

Golcadomide, a potential, first-in-class, oral CELMoD combined with Pola-R-CHP in frontline aggressive B-cell lymphoma: safety and 12-month efficacy

ABCL-142

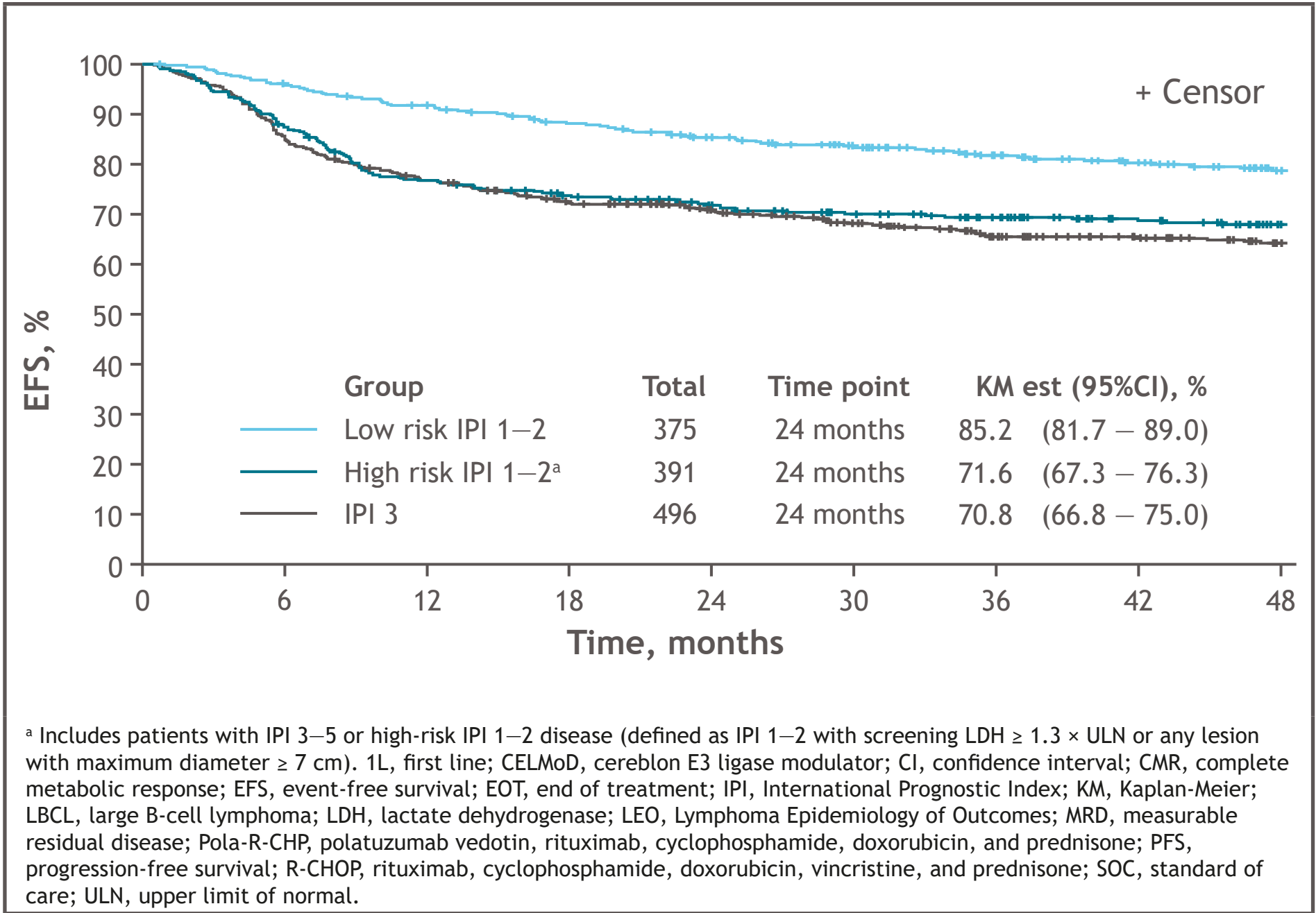
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Introduction

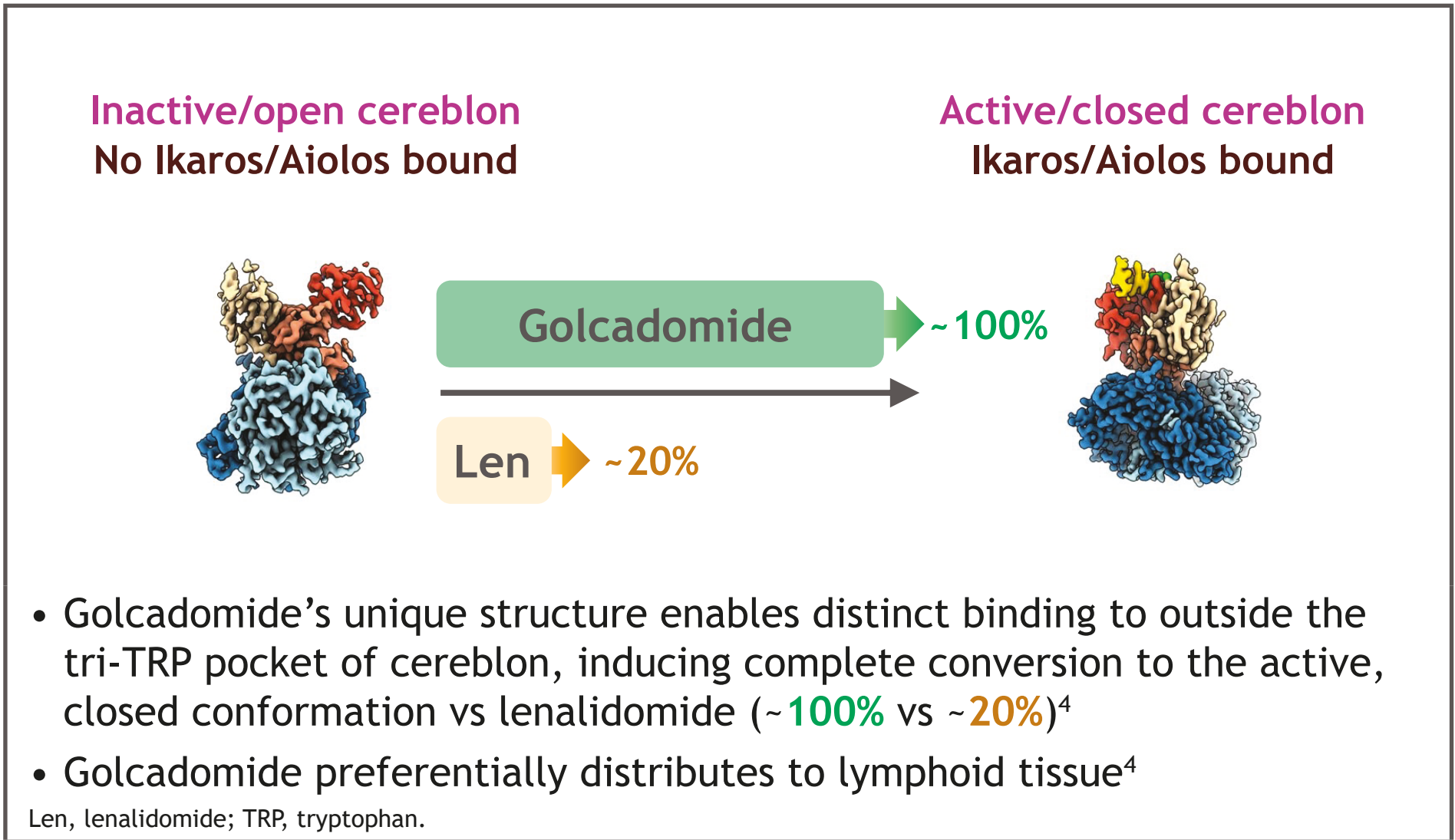
- Large B-cell lymphoma (LBCL) is the most common aggressive lymphoma, with 30–40% of patients not cured by first-line (1L) standard of care (SOC) regimens rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP)¹
- International Prognostic Index (IPI) is widely used to predict 1L outcomes; however, it fails to identify a subset of patients with inferior prognosis despite the lower scores (IPI 1-2; **Figure 1**)^{2,3}
 - Patients with high-risk IPI 1-2 are characterized by elevated LDH (> 1.3 × ULN) and/or bulky disease (single lesion ≥ 7 cm)²

