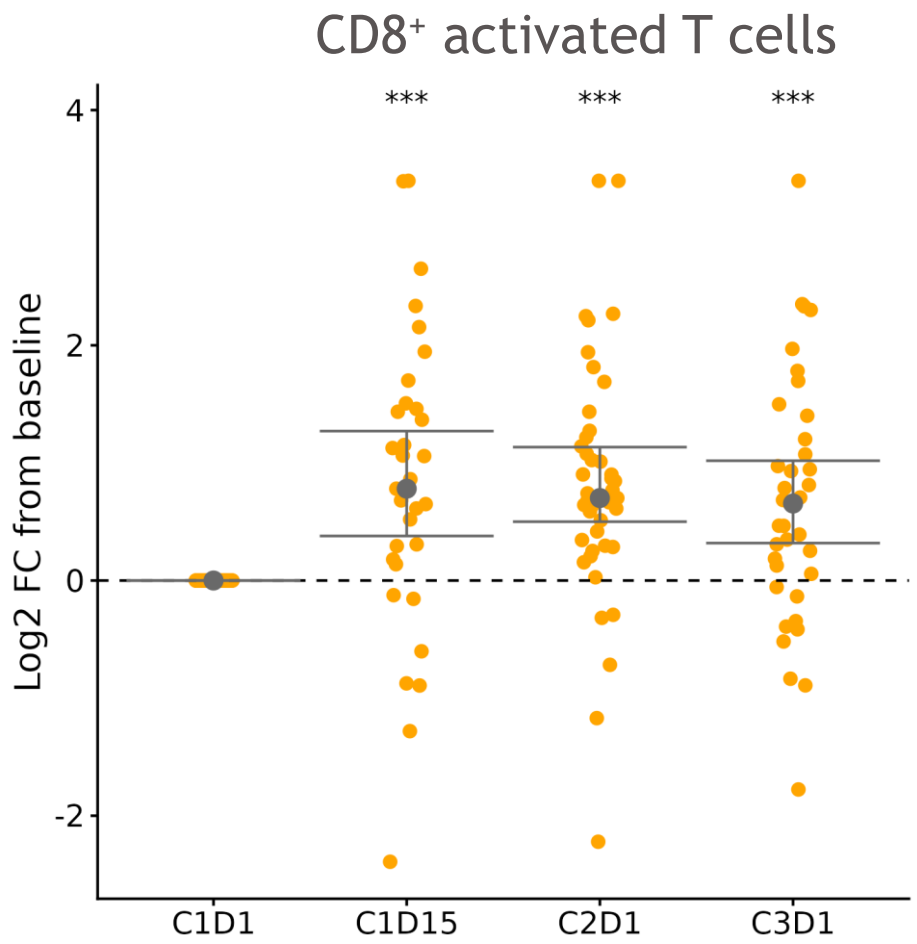
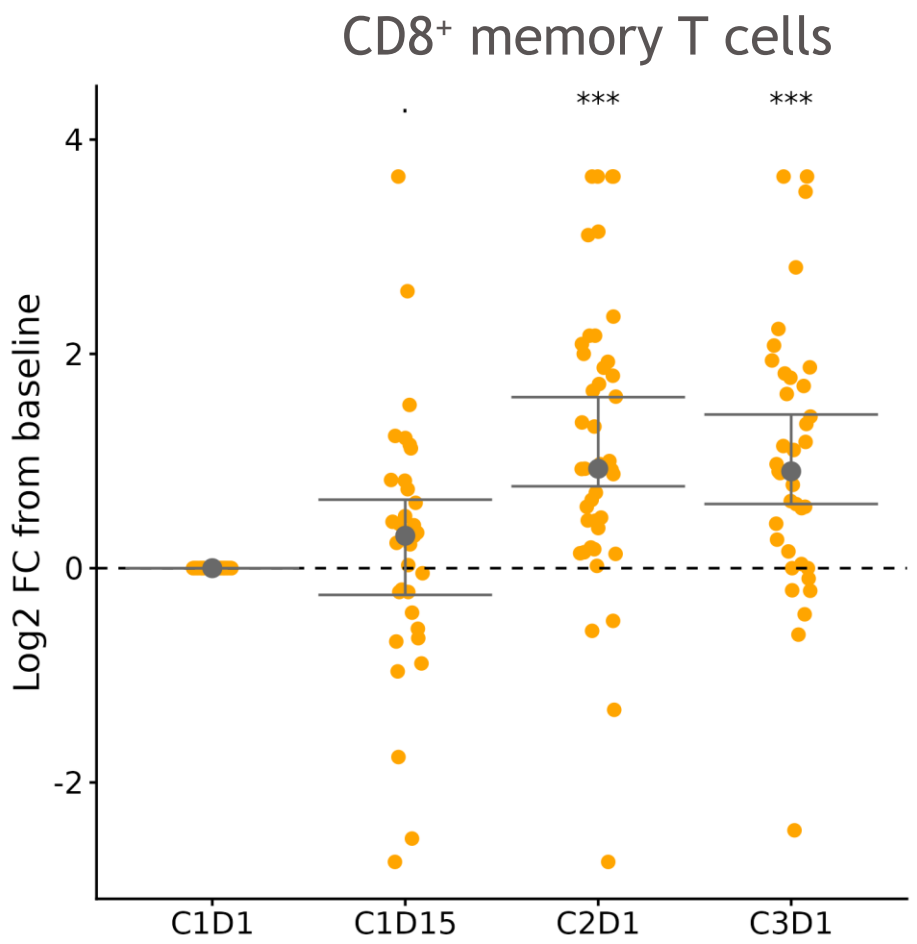
Peripheral T-cell subsets were activated within 2 weeks of golcadomide + RTX treatment





Immunophenotyping confirmed significant immune activation early during treatment, as indicated by increase in CD8+ activated T cells and CD8+ memory T cells

C, cycle; D, day; FC, fold change; RTX, rituximab.

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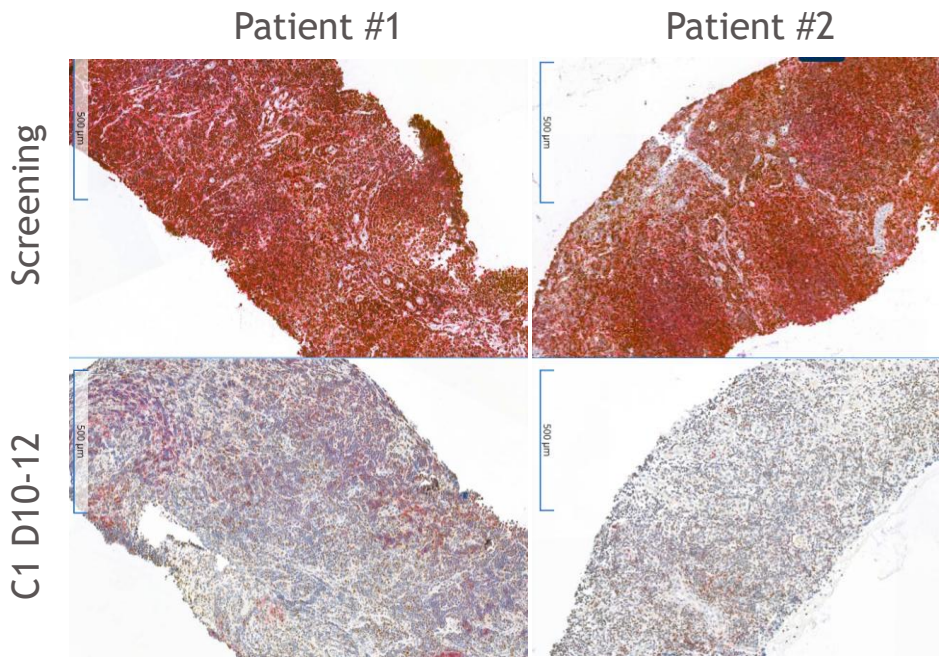
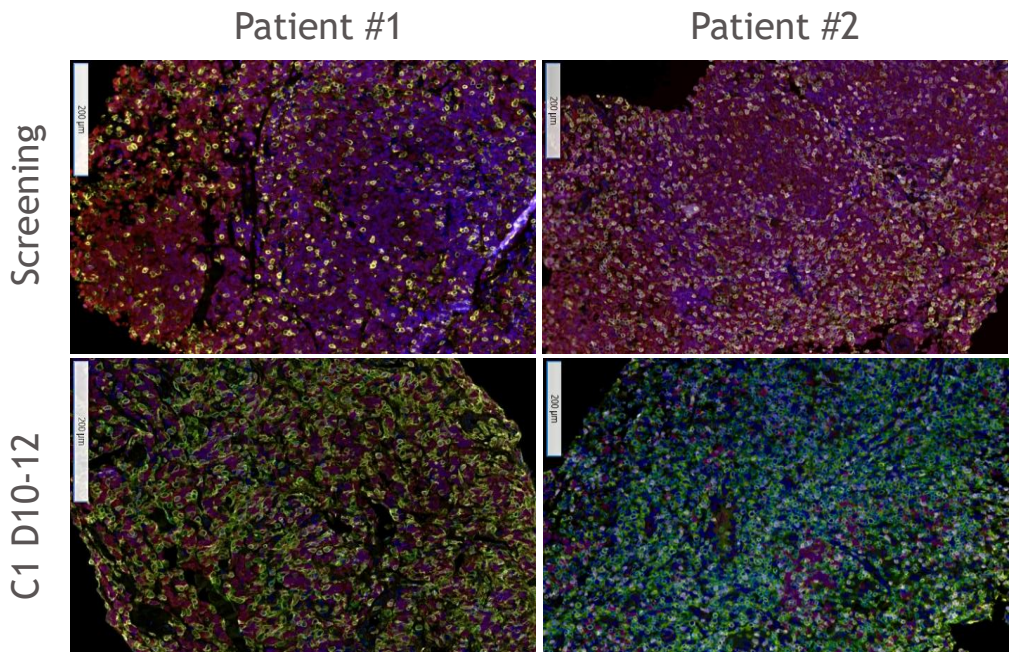
Golcadomide + RTX induced deep Aiolos degradation and increased immune infiltration in lymph nodes of patients with R/R FL