Figure 1. LEO EFS by IPI²



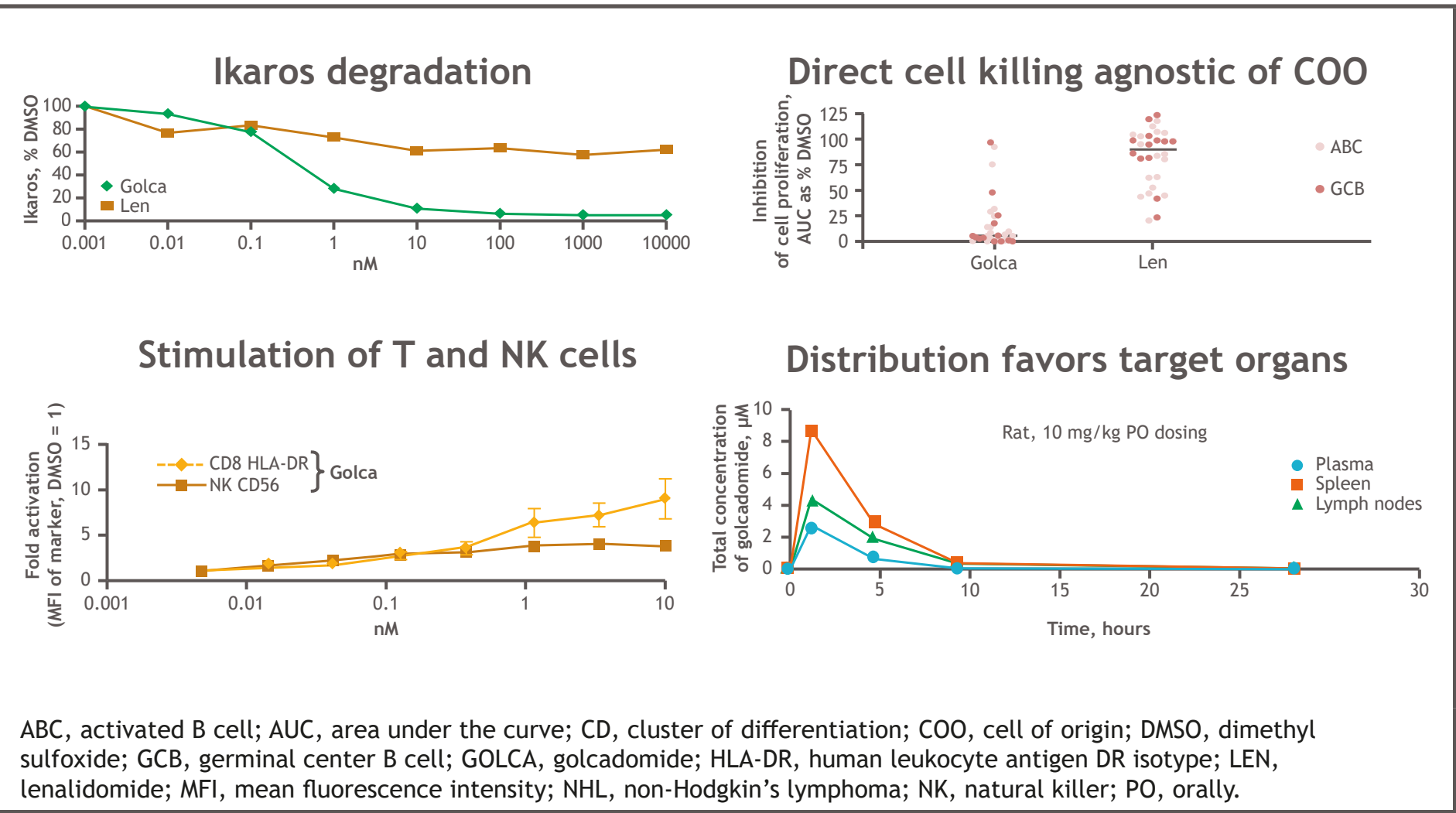
- Golcadomide is a potential, first-in-class, oral cereblon (CRBN) E3 ligase modulator (CELMoD) for lymphoma with preferential lymphoid distribution and enhanced activity in lymphoma cell lines⁴
- Both lenalidomide and golcadomide bind CRBN and modulate its activity to induce target protein degradation. 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 2 and 3**)^{4,6}
 - Golcadomide-induced Ikaros/Aiolos degradation results in direct cell killing, agnostic of cell of origin (COO), and immunomodulatory activity (**Figure 3**)^{7,8}
- CC-220-DLBCL-001 (NCT04884035), is an ongoing Phase 1B trial to assess the safety and preliminary efficacy of golcadomide in combination with Pola-R-CHP in untreated aggressive B-cell lymphoma (a-BCL)
 - In the Phase 1B trial in 1L LBCL, golcadomide 0.4 mg + R-CHOP demonstrated a manageable safety profile with 89% complete metabolic response (CMR) and 2-year progression free survival (PFS) rate of 79% in patients with high-risk disease⁹
- Here we present results for the golcadomide + Pola-R-CHP cohort CC-220-DLBCL-001 in 1L LBCL with a median follow-up exceeding 12 months

Figure 2. Golcadomide as a potential, first-in-class, oral CELMoD for lymphoma



- Golcadomide's unique structure enables distinct binding to outside the tri-TRP pocket of cereblon, inducing complete conversion to the active, closed conformation vs lenalidomide (~100% vs ~20%)⁴
- Golcadomide preferentially distributes to lymphoid tissue⁴
 - Len, lenalidomide; TRP, tryptophan.

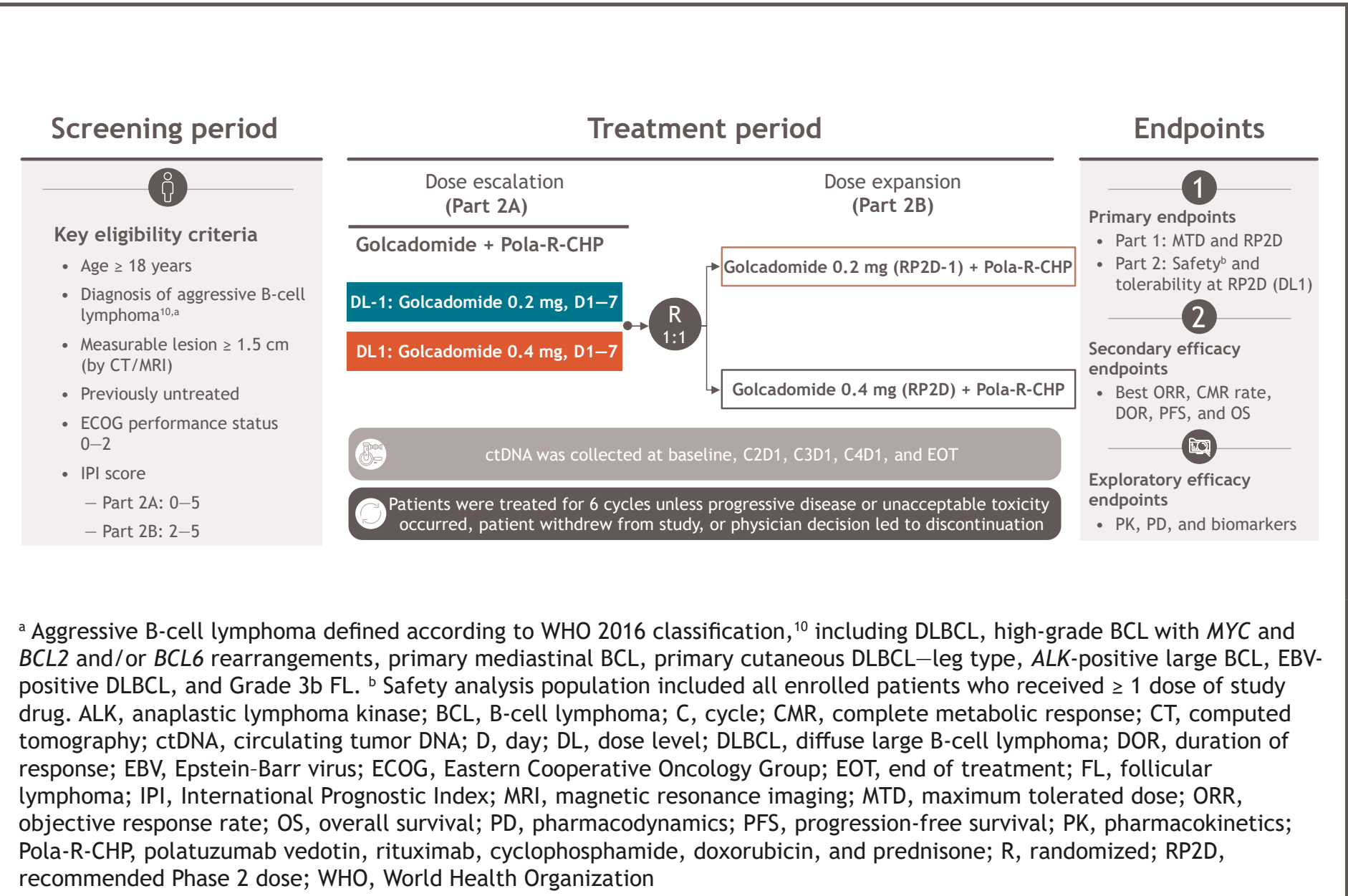
Figure 3. Preclinical rationale for golcadomide in NHL



Methods

- The study design of CC-220-DLBCL-001 is shown in **Figure 4**
- Key eligibility criteria included a diagnosis of a-BCL, at least 18 years of age, measurable lesion of ≥ 1.5 cm by CT or MRI, no prior treatment, ECOG PS 0–2, and an IPI score of 0-5 (Part 1) or 2-5 (Part 2)
- Part 2A was a dose escalation phase to determine the safety and tolerability at the recommended phase 2 dose (RP2D) of golcadomide, which served as the primary endpoints
- Part 2B was a dose expansion phase designed to further assess the safety and preliminary efficacy of golcadomide + Pola-R-CHP
 - Patients were randomized 1:1 to receive golcadomide + Pola-R-CHP at 1 of 2 RP2D, 0.2 mg or 0.4 mg, for 7-day cycles
- Secondary endpoints included objective response rate (ORR), CMR, duration of response, PFS, and overall survival
- Pharmacodynamics, pharmacokinetics, and selected biomarkers served as exploratory endpoints

Figure 4. CC-220-DLBCL-001 study design: 1L golcadomide + Pola-R-CHP in a-BCL



^a Aggressive B-cell lymphoma defined according to WHO 2016 classification, ^b including DLBCL, high-grade BCL with MYC and BCL2 and/or BCL6 rearrangements, primary mediastinal BCL, primary cutaneous DLBCL-les type, ALK-positive large BCL, EBV-positive DLBCL, and Grade 3b FL. ^c Safety analysis population included all enrolled patients who received ≥ 1 dose of study drug. ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; C, cycle; CMR, complete metabolic response; CT, computed tomography; ctDNA, circulating tumor DNA; D, day; DL, dose level; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FL, follicular lymphoma; IPI, International Prognostic Index; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R, randomized; RP2D, recommended Phase 2 dose; WHO, World Health Organization