Golcadomide induced deep Aiolos degradation in lymph node B cells[a]



Pax5 Aiolos

Golcadomide treatment increased immune infiltration in lymph nodes of heavily pre-treated patients[b]



DAPI Pax5 CD3 CD8 FoxP3

[a] Representative images of immunohistochemistry staining with Pax5 (B-cells) and Aiolos in FFPE lymph node samples from 2 different FL patients at screening and on Cycle 1 Day 10, 11 or 12 of treatment with GOLCA and RTX.
[b] Representative images of immune-fluorescence staining with Pax5 (B-cells), CD4 (T-cells), CD8 (cytotoxic T-cells), FoxP3 (T-regs) and DAPI (nucleus) in FFPE lymph node samples from FL patients at screening and on Cycle 1 Day 10, 11 or 12 of treatment with golcadomide and rituximab.
C, cycle; D, day; DAPI, 4',6-diamidino-2-phenylindole; FFPE, formalin-fixed paraffin-embedded; FL, follicular lymphoma; FoxP3, forkhead box P3; Pax5, paired box 5; R/R, relapsed/refractory; RTX, rituximab

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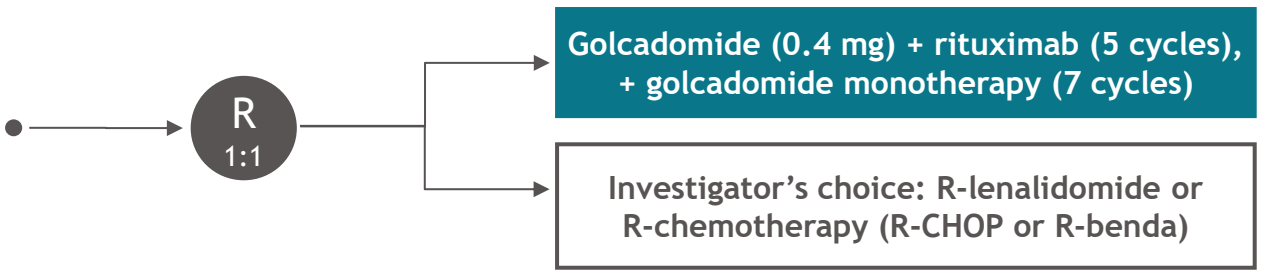
Conclusions

- 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 + rituximab showed promising efficacy 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 an ORR of 97% and a CRR of 78%, vs an ORR of 77% and CRR of 41% with 0.2 mg + rituximab
- Golcadomide + rituximab treatment resulted in early and pronounced immune activation in peripheral blood, which translated to deep Aiolos degradation and increased immune infiltration in tumor cells
- These data continue to support the ongoing development of golcadomide + rituximab as a fixed-duration, chemotherapy-free, outpatient option for patients with FL in the Phase 3 GOLSEEK-4 study in 2L+ FL (NCT06911502)[1]

GOLSEEK-4 study design[1]

Key eligibility criteria
- Age ≥ 18 years
- Histologically confirmed Grade 1–3a FL/classical FL
- R/R FL: ≥ 1 line of therapy, including an anti-CD20 mAb + alkylating agent



Primary endpoint
- PFS by IRAC

Key secondary endpoints
- ORR per IRAC
- OS

2L+, second line plus; CR, complete response; CRR, complete response rate; ctDNA, circulating tumor DNA; FL, follicular lymphoma; IRAC, Independent Radiology Adjudication Committee; LEN lenalidomide; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomized; R/R, relapsed/refractory.

1. Hawkes E, et al. ASH 2025. Abstract 3615.

Acknowledgments

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- The clinical study teams who participated
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