Results

Baseline characteristics and patient disposition

- Patient disposition is shown in **Table 1**
- At the data cutoff (September 15, 2025), the median (range) follow-up was 15.5 (0.8–23.9) months in the overall population
- Patients had similar baseline characteristics between the two treatment groups, with a higher proportion of males in the 0.4 mg group than in the 0.2 mg group (**Table 2**)

Safety

- Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 96% and 93% of patients in the 0.2 mg and 0.4 mg treatment groups, respectively (**Figure 5**)
 - For both treatment groups, the most common TEAEs (occurring in ≥ 10% of patients) included neutropenia, thrombocytopenia, anemia, and febrile neutropenia

Table 1. CC-220-DLBCL-001 patient disposition

	Golcadomide 0.2 mg + Pola-R-CHP (n = 28)	Golcadomide 0.4 mg + Pola-R-CHP (n = 30)	Overall (N = 58)
Treatment disposition, n (%)^a			
Ongoing	0	0	0
Completed	23 (82)	24 (83)	47 (83)
Discontinued	5 (18)	5 (17)	10 (18)
Reasons for discontinuation			
Death ^b	1 (4)	0	1 (2)
AE	1 (4)	0	1 (2)
Progressive disease	1 (4)	0	1 (2)
Withdrawal by subject ^c	1 (4)	3 (10)	4 (7)
Physician Decision	1 (4)	2 (7)	3 (5)
Continued to follow-up period, n (%)			
Yes	25 (89)	27 (93)	52 (91)
No	3 (11)	2 (7)	5 (9)
Disposition from follow-up period			
Ongoing	24 (86)	26 (90)	50 (88)
Completed	0	0	0
Discontinued	1 (4)	1 (3)	2 (4)
Reason for follow-up discontinuation			
Death ^b	1 (4)	0	1 (2)
Withdrawal by subject	0	1 (4)	1 (2)

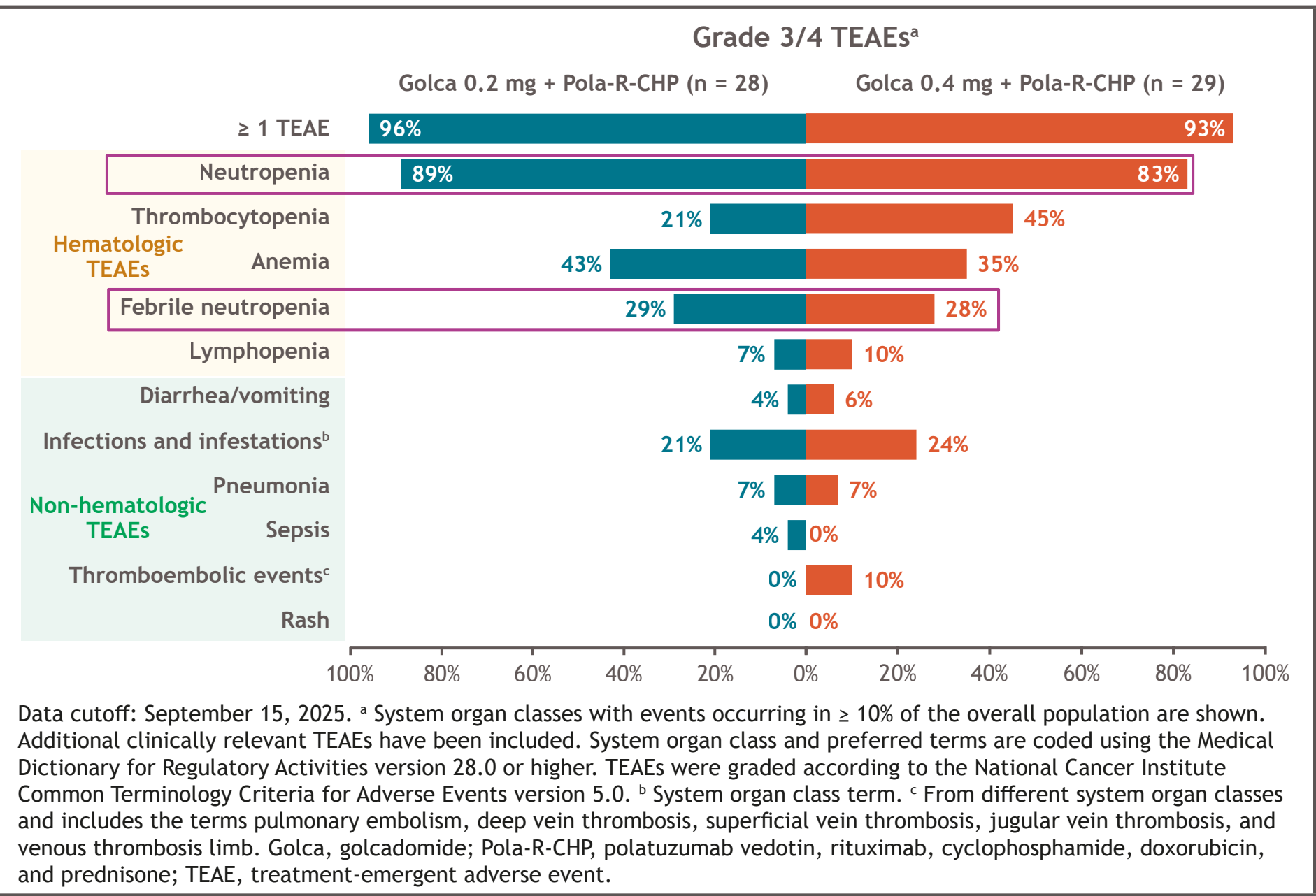
^a All enrolled patients received ≥ 1 dose of study therapy. ^b One death in treatment period due to unknown reason, with history of pneumonia determined to be unrelated to golcadomide and one death in follow-up period due to refractory DLBCL. ^c Withdrawals due to patient preference (1), limited performance status (1), and unknown reasons (2). AE, adverse event; DLBCL, diffuse large B-cell lymphoma; PD, progressive disease; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Table 2. Baseline characteristics

	Golcadomide 0.2 mg + Pola-R-CHP (n = 28)	Golcadomide 0.4 mg + Pola-R-CHP (n = 29)
Age, median (IQR), years	63 (58–74)	64 (54–67)
Male	17 (61)	13 (45)
IPI score at enrollment		
Low- and low-intermediate risk (0–2)	9 (32)	11 (38)
Low-intermediate (1–2) risk with high-risk features ^a	6 (21)	6 (21)
High-intermediate risk (3)	9 (32)	12 (41)
High risk (4 or 5)	10 (36)	6 (21)
High-risk disease^b	25 (89)	24 (83)
Hans COO^c		
GCB	14 (50)	13 (45)
Non-GCB	9 (32)	13 (45)
Other ^d	5 (18)	3 (10)
Histology		
DLBCL NOS	22 (79)	26 (90)
Grade 3b FL	1 (4)	0
High-grade BCL with MYC and BCL2 and/or BCL6 rearrangements	3 (11)	1 (3)
PMBL	1 (4)	1 (3)
Elevated LDH (≥ 1 × ULN)	23 (82)	21 (72)
Extranodal involvement		
≤ 1 site	14 (50)	16 (55)
> 1 site	14 (50)	13 (45)

Data are n (%) unless otherwise noted. ^a Defined as IPI 1–2 with ≥ 1 lesion with a maximum diameter ≥ 7 cm and/or screening LDH ≥ 1.3 × ULN. ^b High-risk subgroup includes patients with IPI 3–5 disease or those with IPI 1–2 with ≥ 1 lesion with a maximum diameter ≥ 7 cm and/or screening LDH ≥ 1.3 × ULN. ^c Determined by immunohistochemistry. ^d Includes testing not done or unknown or not classified. ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; COO, cell of origin; D, day; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FL, follicular lymphoma; GCB, germinal center B-cell; IPI, International Prognostic Index; IQR, interquartile range; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; NOS, not otherwise specified; PMBL, primary mediastinal B-cell lymphoma; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; PMBL, primary mediastinal B-cell lymphoma; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R, randomized; RP2D, recommended Phase 2 dose; WHO, World Health Organization

Figure 5. Grade 3/4 TEAEs



Data cutoff: September 15, 2025. ^a System organ classes with events occurring in ≥ 10% of the overall population are shown. Additional clinically relevant TEAEs have been included. System organ class and preferred terms are coded using the Medical Dictionary for Regulatory Activities version 28.0 or higher. ^b TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. ^c System organ class term. ^d From different system organ classes and includes the terms pulmonary embolism, deep vein thrombosis, superficial vein thrombosis, jugular vein thrombosis, and venous thrombosis limb. Golca, golcadomide; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; TEAE, treatment-emergent adverse event.

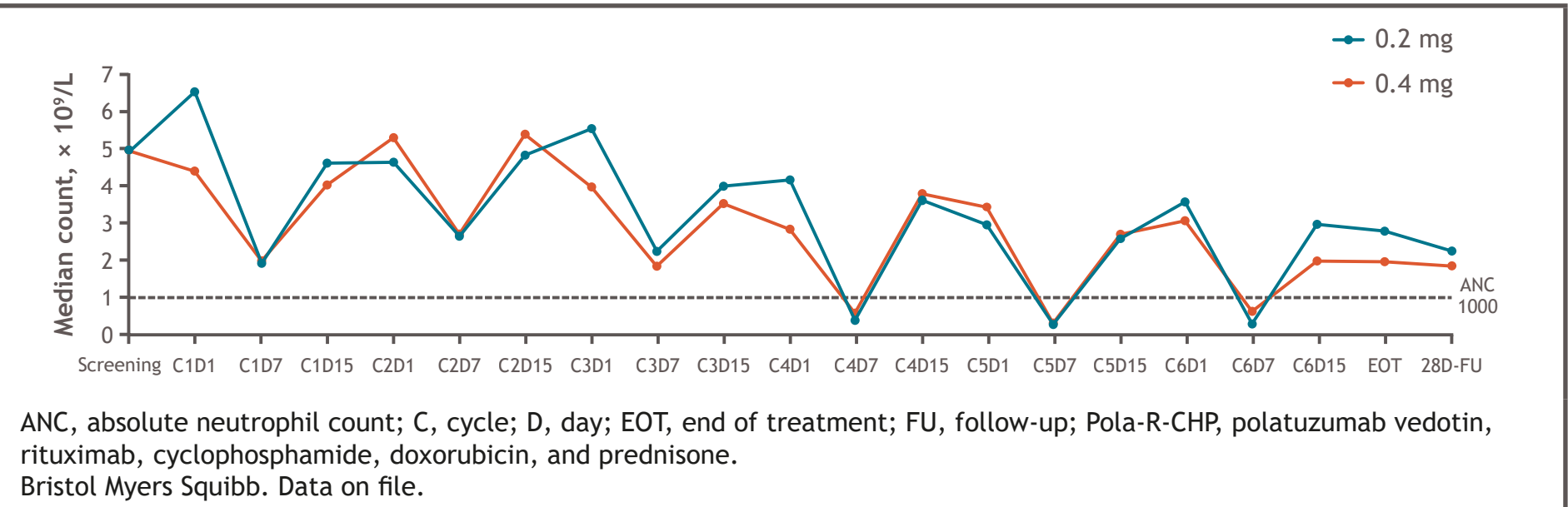
- Across treatment groups, the median relative dose intensity of golcadomide + Pola-R-CHP ranged from 95% to 100% (**Table 3**)

Table 3. Median relative dose intensity

	Golcadomide 0.2 mg + Pola-R-CHP (n = 28)	Golcadomide 0.4 mg + Pola-R-CHP (n = 29)
Golcadomide, %	99	95
Polatuzumab vedotin, %	98	98
Cyclophosphamide, %	100	99
Doxorubicin, %	100	99

- The nadir and recovery of the median neutrophil count were similar between the 0.2 mg and 0.4 mg treatment groups, and occurred in a predictable fashion (**Figure 6**)
 - Only 1 (3%) patient had an absolute neutrophil count of < 1000 cells/μL by the start of the next cycle at golcadomide 0.4 mg

Figure 6. Median neutrophil count over time

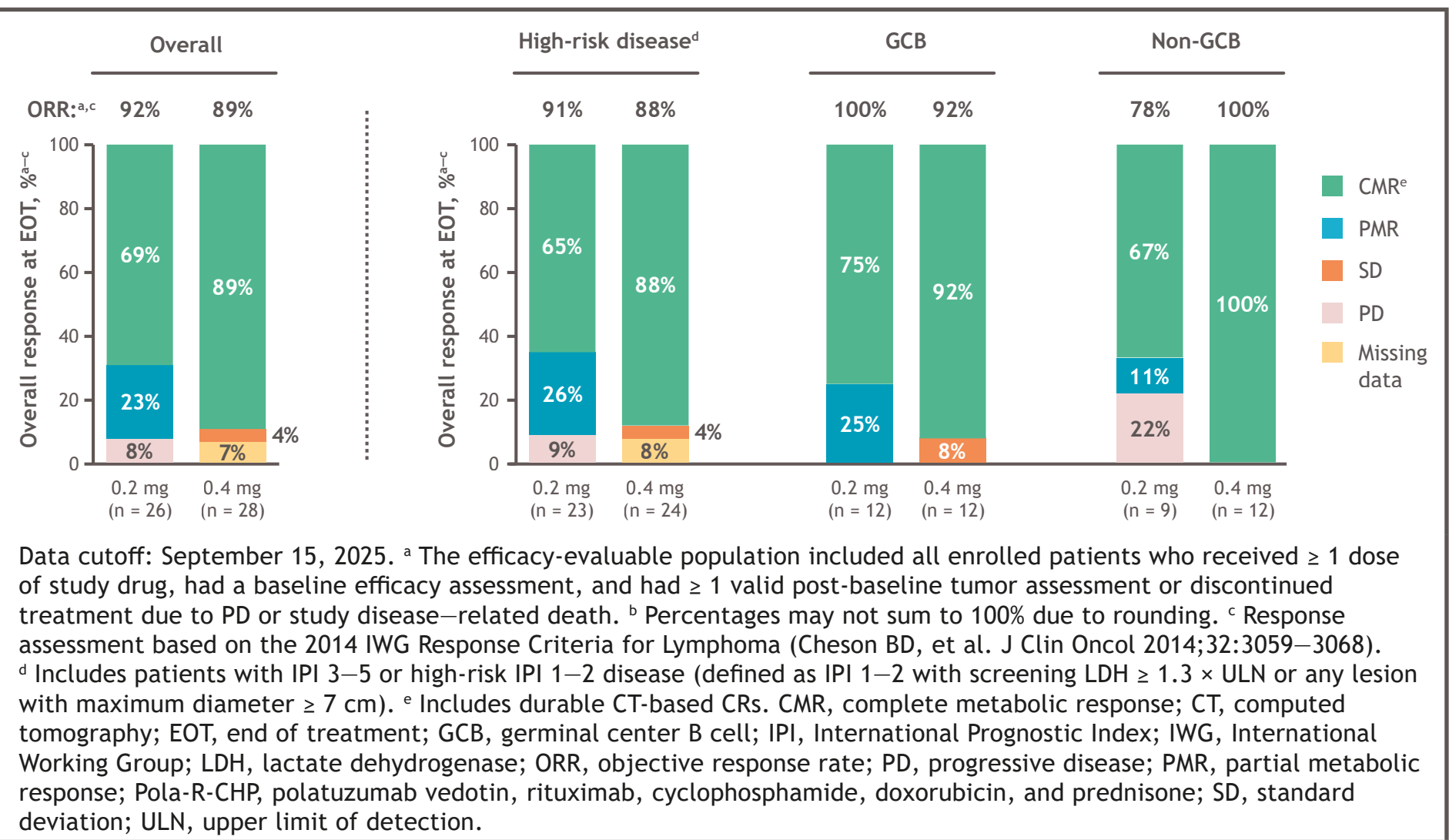


ANC, absolute neutrophil count; C, cycle; D, day; EOT, end of treatment; FU, follow-up; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Efficacy

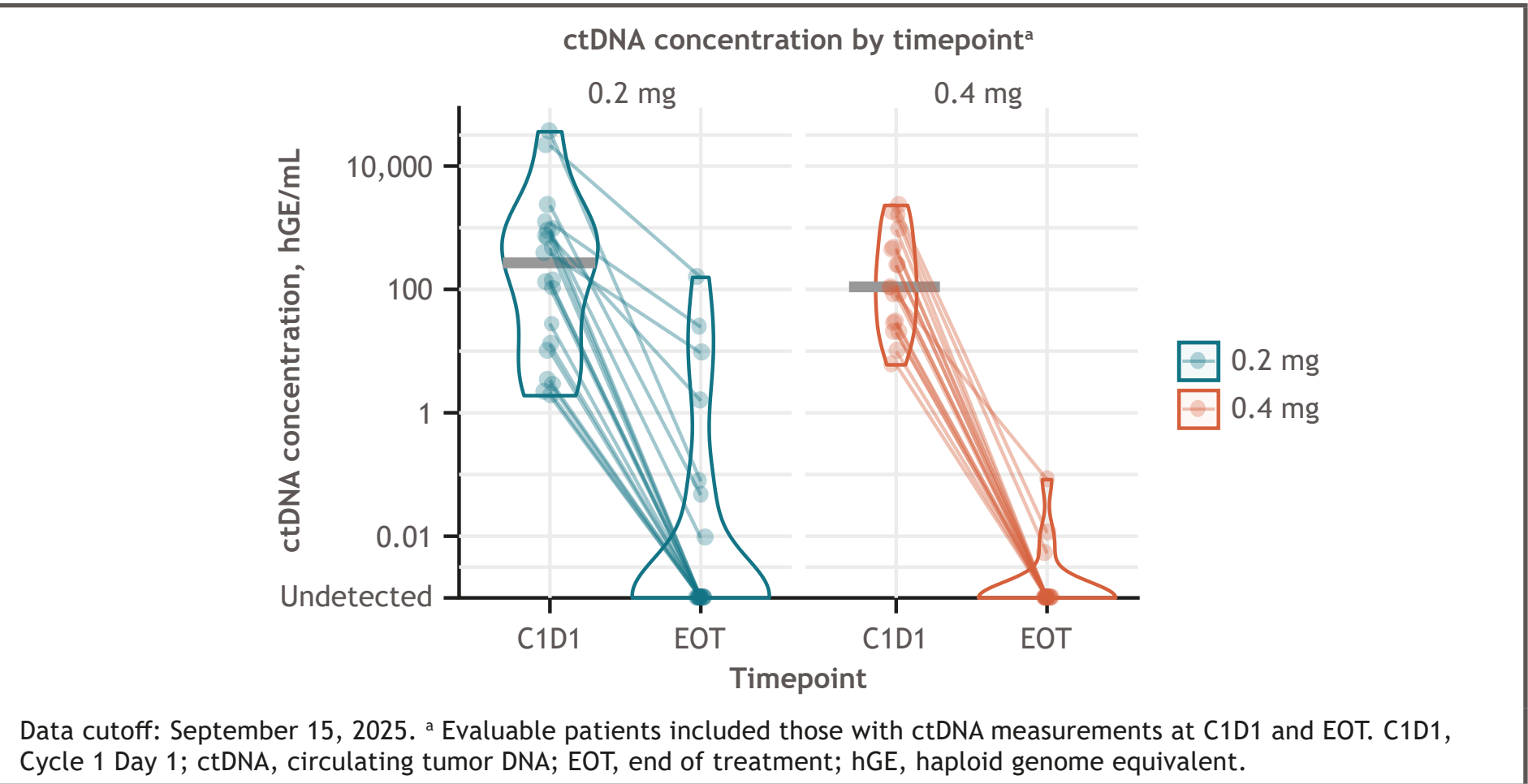
- Golcadomide 0.4 mg + Pola-R-CHP resulted in high CMR rates at end of treatment (EOT); these were consistent across the overall and high-risk disease populations and irrespective of COO (**Figure 7**)
- ctDNA levels decreased by EOT with both golcadomide 0.2 and 0.4 mg doses, although to a greater degree with 0.4 mg (**Figure 8**)
- Among patients treated with golcadomide 0.4 mg, 83% and 80% achieved MRD negativity at EOT (by PhasED-Seq) in the overall and high-risk disease populations, respectively (**Figure 9**)
- Golcadomide 0.4 mg + Pola-R-CHP resulted in a high rate of durable remissions at a median follow-up of 16.7 months, and promising 12-month PFS rates, in both the overall cohort and in patients with high-risk disease (**Figure 10**)

Figure 7. Overall response



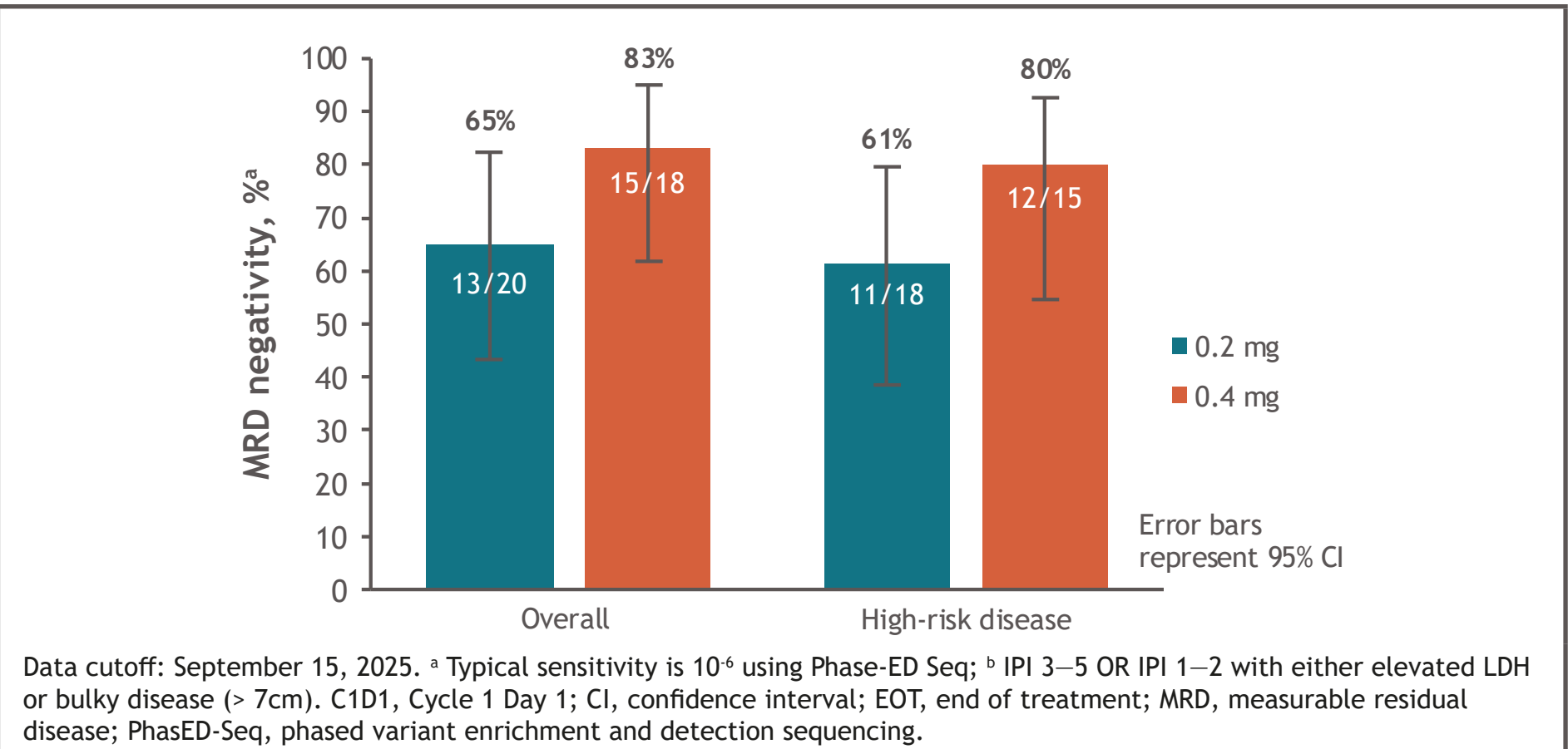
Data cutoff: September 15, 2025. ^a The efficacy-evaluable population included all enrolled patients who received ≥ 1 dose of study drug, had a baseline efficacy assessment, and had ≥ 1 valid post-baseline tumor assessment or discontinued treatment due to PD or study disease–related death. ^b Percentages may not sum to 100% due to rounding. ^c Response assessment based on the 2014 IWG Response Criteria for Lymphoma (Cheson BD, et al. J Clin Oncol 2014;32:3059–3068). ^d Includes patients with IPI 3–5 or high-risk IPI 1–2 disease (defined as IPI 1–2 with screening LDH ≥ 1.3 × ULN or any lesion with maximum diameter ≥ 7 cm). ^e Includes durable CT-based CRs. CMR, complete metabolic response; CT, computed tomography; EOT, end of treatment; GCB, germinal center B-cell; IPI, International Prognostic Index; IWG, International Working Group; LDH, lactate dehydrogenase; ORR, objective response rate; PD, progressive disease; PMR, partial metabolic response; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; SD, standard deviation; ULN, upper limit of detection.

Figure 8. Baseline and EOT ctDNA levels by dose



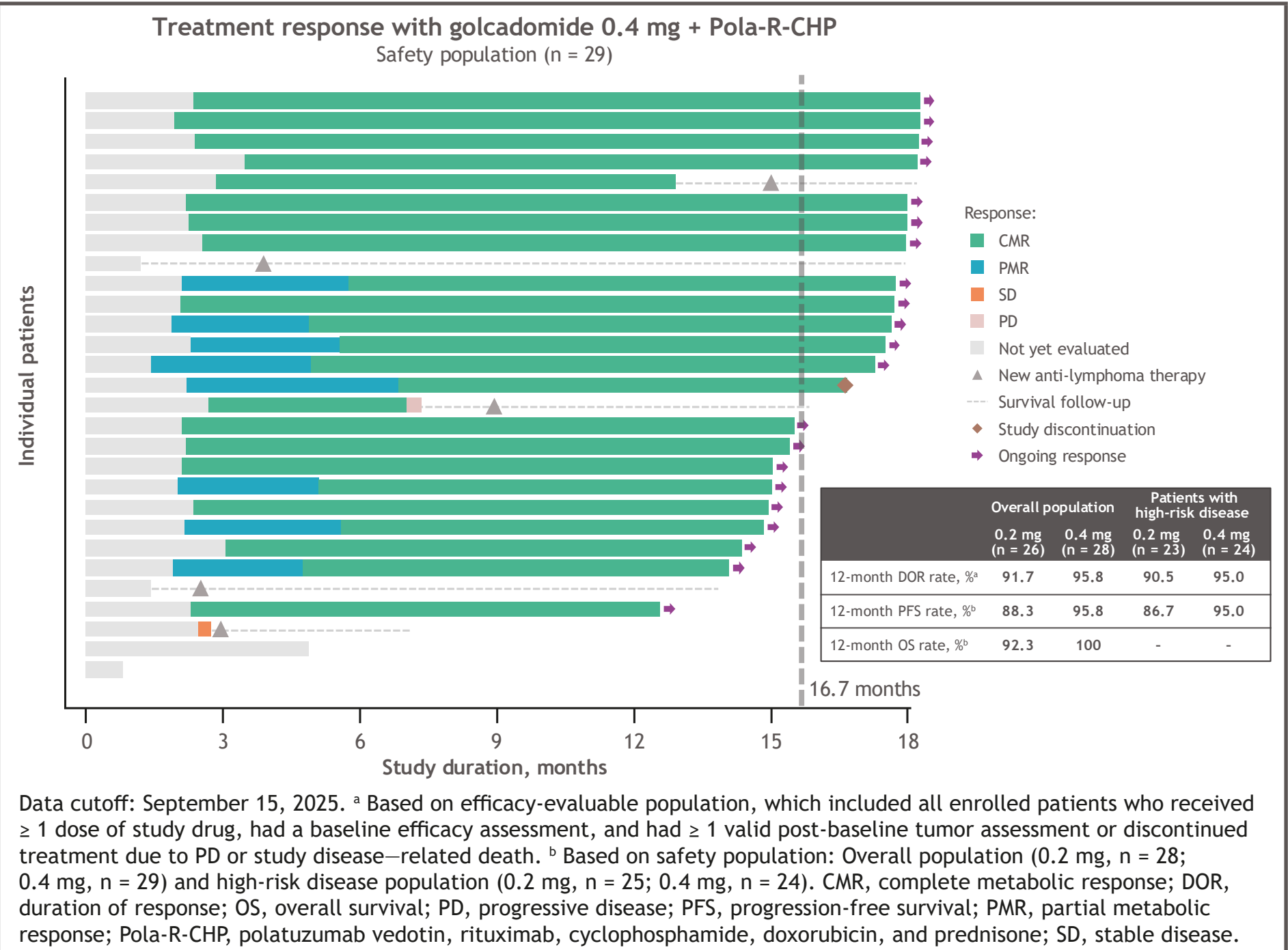
Data cutoff: September 15, 2025. ^a Evaluable patients included those with ctDNA measurements at C1D1 and EOT. C1D1, Cycle 1 Day 1; ctDNA, circulating tumor DNA; EOT, end of treatment; ng/mL, haploid genome equivalent.

Figure 9. EOT MRD negativity using PhasED-Seq^a in the overall and high-risk disease^b populations



Data cutoff: September 15, 2025. ^a Typical sensitivity is 10⁴ using PhasED-Seq. ^b IPI 3–5 or IPI 1–2 with either elevated LDH or bulky disease (> 7 cm). C1D1, Cycle 1 Day 1; CI, confidence interval; EOT, end of treatment; MRD, measurable residual disease; PhasED-Seq, phased variant enrichment and detection sequencing.

Figure 10. Treatment response



Data cutoff: September 15, 2025. ^a Based on efficacy-evaluable population, which included all enrolled patients who received ≥ 1 dose of study drug, had a baseline efficacy assessment, and had ≥ 1 valid post-baseline tumor assessment or discontinued treatment due to PD or study disease–related death. ^b Based on safety population: Overall population (0.2 mg, n = 28; 0.4 mg, n = 29) and high-risk disease population (0.2 mg, n = 25; 0.4 mg, n = 24). CMR, complete metabolic response; DOR, duration of response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PMR, partial metabolic response; Pola-R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; SD, stable disease.

Conclusions

- Golcadomide 0.4 mg + Pola-R-CHP resulted in high CMR rates (89%) that were durable and promising 12-month PFS rates (96%). Results were consistent in overall and high-risk populations
- TEAEs were primarily hematologic, while non-hematologic AEs were infrequent and mostly low grade; the addition of golcadomide to Pola-R-CHP did not compromise the delivery of chemotherapy
- Treatment with golcadomide 0.4 mg in combination with Pola-R-CHP or R-CHOP demonstrated comparable outcomes, with similar EOT CMR rates and Grade 3/4 hematologic AE rates⁹
- These data continue to support the potential of golcadomide in combination with the SOC regimens R-CHOP and Pola-R-CHP to improve cure rates in newly diagnosed high-risk LBCL
- Golcadomide 0.4 mg + R-CHOP is being evaluated in the ongoing Phase 3 GOLSEEK-1 trial in high-risk 1L LBCL (NCT06356129)¹¹

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